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The role of neural impulse control mechanisms for dietary success in obesity

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Abstract

Deficits in impulse control are discussed as key mechanisms for major worldwide health problems such as drug addiction and obesity. For example, obese subjects have difficulty controlling their impulses to overeat when faced with food items. Here, we investigated the role of neural impulse control mechanisms for dietary success in middle-aged obese subjects. Specifically, we used a food-specific delayed gratification paradigm and functional magnetic resonance imaging to measure eating-related impulse-control in middle-aged obese subjects just before they underwent a twelve-week low calorie diet. As expected, we found that subjects with higher behavioural impulse control subsequently lost more weight. Furthermore, brain activity before the diet in VMPFC and DLPFC correlates with subsequent weight loss. Additionally, a connectivity analysis revealed that stronger functional connectivity between these regions is associated with better dietary success and impulse control. Thus, the degree to which subjects can control their eating impulses might depend on the interplay between control regions (DLPFC) and regions signalling the reward of food (VMPFC). This could potentially constitute a general mechanism that also extends to other disorders such as drug addiction or alcohol abuse.

1. Introduction

Obesity is a major and increasing worldwide health problem due to its high prevalence and severe medical consequences (Bray, 2004). A variety of factors in the development and maintenance of obesity are currently discussed, including psychological (e.g., Weygandt et al., 2012; Rothemund et al., 2007; Torres et al., 2007; Ng & Jeffrey, 2003; Rodin et al., 1989), behavioural (e.g., Hays et al., 2008; Bellisle et al., 2004), genetic (e.g., Dina et al., 2007; Frayling et al., 2007), and endocrinological (e.g., Page et al., 2011; Ahima, 2008; Rosenbaum et al., 2008; Farooqi et al., 2007; Klok et al., 2007). Within the latter framework, also (insufficient) cerebral insulin suppression during stressful events is discussed, a topic especially referred to in the literature on the 'selfish-brain theory' (c.f. Peters et al., 2011). Among psychological factors, impaired impulse control is believed to play an important role for obesity (e.g., McGuire et al., 2001; Masheb et al., 2002; Weller et al., 2008; Nijs et al., 2010; Batterink et al., 2010; Kishinevsky et al., 2012) as well as for other major health problems, such as drug addiction (e.g., Volkow et al., 2004; Goldstein et al., 2007; Barrós-Loscertales et al., 2011) and alcohol abuse (e.g., Li et al., 2009). The association of obesity and impulse control has been tested in behavioural studies that found that impulse control measured with delay discounting (DD) paradigms or questionnaires is negatively associated with body weight (Weller et al., 2008; Masheb et al., 2002; McGuire et al., 2001). Neuroimaging studies have investigated the neural foundations of decision-making and impulse control in eating-related tasks (Hare et al., 2009; 2011). They suggest that food decisions in self-reported dieters rely not only on value signals in ventromedial prefrontal cortex (VMPFC), but also on the degree to which control signals in dorsolateral prefrontal cortex (DLPFC) exert an influence over these value signals. Studies searching for neural correlates of longitudinal weight changes and impulse control exclusively investigated non-dieting subjects and either failed to identify such signals (Batterink et al., 2010), or they were

able to identify neural predictors of weight changes but without being able to link them to control behaviour (Kishinevsky et al., 2012). Correspondingly, the complex relation between neurobehavioural parameters of impulse control and dietary success in obese subjects is still unclear.

Here, we investigated the link between behavioural impulsivity and their neural correlates *acquired before the onset* of a twelve-week low calorie diet in obese subjects and the corresponding weight loss obtained after the diet. We separately assessed the prognostic information contained in behavioural parameters of control, its neural correlates and the network connectivity of areas involved in decision-making. We found that a) higher impulse control is associated with better dietary success, b) future dietary success correlates with local brain activity in reward-related areas and areas involved in impulse control, and finally c) that dietary success correlates with functional connectivity between reward- and control-related brain structures reflecting the degree of control applied to food-decisions.

2. Methods and materials

2.1 Participants

Participants were first invited via newspaper announcements and notifications in hospitals to participate in a larger dietary study. The inclusion criteria for this study were an age in the range of 18 to 70 years and a BMI of at least 30 when no cardiovascular risk factor such as arterial hypertension was present or a BMI of at least 27 when such a factor was present. Subjects with endocrine diseases, malabsorption, food allergies, hypertonia, recent changes in smoking behaviour, pharmacological treatments known to affect energy homeostasis, subjects participating in a diet in a two month interval preceding the study and subjects with weight changes of more than 5 kilograms in this period were excluded. Subjects included in the

larger diet study were invited verbally to participate in the fMRI study. If they agreed, they were screened with a standardized clinical interview for mental disorders (Margraf et al., 2005) by a clinical psychologist (MW) in the second stage. When screening indicated an affective, anxiety, or delusional disorder, borderline personality disorder, or substance abuse, the subject was excluded. Furthermore, subjects were asked if they ever had a / whether they were ever diagnosed with Multiple Sclerosis, Parkinson's Disease, dementia, stroke, epilepsy, brain tumor, or whether they have ever had a brain surgery. When this screening indicated a positive result, subjects were excluded. 22 subjects that passed this screening procedure and did not have standard MRI contraindications performed a delayed gratification pilot run (see section 2.3.1 Delayed gratification task). Four of the 22 subjects did not show variations in decision behaviour (e.g., always chose the delayed meal option) and were thus excluded. Finally, another two subjects were excluded that showed inconsistent decision behaviour between the behavioural pilot and fMRI delayed gratification runs (c.f., Kishinevsky et al., 2012). Thus, finally 16 (13 female) subjects were included in the fMRI study. Their mean age was M = 43.0 yrs (SD = 12.2 yrs; range: 23.5 yrs – 66.5 yrs). Their mean pre-diet BMI was M = 34.5 (SD = 3.2; range: 29.8 – 41.5). On average, the dietary BMI-reduction was M = 4.3 (SD = 1.8; range: 0.7 – 7.7). The mean weight loss in kilograms was M = 12.7 kg (SD = 5.4 kg; range = 1.9 kg – 20.5 kg). Finally, on average the subjects dropped to M = 87.4% (SD = 5.2%; range: 77.0% - 98.0%) of their baseline weight in kilogram during the weight reduction program. Subjects obtained 10€ for participation in the screening session and 30€ for participation in the fMRI session. All participants provided written, informed consent. The study was approved by the ethics committee of the Charité - Universitätsmedizin Berlin.

2.2 Diet protocol

Weight loss was induced using a dietary protocol with a length of 12 weeks. The protocol consisted of three components: caloric restriction, nutritional counselling and physical exercises. Caloric restriction applied in the weight reduction program can be separated in two stages. In the first stage that lasted for 8 weeks, energy intake was restricted to 800 kilocalories per day by using a formula diet (Optifast 2®, Nestlé HealthCare Nutrition GmbH, Frankfurt am Main, Germany). During this period, subjects received 35 portions of the formula diet for a week (i.e. 5 per day) in weekly meetings with a nutritionist and were advised not to consume any additional food. For the case that they were not able to follow this caloric restriction, they were instructed to document the amount of additional food consumed. The amount of consumed formula diet portions (and if applicable: additional food) was then documented in the meeting of the next week. In these meetings, also a medical monitoring was performed by a physician including a patient interview, arterial blood pressure measurement, and a blood test. Based on the blood sample, parameters for sodium, potassium, calcium, triglycerides and creatinine were determined in order to guarantee a compatible course of the weight reduction in terms of e.g. kidney and cardiac functioning. In the second stage of the weight reduction that lasted for 4 weeks, subjects were instructed to follow a calorie restricted standard diet composed in accordance with guidelines of the German Association of Nutrition (1500 kilocalories per day; 30% fat, 55% carbohydrates, 15% protein; c.f. http://www.dge.de). Observance of the standard diet was supported by providing specific recipes, cooking advices, and instructions for behaviour modifications (only 3 meals per day, at least 4 hours break between the meals, reduced carbohydrate intake at dinner, support of increased physical activity independent of guided exercise training; see below). During that period, at least one body weight measurement per week was performed by a nutritionist at study site. During both stages of the program, i.e. the full 12-week period, weekly nutritional counselling group meetings (cooking courses) with a duration of 90 minutes were performed. In these group meetings subjects also performed guided physical

exercise (aqua fitness or therapeutic exercise training) subsequent to the cooking courses for 30 minutes. On average, the dietary intervention program started M = 5.3 days (SD = 4.6 days; range: 0 days – 14 days) after the fMRI session.

2.3 Stimuli and task

2.3.1 Delayed gratification task

This task was conducted twice during the study, i.e. once within a behavioural pilot on the day of recruitment in the hospital and once during fMRI scanning in four consecutive runs performed on a subsequent day. In both cases, the task was conducted between 8 and 11 a.m. to control for circadian oscillations of hormonal parameters. Subjects were asked to stop eating at 8 pm on the day before to guarantee that they were in a fasted state.

To tailor the paradigm to the individual subjects' food preferences, subjects had to state a preferred meal out of seven meals that varied in terms of calorie content on the day of recruitment in the hospital before the pilot. These meal options included typical breakfast and lunch meals. Specifically, subjects could chose among tomatoes with mozzarella, eggs and tomatoes, cereals with dried fruit, pasta salad, muffins, scallop, and pizza (Figure 1). Subjects were told that they would not be gratified with a meal at the end of the task, but that decisions were made in an "as if" situation.

Each trial began with the presentation of a fixation screen, which was shown for two (behavioural pilot) or four to eight (fMRI scanning) seconds. In the following choice stage, a small portion of the favourite meal with the label 'immediately' appeared on one randomly selected side of the screen. On the other side, a larger portion of the meal was shown together with a label indicating a specific delay of gratification for the larger alternative. The subject was instructed to select their preferred choice with a button press. After the button press the

arrow beneath the chosen meal changed its colour from yellow to red to indicate successful selection in the feedback stage. The total duration of the choice and feedback stage was 6 seconds. After the feedback stage, the next trial started (see Figure 1).

During the pilot, we presented delayed meals of four larger magnitudes compared to the immediate meal and used 22 delay levels after which the subject would receive the meal (1 - 10, 12 14, 16, 18, 20, 30, 40, 50, 60, 75, 90, and 120 minutes). Each magnitude was paired with each delay level, yielding 88 trials in total. Correspondingly, the duration of the pilot was 11.73 minutes. The high number of delay levels was used to define a maximal level of accepted delay for the fMRI runs. In the fMRI runs, we had only ten levels. Here, the maximal level corresponded to the maximally accepted delay determined in the behavioural pilot run of that subject plus ten percent. The ten distinct levels then corresponded to the ten deciles of this maximum. Each magnitude was paired with each delay level, yielding a total number of 40 trials. The duration of each run was 8 minutes.

2.3.2 Cue-reactivity task

Cue-reactivity denotes the responsivity of a subject to stimuli (cues) that are coupled to reinforcing stimuli of a certain tvpe (e.g. food) via classical conditioning (Drummond, 2000). Furthermore, cue-induced desire to consume (i.e. craving) is assumed to be a conditioned consequence of cue-reactivity and thus an index of this parameter (Pelchat et al., 2009). Food cue-reactivity is elevated in obese subjects as compared to normal weight controls and goes along with an increased vulnerability of cue-induced overeating (Jansen et al., 2003). Neuroimaging studies have shown that reward-related brain areas code for food cue-reactivity in obese subjects (e.g., Rothemund et al., 2007; Weygandt et al., 2012). Simultaneously, food-cue induced activity in these areas is linked to the BMI (Rothemund et al., 2007). Since the

DD task conducted in our study includes the presentation of such stimuli, we measured the self-reported desire to consume food-items presented in a picture perception paradigm and used it to control for inter-individual differences in cue-reactivity in all analyses conducted in the study.

In order to acquire the marker for food-cue reactivity, each subject was shown a set of 40 pictures including two food-related picture categories (high- and low-calorie foods) and two control categories (eating-related utensils and neutral stimuli) with 10 images each. High-calorie pictures included images of items such as hamburgers and ice cream. Low-calorie foods consisted of e.g., fruits and vegetables. The utensil category included images of forks and spoons etc. Finally, the pictures in the neutral control condition comprised pictures of e.g., flowers and rocks. The stimuli were previously used in Rothemund et al. (2007). For more details on the stimuli, please refer to this study.

The stimuli of the two food-related categories were rated separately with respect to the urge that they induce to consume the depicted food (i.e. craving) and the induced appetite. The rating on these two dimensions was performed with a visual analogue scale ranging from 0, representing no stimulation of craving/appetite, to 100, indicative of very strong stimulation of craving/appetite. Pictures of all four categories were rated additionally on the dimensions valence, arousal, and dominance using the Self Assessment Manikin (Lang, 1980) approach. Pictures were presented in a randomized sequence. The rating was performed directly after the fMRI scanning in a self-paced fashion, i.e. subjects could take as much time as they desired to rate each of the images on each of the scales.

The subject-specific parameter for food-cue reactivity was calculated as the difference of the mean craving rating for pictures of the high-calorie category minus the mean craving rating for the low calorie category. Thus, the marker can be seen as the relative incentive

salience of foods promoting obesity as compared to healthy foods. For the present study, only this parameter was evaluated.

2.4 fMRI data acquisition and preprocessing

Brain scans were acquired using a 1.5 Tesla whole-body tomograph (Magnetom Sonata, Siemens, Erlangen, Germany) with a standard head coil. For the functional imaging four runs consisting of 245 volumes each were measured using a T2*-weighted gradient echo-planar imaging sequence with 35 slices covering the whole brain (slice thickness = 3 mm; 0.6 mm gap, interleaved; TR= 2000 ms; TA = 57.143 ms; TE = 40 ms; flip angle = 90°; field of view = 192 mm x 192 mm; matrix size = 64 x 64). The orientation of the axial slices was parallel to the AC-PC line.

We applied standard preprocessing including realignment, slice time correction, and spatial normalization of images to the Montreal Neurological Institute (MNI) brain template (Tzourio-Mazoyer et al., 2002) using SPM8 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, London UK - http://www.fil.ion.ucl.ac.uk/spm). The voxel size of the normalized images was 3 * 3 * 3 mm. Finally, we created a combined mask for all fMRI analyses conducted within the study consisting of eight bilaterally defined regions of interest (ROI) and excluded all brain regions from the fMRI analyses that were located outside this mask. These ROIs were the anterior insula, the ventral, and dorsal striatum, hypothalamus, DLPFC, DMPFC, VMPFC, and posterior cingulate cortex and were based on a neuroanatomic atlas (Maldijan et al., 2003) that defines ROIs in the standard space of the MNI-brain template (Tzourio-Mazoyer et al., 2002). The sum of all voxels in the combined mask (i.e., the area of our search in the fMRI analyses) was 6149 voxels. The masking step was performed in order to focus on brain regions previously discussed in the literature on

obesity (e.g., Rothemund et al., 2007; Grill et al., 2007) and value-based decision-making (e.g. Hare et al., 2011; 2009; Kahnt et al., 2011; 2010; Kable & Glimcher, 2007; McClure et al., 2004).

2.5 Analysis 1: Association of behavioural impulsivity and dietary weight loss

Here, we investigated the degree to which future BMI changes correlate with a behavioural parameter that is considered a measure of impulsivity (Ainslie, 1974) assessed *prior to onset of the diet* in a food-specific delayed gratification task. This parameter (k) was identified for each subject with an iterative optimization procedure and a hyperbolic discounting function (c.f. Mazur, 1987). In that optimization procedure, we first defined a value for k in each iteration and then calculated the predicted meal value for each trial of all four fMRI runs of a subject (having a certain meal magnitude and delay level of the delayed meal) following: predicted delayed meal $value_{trial}$ = delayed meal $magnitude_{trial}$ / (1 + k * delayed meal $delay_{trial}$). Specifically, we started with k = 0.0001 and increased it in each iteration by 0.0001 until we reached an upper level of k = 2. In each iteration (i.e., for each level of k), we computed the sum of squared differences between predicted and true meal values across all trials. The subject's choice (immediate = 0, delayed = 1) was used as indicator of the true meal value for a given trial. Finally, the value for k was selected as subject-specific impulsivity measure k for which the minimal sum of squared differences between true and predicted meal values resulted. Thus, k reflected the influence of the magnitude and delay of delayed meals on choice. Next, we determined a weight loss score for each subject, i.e. we subtracted the post-diet from pre-diet BMI. The naked pre- and the post-diet body weight was measured directly after subjects arrived at the imaging center (i.e. after an overnight fast and between 8 and 10 a.m.) using a calibrated scale (Kern, Balingen-Frommern, Baden-Württemberg, Germany). On average, the post-diet weight measurement took place 108 days

after pre-diet measurement (SD = 28 days). The deviations from the exact twelve-week interval had organizational reasons.

Next, we regressed out the variance in the impulsivity and the weight loss score that could be explained by four covariates of no interest, i.e. baseline BMI, cue-reactivity, age and gender (plus constant) using a general linear model (GLM) for each of the two measures separately. This yielded the corrected impulsivity parameter (kc) and a corrected weight loss score (ΔBMIc). In particular, we corrected for baseline BMI, since subjects with a higher baseline BMI might easier/faster lose weight during the diet as compared to subjects with a lower baseline BMI. Furthermore, we controlled for cue-reactivity since our DD task applied for determination of behavioural impulsivity included the presentation of food pictures. We controlled for age primarily due to changes of the secretion of potentially eating relating hormones across lifetime. Finally, we controlled for gender since Weller et al. (2008) could show that discounting behaviour in a DD task can differ between men and women in obesity.

To clarify, whether ΔBMI should additionally be corrected for the variation in the temporal delay between pre- and post-diet body weight measurement across subjects (see above), we computed the association between these measures. Specifically, we first regressed out the variance in the two measures that could be explained by the four covariates of no interest and a constant using a GLM and then computed the correlation of the residuals that however turned out to be very small ($r = 0.02$; $p = 0.502$). Due to the weakness of the association, the temporal delay of pre- and post-diet weight measurements was not additionally included into our set of covariates of no interest.

In order to assess the link between behavioural impulsivity and dietary success, we finally calculated the correlation between kc and ΔBMIc. To test for significance, we assessed the probability of observing the obtained correlation by chance using a permutation test. Specifically, we permuted the corrected ”BMIc vector ten thousand times and calculated

correlations using permuted vectors (Good, 2005). We used the resulting distribution of correlations to estimate the probability under the null-hypothesis. Please note, that we decided to use permutation tests for all analyses conducted in the study due to their high robustness to violations of distributional assumptions (Good, 2005) that might be problematic for parametric procedures applied to moderately sized data sets.

2.6 Analysis 2: Association of brain activity and dietary weight loss

In a second analysis, we assessed the correlation of dietary weight loss and pre-diet brain responses reflecting the subjective value (SV) of food-cues. Due to consistency reasons, this and all other fMRI analyses were performed using in-house software (c.f., Weygandt et al., 2012) that also allows to compute voxel-specific stepwise regression models needed in supplementary analysis 2 and 4.

In the first of two processing steps conducted in analysis 2, we started by computing the SV of each trial and run of a subject using the subject-specific impulsivity parameter k (please see analysis 1) following: SV_{trial} = meal $magnitude_{trial}$ / (1 + k * meal $delay_{trial}$). Then, we estimated a GLM for each subject, run, and voxel with a boxcar regressor weighted by trial SV. This regressor modelled the three successive TRs during the choice and feedback-stage (see Figure 1) as one short block and was convolved with the hemodynamic response function. We also included the six motion parameters determined during realignment, seven discrete cosine transform basis functions (i.e., a high-pass filter, cutoff = 128 sec) and a constant in the model as covariates of no interest. The resulting parameter maps of each subject were averaged across runs to give one subject-specific map characterising the regional responsiveness to variations in the SV of delayed meals. To further control for covariate effects, we finally removed the variance in each voxel of these maps across subjects that

could be explained by cue-reactivity, pre-diet BMI, gender, age and a constant term with a GLM.

In the second step, the map of each subject was entered into a between-subject analysis used to identify brain areas located in the combined mask that contain prognostic information for weight loss (ΔBMIc). Specifically, we calculated the correlation coefficient between a subject's ”BMIc and activity in each voxel reflecting the local responsiveness to variations in the SV of food-cues. To assess the probability of observing the obtained correlations by chance, we used permutation testing. In particular, we calculated correlations between permuted ”BMIc vectors and the non-permuted activity vector of a given voxel until: number of voxels included in the combined mask (6149) / $\pm_{uncorrected}$ (0.025) = 245960 permutations were reached. The resulting distribution of correlations was used to assess the probability of the observed correlation under the null hypothesis. The false-discovery-rate criterion (FDR; Benjamini & Hochberg, 1995) was used to correct for multiple comparisons ($\pm_{FDR}$ = 0.025). Please note, that the application of the FDR-criterion also determined the number of permutations conducted per voxel coordinate (245960). Within the FDR-criterion, at least one test/voxel has to be significant following a Bonferroni-corrected significance threshold and this threshold corresponds to the uncorrected significance threshold divided by the number of tests conducted. Correspondingly, a test would be significant on a Bonferroni-corrected significance threshold within the permutation framework if at least 245960 permutations were conducted without revealing a single correlation reaching the level of the empirically observed correlation. The alpha level was to 0.025 since we tested for significance of positive as well as negative correlations.

Additionally, we conducted two supplementary analyses related to analysis 2. Specifically, we investigated the association of weight-loss prognostic DLPFC activity and behavioural control in supplementary analysis 1. Moreover, we investigated the potential

benefit of using a combination of behavioural control and brain activity for weight loss modeling in supplementary analysis 2.

2.7 Analysis 3: Association of functional brain connectivity and dietary weight loss

Here, we assessed the correlation of future dietary weight loss and functional connectivity of brain areas with the VMPFC acquired before the onset of the diet. The VMPFC (coordinate identified in analysis 2 [MNI: -6, 48, -9]) was selected as seed region since activity in this area correlates with the SV of food-items while simultaneously being modulated by DLPFC activity reflecting food-related self-control (Hare et al., 2009). Consequently, the VMPFC integrates two key aspects of food-related decision making in dieting – reward-related features of food-items and impulse control related aspects. The analysis was performed in a three-step procedure using in-house software (c.f., Weygandt et al., 2012).

In the first step, we filtered the fMRI voxel signals of each subject and run in the temporal domain. This was done with a GLM including the six head motion parameters determined during the realignment procedure, seven discrete cosine transform basis functions (high-pass filter, cutoff = 128 sec), and a constant. Then, the residual voxel time series were corrected for signal variations in white matter (WM) and cerebro-spinal fluid (CSF) areas. In particular, we extracted the time courses of all voxels located in WM and CSF areas according to a neuroanatomic atlas (Maldijan et al., 2003), but excluded those voxels that were also located in the combined mask described above. This exclusion step was peformed since the functional areas used to construct the combined mask and areas of WM and CSF areas are defined in a non-disjunct fashion within the atlas (Maldijan et al., 2003). Finally, we calculated the first temporal eigenvariate of the extracted residual time series and used a GLM

to remove the corresponding signal variation (and the signal mean) from the residual time courses of voxels located in the combined mask.

In the second step, we calculated voxel parameter maps for each subject and run that assessed the functional connectivity between the VMPFC coordinate identified in analysis 2 (MNI: -6, 48, -9) and all other brain areas located in the combined mask. In particular, we first extracted the residual time series for each subject and run of the informative VMPFC voxel. Then, we extracted the residual time series for another voxel position in the combined mask and calculated the correlation coefficient between the two time series. Finally, we averaged the correlation coefficients across runs and noted the resulting value at the given voxel position in the combined mask of that subject. The procedure was repeated for each voxel position in the combined mask and yielded a VMPFC connectivity map for each subject. After these VMPFC connectivity maps were determined for each subject, we removed the variance of each voxel of these maps across subjects that could be explained by food-cue reactivity, baseline BMI, gender, age, and a constant with a GLM to control for covariate effects on food-related brain activity.

In the third step, these maps were entered into a second level between-subject analysis using a permutation test as in analysis 2.

Finally, we conducted two supplementary analyses related to analysis 3. In particular, we investigated the association of weight-loss prognostic VMPFC - DLPFC connectivity and behavioural control in supplementary analysis 3. Moreover, we investigated the potential benefit of using a combination of behavioural control and connectivity for weight loss modeling in supplementary analysis 4.

3. Results

3.1 Analysis 1: Association of behavioural impulsivity and dietary weight loss

In this analysis, we investigated the degree to which future dietary weight loss is associated across subjects with pre-diet behavioural impulsivity assessed in a food-specific delayed gratification task by calculating the Pearson correlation coefficient for the two variables. The results show that higher impulsivity was associated with poorer dietary success ($r = -0.42$; $p = 0.048$), i.e. subjects with better impulse control lost more weight. See Figure 2 for details.

3.2 Analysis 2: Association of brain activity and dietary weight loss

Here, we assessed the degree to which dietary weight loss correlates with local brain activity reflecting SV of delayed meals measured prior to the onset of the diet in a between-subject analysis. Coordinates showing significant correlations between value-related voxel activity and weight loss were found in the VMPFC ([MNI: -6, 48, -9], $r = 0.86$; $p = 8.2 * 10^{-6}$) and two coordinates in the anterior insula ([MNI: -33, 18, -6], $r = -0.82$, $p = 1.4 * 10^{-5}$; ([MNI: -36, 15, 12], $r = -0.85$, $p = 1.7 * 10^{-5}$). Furthermore, two coordinates in the dorsomedial prefrontal cortex (DMPFC; [MNI: 3, 39, 24], $r = 0.87$, $p < 4.1 * 10^{-6}$; [MNI: 3, 36, 39], $r = -0.87$, $p = 6.8 * 10^{-6}$) were informative regarding weight loss. Finally, also two coordinates in the DLPFC ([MNI: -24, 42, 18], $r = 0.82$, $p = 2.3 * 10^{-5}$; [MNI: 42, 51, 21], $r = 0.85$, $p = 2.4 * 10^{-5}$) contained prognostic information. See Figure 3 for an overview.

In supplementary (post-hoc) analysis 1, we investigated the direct link between the degree of impulse control applied to food decisions and value-related DLPFC activity that correlated with dietary weight loss. The analysis revealed that activity in the DLPFC coordinate (MNI: -24, 42, 18) correlated negatively with impulsivity on trend level ($r = -0.49$, $p = 0.027$). Please see Supplementary material for further details. For further results related to

analysis 2, i.e. the relative contribution of behavioural impulsivity and brain activity for modelling of dietary success, please see supplementary analysis 2.

3.3 Analysis 3: Association of functional brain connectivity and dietary weight loss

Here, we assessed the degree to which dietary weight loss is linked to functional connectivity with the VMPFC coordinate identified in analysis 2 (MNI: -6, 48, -9). We found that connectivity of the VMPFC with a coordinate located in the DLPFC ([MNI: 27, 48, 15], $r = 0.82$, $p = 1.5 * 10^{-5}$) contained significant prognostic information for weight loss. Moreover, also connectivity of VMPFC and an area in the dorsal striatum ([MNI: -21, 18, 9], $r = -0.82$, $p < 4.1 * 10^{-6}$) and with three coordinates located in the DMPFC ([MNI: 0, 42, 12], $r = 0.90$, $p < 4.1 * 10^{-6}$; [MNI: 6, 21, 24], $r = 0.85$, $p = 1.1 * 10^{-5}$; [MNI: 0, 45, 48], $r = 0.85$, $p = 5.5 * 10^{-6}$) contained prognostic information. See Figure 4 for an overview.

In supplementary (post-hoc) analysis 3, we investigated the direct link between the degree of impulse control applied to food decisions and functional connectivity of the VMPFC seed region (MNI: -6, 48, -9) and DLPFC. Here, the correlation between connectivity and impulsivity was $r = -0.55$ ($p = 0.012$) for the DLPFC coordinate (MNI: 27, 48, 15). Please see Supplementary material for further details. For further results related to analysis 3, i.e. the relative contribution of behavioural impulsivity and brain connectivity for modelling of dietary success, please see supplementary analysis 4.

4. Discussion

In this study, we demonstrate that behavioural impulse control and neural substrates of decision-making measured preceding a diet contain information for the weight loss obtained

by middle-aged obese subjects during the twelve-week low calorie diet. Moreover, we show that functional connectivity between brain regions involved in impulse control and reward signalling measured before the onset of the diet correlates with dietary success and simultaneously the degree of control applied to food-decisions.

Three main analyses were conducted. In analysis 1, we computed the correlation of future dietary success and pre-diet behavioural impulse control assessed using a food-specific delayed gratification paradigm. As expected, we found a negative correlation of food-related impulsivity and dietary success. In analysis 2, we searched for value-related brain activity that encodes prognostic information on weight loss. We identified informative areas in the VMPFC and the DLPFC. This is in line with results of recent studies investigating the neural foundations of food-related decision-making (Hare et al., 2009; 2011). Specifically, these studies showed that VMPFC computes a signal coding for the subjective value of food items. Furthermore, they showed that activity in the DLPFC biases decisions towards more controlled or healthier food choices respectively. Consistently, a post-hoc analysis conducted in our study to evaluate the direct association of weight loss prognostic DLPFC activity (MNI: -24, 42, 18) and food-related impulsivity revealed a negative correlation ($r = -0.49$, $p = 0.027$; supplementary analysis 1). Thus, results of our study complement the abovementioned findings by showing that DLPFC brain activity does not only reflect behavioural control but simultaneously dietary weight loss. In analysis 3, we searched for brain regions that contain prognostic information for weight loss in terms of their functional connectivity with the VMPFC region identified in analysis 2. In line with Hare et al., (2009), we identified weight loss prognostic functional connectivity with a coordinate in the DLPFC. To assess the direct association of weight loss prognostic connectivity and behavioural impulsivity, we calculated the correlation between these measures (supplementary analysis 3), what revealed a negative association ($r = -0.55$, $p = 0.014$) of connectivity and behavioural impulsivity. This is again in

line with results of Hare et al. (2009), who could show that stronger connectivity of the DLPFC and the VMPFC is associated with healthier food choices.

In order to better understand the nature of our behavioural impulsivity parameter derived from meal choice in a food-specific DD task, we calculated its correlation with behavioural cue-reactivity. As expected, this revealed a significant positive association of the factors that were corrected for baseline BMI, gender, age and a constant with a GLM before ($r = 0.52$; $p = 0.034$). Thus, a relatively higher incentive salience of obesity promoting high-calorie foods (the craving parameter was determined as craving for high minus low-calorie pictures) was positively linked to behavioural impulsivity. This is in line with behavioural studies that found that impulsivity is linked to cue-elicited craving in other disorders connected to impulse control deficits, i.e. alcohol- (Papachristou et al., 2013; 2012) and nicotine dependence (Doran et al., 2007). Specifically, Papachristou et al. (2012) found an interaction effect of symptom severity and impulsivity on cue-elicited craving, i.e. higher impulsivity was coupled to higher craving in heavy but not light social drinkers. Furthermore, an association of impulsivity and cue-elicited craving in a group of heavily alcohol-dependent inpatients was also found by another study of this group (Papachristou et al. 2013). From that the authors concluded, that the combination of heavy drinking and impulsivity is a risk factor for failing to inhibit the urge to consume alcohol triggered by the presentation of disorder-related cues. Furthermore, Doran et al. (2007) showed that impulsive smokers with a preference for immediate over delayed reward scored higher on cue-elicited craving for cigarettes and concluded that higher impulsivity goes along with a worse ability to quit cue-triggered consumption.

Importantly, Doran et al. (2007) could also show that the choice behaviour in the DD task was independent of whether real or hypothetical rewards were used (Doran et al., 2007). This is in line with results form a variety of further studies comparing the discounting

behaviour of true and hypothetical rewards (e.g. Lagorio & Madden, 2005; Johnson & Bickel, 2002) that could also show that real or hypothetical rewards are discounted similarly. Finally and maybe most important, Weller et al. (2008) could show that obese subjects scored higher on impulsivity as compared to normal-weight controls as determined by a DD task using hypothetical rewards. Thus, together these results suggest that the use of hypothetical food rewards in our study should not have had a detrimental effect on the validity of our results.

Besides similar behavioural results in our obesity study and in behavioural studies on substance disorders (Papachristou et al., 2013; 2012; Doran et al., 2007), the overlap of brain regions and connectivity patterns identified in our study with corresponding findings in the imaging literature on substance dependence (e.g. Goldstein & Volkow, 2002) points to a common basis of the diseases (see also e.g., Pelchat et al., 2009). In the latter field, results from a variety of imaging studies have been integrated in an influential model for substance dependence, the ‚impaired response inhibition and salience attribution theory' (Goldstein & Volkow, 2002). A key assumption of this model holds that inhibitory influences of the (dorsal) prefrontal cortex on structures belonging to the dopamine-reward system such as the oribitofrontal cortex (OFC; that includes the VMPFC) are reduced in drug addiction due to an insensitivity of that system induced by repeated overstimulation. Subsequently, this reduced top-down influence leads to a disinhibition of stimulus driven behaviours such as cue-elicited drug craving and consumption coded for by e.g. the OFC.

These assumptions are well in line with our finding of a) a positive correlation of VMPFC - DLPFC connectivity and dietary success ($r = 0.82$) and b) a simultaneous negative correlation of that connectivity with impulsivity ($r = -0.55$). However, the *positive* correlation of the activity of the VMPFC coordinate (used as seed region in the connectivity analysis, i.e. analysis 3) and dietary success ($r = 0.86$) in analysis 2 does not fit to the model because this would then suggest that patients with higher craving are more successful in a diet.

Furthermore, also a non-significant correlation of activity in this area (corrected for baseline BMI, gender, age and a constant with a GLM) and our craving marker (corrected for the same factors) of $r = -0.14$ ($p = 0.308$) seriously questions whether the signal in the identified VMPFC coordinate is a craving signal. More plausibly, this diet predictive and cue-triggered VMPFC signal reflects the rewarding properties of direct substance intake that decreased by repeated overstimulation of the dopaminergic brain reward system in the course of the disease. The idea that the cue-triggered VMPFC signal reflects the strength of a stimulus as a reinforcer (i.e. of direct food intake) would be consistent with findings of Hare et al. (2009) who also concluded from their study involving visual food-cue presentation (and not food consumption) that the signal in the VMPFC reflects the reward value of a food stimulus. Furthermore, the interpretation would be in line with a frequently reported reduced metabolism of prefrontal dopaminergic reward areas due to repeated overstimulation in subjects suffering from substance dependence that is associated with a reduced strength of disease-related reinforcers (i.e, drugs; Volkow et al, 2010). Thus, in other words, the VMPFC activity could potentially reflect a cue-triggered reward expectation signal mirroring the current strength of a given substance as a reinforcer that decreases in case of reduced VMPFC – DLPFC connectivity which in turn is closely linked to impulse control.

The results of our study complement findings of two longitudinal fMRI studies, that investigated the link between neurobehavioural impulse control parameters and BMI (changes) in non-dieting subjects (Batterink et al., 2010; Kishinevsky et al., 2012). In the first study (Batterink et al., 2010) the authors measured reaction times and neural activity of subjects during a go-/nogo-task and correlated these measures with the BMI at baseline and one year later. However, the study could only reveal an association of neurobehavioural control measures and BMI at baseline that did not extend to a prediction of longitudinal BMI changes. The second study (Kishinevsky et al., 2012) found neural predictors of longitudinal

BMI variations in non-dieting obese subjects derived from a DD paradigm. However, it is unclear how these predictors relate to behavioural control as the latter did not correlate with longitudinal BMI variations. Speculatively, the latter can be explained by two factors. First, monetary stimuli were used in the DD task. The association of monetary discounting and BMI variations might underestimate the association of food-related discounting and BMI variations as a recent behavioural study (Odum et al., 2006) showed that money and food stimuli are discounted differently. Second, the follow-up weight measurement was conducted with large variations regarding the delay to the baseline measurement (1.3 - 2.9 yrs).

Besides evaluating diet prognostic information of behavioural impulsivity and related neural activity and connectivity in an isolated fashion, we also aimed to contribute to the current debate in psychology on whether information assessed with fMRI adds information above that obtained by observation of behaviour, i.e. to evaluate the relative information contained in behavioural and neuronal factors. In particular, we investigated whether the modeling of dietary success can benefit from a combined modeling using value-related brain activity / brain connectivity and behavioural impulsivity information (supplementary analysis 2 / 4). In particular, we tested whether and where in the brain weight loss modeling using brain activity / connectivity can benefit from the additional consideration of behavioural information and vice versa whether and where modeling based on behaviour can benefit from the additional consideration of activity / connectivity. In neither of the two supplementary analyses, the combined approach did improve modeling as compared to activity- / connectivity-based modeling but the combined approach was significantly better than behaviour-based modeling in coordinates in the DMPFC and DLPFC in both analyses. This finding underlines the informative quality of fMRI data for real-world outcome measures.

Furthermore, results obtained in the present study are promising in the sense that they suggest that fMRI could be used in the future to select the best suited treatment protocol for

individual obese patients within a personalized medicine framework. However, several aspects would have to be clarified before such an expert system approach could be considered for application in clinical practice. First, the results of this study would have to be reproduced in a larger sample in order to guarantee that markers of dietary success derived from a fMRI-based expert system is reliable for at least the specific diet protocol applied in the present study. Second, if such an approach should be used to select among several conceivable treatment types, the procedure would have to be conducted for any such treatment since it is not clear whether the results obtained for this specific setting can be generalized to other treatments. Third, extraordinarily high precision in treatment outcome prognosis would be necessary in order to apply such an approach for treatment optimization in severe forms of obesity due to the comparably high mortality of these medical states (Flegal et al., 2013).

The moderate number of subjects investigated (N = 16) in the study might be viewed as a drawback of the study. However, we believe that the study contains meaningful insights into the role of neural impulse control mechanisms for dietary success in obesity despite this fact for two reasons. First, our sample size is in good accordance with findings of a recent study (Friston, 2012) that investigated the optimal sample size for between-subject fMRI studies using power analyses. Following this study, the number of subjects investigated should be between 16 and 32 participants. Furthermore, we deployed permutation tests for all analyses conducted in the study. Since permutation tests do not rely on the fulfilment of certain distributional assumptions – a problem especially relevant when dealing with data sets of small to moderate size - they are especially well suited for data sets of this size (Good, 2005).

Another aspect that might be improved in a future study is the duration of the sports courses included in the weight reduction program, since a 30 minutes sports intervention per week is comparably short. However, one has to keep in mind that obese subjects frequently

do not participate at all in any such activity on their own. Correspondingly, besides aiming to directly reduce body weight, the courses also tried to motivate subjects to do physical exercise independent of the guided exercise training.

Finally, additional research might be useful that allows investigating the mutual causal influences of reward- and control-related brain regions (such as the VMPFC and the DLPFC) and clinical (dietary weight loss) and psychological factors (behavioural craving and impulsivity). This might be realized by the application of Dynamic Causal Modeling or noninvasive brain stimulation techniques like Transcranial Magnetic Stimulation or Transcranial Direct Current Stimulation.

5. Conclusion

To summarize, we have shown that behavioural impulse control measures and neural substrates of decision-making measured preceding a diet contain information for the degree of dietary weight loss of obese subjects. Moreover, the study shows that connectivity between brain regions involved in impulse control and reward signalling reflects dietary success in obese subjects and simultaneously the degree of control applied to food-decisions. Specifically, stronger connectivity of these regions is associated with more control as well as better dietary success. Thus, the ability to resist the urge to eat and thus the success in a short term diet seem to rely on the interplay of control-related brain regions and regions signalling the rewarding properties of food. This might constitute a general mechanism that could also extend to other disorders such as substance abuse.

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7. Disclosure statement

The authors report no biomedical financial interests or potential conflicts of interest in the context of this work.

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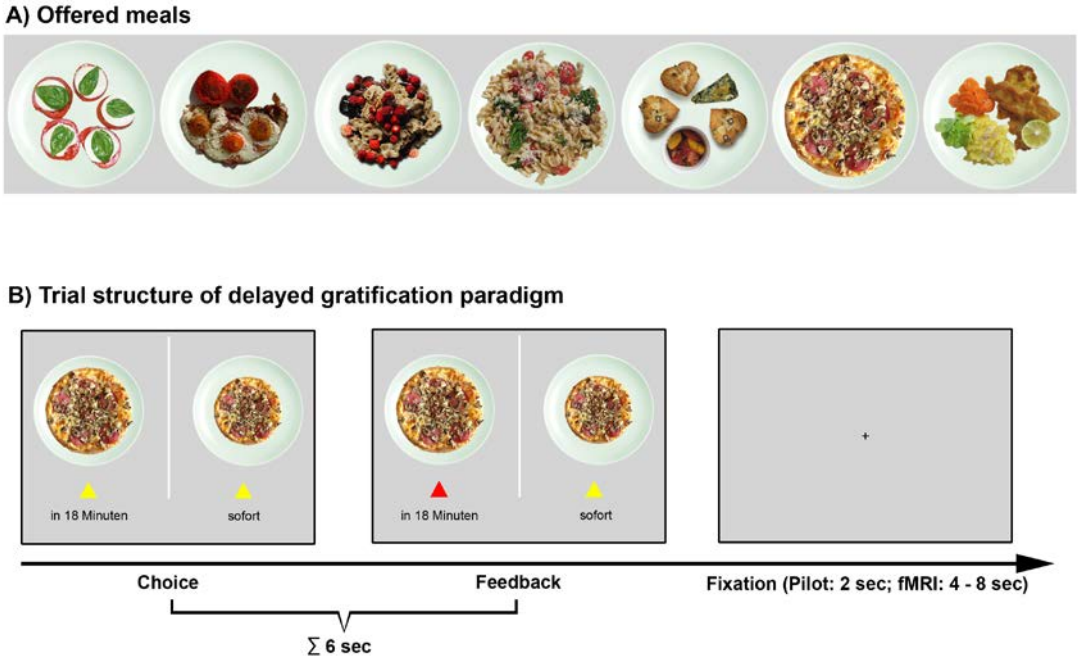

Figure 1. Food-specific delayed gratification task performed in the behavioural pilot and during fMRI scanning. A) Different meals that were offered to the subjects prior to the behavioural pilot run. The meals varied in terms of energy content and included typical breakfast but also typical lunch meals. B) Trial structure of the task. On each trial, subjects had to chose between an immediately gratified and small or a delayed but larger version of the meal selected preceding the pilot. Each trial began with the presentation of a fixation screen, which was shown for two (pilot) or four to eight (fMRI) seconds respectively. In the following choice stage, a small version of the favourite meal with the label 'sofort' (i.e.,'immediately') appeared on one randomly selected side of the screen. On the opposite side, a larger version of the meal was shown together with a label indicating a specific delay of gratification for the larger choice alternative. The subject was instructed to select its preferred choice with a button press. After the button press, the arrow beneath the chosen meal changed its colour from yellow to red to indicate successful selection in the feedback stage. The total duration of the choice and feedback stage was 6 seconds. With the end of the feedback stage, the next trial started. We had alternative meals of four larger magnitudes as compared to the reference meal and ten delay levels. Each alternative meal magnitude level was paired with each delay level, yielding a total number of 40 trials.

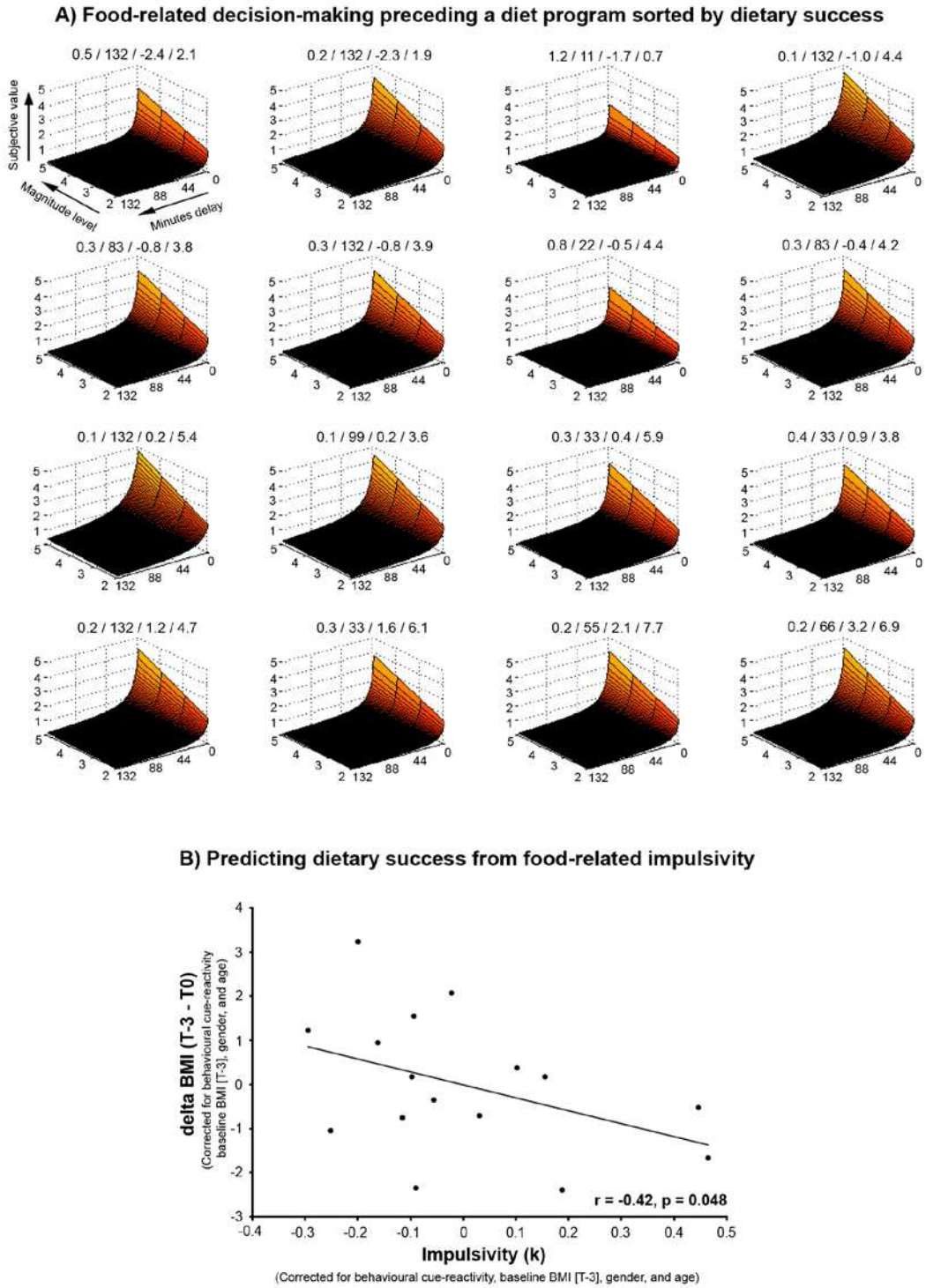

Figure 2. Association of weight loss and behavioural impulsivity. A) Food-related impulsivity was assessed for each subject individually by numerically determining a parameter k that minimized the sum of the squared differences between true and predicted value of delayed meals acquired across all trials and runs of a subject. In particular, the value of delayed meals was modelled using a hyperbolic discounting function with the form meal $value_{Trial}$ = meal $magnitude_{Trial}$ / (1 + k * meal $delay_{Trial}$). The corresponding value graphs are sorted by the dietary success obtained by each subject, starting with the least successful dieter

in the upper left and ending with the most successful dieter in the lower right. Dietary success is assessed in terms of the difference of the body-mass-index (BMI) between baseline and after the diet corrected for covariate effects of food-related cue-reactivity measured in a behavioural paradigm, baseline BMI, gender, and age. Numbers above each value graph depict the uncorrected food-related impulsivity parameter k / the maximally accepted delay time / the corrected weight loss score / the uncorrected weight loss score. The latter parameter is depicted for illustrative purposes only. B) Correlation of weight loss and food-related impulsivity. To control for potential covariate effects of food-related cue-reactivity, baseline BMI, gender and age on the relation of weight loss and food-related self-control, we removed the variance in both k and weight loss that could be explained by a linear combination of these covariates prior to calculating the correlation of impulsivity and weight loss. Please note that impulsivity scores depicted in A were uncorrected and thus do not equal the impulsivity scores shown in B.

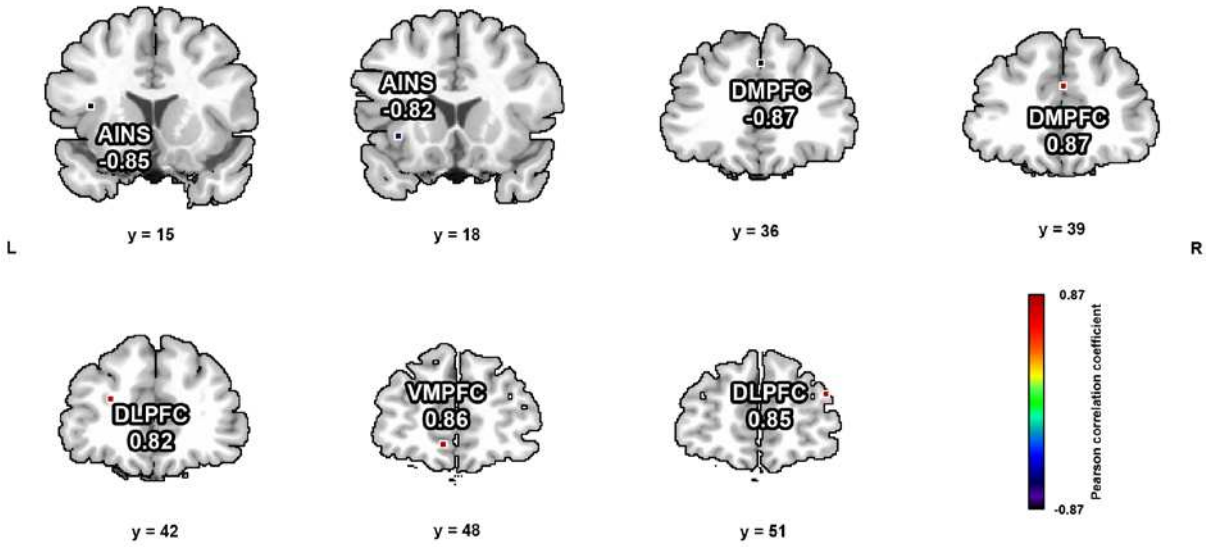

Figure 3. Brain regions with prognostic information for dietary weight loss determined based on value-related voxel activity parameters. Value-related voxel activity parameters and the weight loss scores were corrected for food-related cue-reactivity, baseline BMI, gender, and age prior to the analysis. Brain area abbreviations highlight regions with above chance correlations obtained by using permutation testing. Significance threshold was set at $p < 0.025$ corrected for multiple comparisons using False-Discovery-Rate. Numbers beneath abbreviations correspond to Pearson correlation coefficients obtained in these areas. Indices beneath each coronar brain slice report the y-coordinate of this slice in the standard space of the Montreal Neurological Institute brain template (19). Slices are displayed in neurological orientation. AINS, anterior insula; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; VMPFC, ventromedial prefrontal cortex.

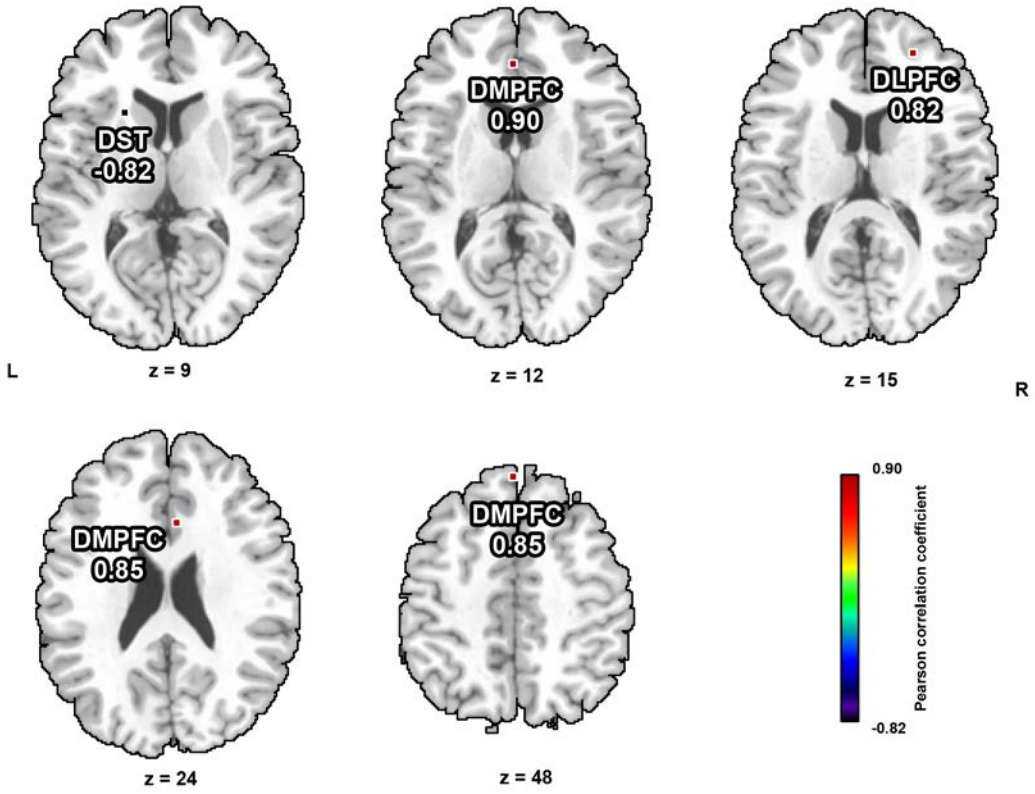

Figure 4. Functional connectivity of the VMPFC with prognostic information for weight loss. Prognostic information was determined based on voxel parameters characterizing the connectivity of a given voxel with the VMPFC area identified in analysis 2 (MNI: -6, 48, -9). Voxel connectivity coefficients and the weight loss scores were corrected for food-related cue-reactivity, baseline BMI, gender, and age prior to the analysis. Brain area abbreviations highlight regions with above chance correlations obtained by using permutation testing. The significance threshold was set at $p < 0.025$ corrected for multiple comparisons using False-Discovery-Rate. Numbers beneath abbreviations correspond to Pearson correlation coefficients obtained in these areas. Indices beneath each transversal brain slice report the z-coordinate of this slice in the standard space of the Montreal Neurological Institute brain template (19). Slices are displayed in neurological orientation. DST, dorsal striatum; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; MNI: Montreal Neurological Institute.