Running title: Mindful eating and reward anticipation

The effect of an 8-week mindful eating intervention on anticipatory reward responses in the midbrain

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Number of:

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42	4	4	213	518	1341

Conflict of interest statement:

The authors declare no competing financial interests.

Acknowledgements:

This work was supported by a VENI grant (016.135.023) of The Netherlands Organization for Scientific Research (NWO) and an AXA Research Fund fellowship (Ref: 2011) to E.A. R.C. was supported by the James S. McDonnell Foundation (220020328) and a VICI grant (016.150.064) of NWO.

The authors wish to thank the participants and all people who were involved in developing, teaching, and arranging the logistics of the intervention programs. Specifically, we would like to thank Ellen Jansen and Nicole Schoonbrood of the Radboud university medical center for Mindfulness for developing and leading the mindful eating intervention groups at the center. We would also like to thank Desiree Lucassen for developing the educational cooking intervention in collaboration with the Division of Human Nutrition of Wageningen University, and for leading it. She was assisted by chef Pieter Paul de Grood and bachelor student Hanne de Jong. In addition, we are thankful to Susanne Leij-Halfwerk and Suzan de Bruijn of the department of Nutrition and Dietetics at HAN University of Applied Sciences for access to their cooking classrooms.

Abstract

Obesity is a highly prevalent disease, usually resulting from chronic overeating. Accumulating evidence suggests that increased neural responses during the anticipation of high caloric food play an important role in overeating. A promising method to counteract enhanced food anticipation in overeating might be mindfulness-based interventions (MBIs). However, how MBIs can affect food reward anticipation neurally has never been studied. In this randomized, actively controlled study we aimed to investigate whether an 8-week mindful eating intervention decreases reward anticipation in striatal and midbrain reward regions. Using functional Magnetic Resonance Imaging, we tested 58 healthy subjects with a wide body mass index range (BMI: 19-35 kg/m^2), who were motivated to change their eating behavior. During scanning they performed an incentive delay task, measuring neural reward anticipation responses to caloric and monetary cues before and after 8 weeks of mindful eating or educational cooking (active control). Relative to educational cooking (active control), mindful eating decreased reward anticipation responses to food, but not to monetary reward cues, in the midbrain, but not the striatum. The effects were specific to reward anticipation and did not extend to reward receipt. These results show that an 8-week mindful eating intervention may decrease the salience of food cues specifically, which could result in decreased food-cue triggered overeating on the long term.

Significance statement

Mindfulness-based interventions have been shown effective in reducing disordered eating behavior in clinical as well as non-clinical populations. Here, we present the first randomized actively controlled study investigating the effects of mindfulness on reward anticipation in the brain. Using fMRI we show that midbrain responses to caloric, but not monetary, reward cues are reduced following an 8-week intervention of mindful eating relative to educational cooking (active control). Mindful eating interventions may thus be promising in counteracting reward cue-driven overeating, particularly in our obesogenic environment with food cues everywhere. Moreover, our data show that specific mindfulness-based interventions can target specific reward-cue responses in the brain, which might be relevant in other compulsive behaviors such as addiction.

Introduction

Reward-related disorders such as addiction, binge-eating disorder and obesity, are characterized by altered responses to reward cues related to the target of abuse (Volkow et al., 2008; García-García et al., 2014; Val-Laillet et al., 2015). Regions in the striatum and midbrain respond to increases in appetitive motivation induced by reward cues (Knutson et al., 2005). Altered responses of these subcortical reward regions have been related to reward-related disorders. For example, greater BMI was associated with increased midbrain responses to risky rewards in adolescents (Delgado-Rico et al., 2013). Furthermore, greater midbrain responses to alcohol-related stimuli have been suggested to contribute to an attentional bias towards those stimuli in alcoholics (Muller-Oehring et al., 2013). In addition, greater responses of ventral striatum to reward cues have been associated with subsequent food intake (Lawrence et al., 2012) and future weight gain (Stice et al., 2011; Demos et al., 2012; Lawrence et al., 2012). Interventions that diminish subcortical responses to food reward cues may therefore be promising for treating and preventing obesity.

Mindfulness-based interventions are aimed at cultivating attention to present-moment experience, without judgment (Kabat-Zinn, 1984). Protocolized mindfulness interventions, such as mindfulness-based stress reduction (MBSR) have shown to be effective in reducing subcortical responses to emotional stimuli in anxiety (Goldin et al., 2012) as well as in healthy individuals (Lutz et al., 2013). Importantly, mindfulness-based interventions aimed at changing eating behavior reduced obesity-related eating behavior in clinical populations (Leahey et al., 2008; Kristeller et al., 2013) as well as abdominal fat (Tapper et al., 2009; Daubenmier et al., 2011), and increased self-reported mindful eating in obese individuals (Mason et al., 2015). However, only two of these studies were actively controlled (Kristeller et al., 2013; Mason et al., 2015). It is therefore unclear whether these beneficial effects can be attributed to mindfulness per se. In fact, Kristeller and colleagues (2013) found that mindfulness-based eating awareness training (MB-EAT) and a psycho-educational/cognitive-behavioral (i.e., active control) intervention similarly decreased binge-eating symptoms relative to a waitlist control group. Given the different nature of these interventions, it is possible that reduced symptomatology was mediated by distinct brain mechanisms, as was suggested by an actively controlled clinical trial on social anxiety (Goldin et al., 2012). Studies investigating the neurocognitive mechanism underlying mindful eating are required to address this issue.

Here, we present the first actively controlled randomized study investigating the effects of mindfulness on reward anticipation in the brain to be able to understand its mechanisms of action. Using functional Magnetic Resonance Imaging (fMRI) we investigated the effects of an 8-week mindful eating intervention and a carefully matched educational cooking intervention (active control) on subcortical reward region responses when rewards could be earned in an incentive delay task (Knutson et al., 2001) that has been consistently shown to produce reliable subcortical responses to reward cues (Haber and Knutson, 2010). We hypothesized that the mindful eating intervention would reduce reward cue responses of these subcortical reward regions. We included both monetary and caloric rewards in the task, which enabled us to explore whether the effect on anticipatory reward responses is specific to the caloric domain, or generalizes to the monetary domain.

Materials and methods

Subjects

The results reported in this study are based on data from 58 healthy right-handed subjects (48 women; mean age: 31.6, SD: 11.0, range: 19 – 52 years; mean body mass index (BMI): 26.0, SD: 3.68, range: 19.7 – 34.7). Subjects were recruited from Nijmegen and surroundings through advertisement. Only subjects (aged: 18 – 55 years old; BMI: 19 – 35 kg/m^2) with no (history of) eating disorders or current dieting and who were highly motivated to change their eating behavior were included in the study (not per se to lose weight). All subjects gave written informed consent and were reimbursed for participation according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, the Netherlands, 2013-188).

Crucially, subjects who previously participated in an MBSR (Mindfulness-Based Stress Reduction) or MBCT (Mindfulness-Based Cognitive Therapy) course were not included in the study. Other exclusion criteria were: left-handedness, inadequate demand of Dutch, current pregnancy, MRI-incompatibility, diabetes mellitus, (history of) hepatic, cardiac, respiratory, renal, cerebrovascular, endocrine, metabolic or pulmonary diseases, uncontrolled hypertension (diastolic pressure > 90 mmHg, systolic pressure > 160 mmHg), (history of) eating, neurological, or psychiatric disorders, depression/anxiety state scores > 11 on the Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983), current strict dieting, high restrained eating score on the Dutch Eating Behavior Questionnaire (DEBQ ≥ 3.60 for females and ≥ 4.00 for males; Strien & Frijters, JER, 1986), current psychological or dietary treatment, taste or smell impairments, use of neuroleptica or other psychotropic medication, food allergies relevant to the study, deafness, blindness, and sensori-motor handicaps, drug or alcohol addiction, and a change in body weight of more than 5 kg in the past two months. Crucially, subjects with previous MBSR (Mindfulness-Based Stress Reduction) or MBCT (Mindfulness-Based Cognitive Therapy) experience were excluded from the study. For a flow diagram of all excluded subjects, see **Figure 1**.

Protocol

All subjects were screened for inclusion and exclusion criteria, and matching criteria (age, gender, BMI, experience with meditation and yoga) were assessed by taking physical measures and administering self-report questionnaires on a separate intake session. To assess education, the Dutch version of the National Adult Reading Test was administered at the (Schmand et al., 1991).

After inclusion, subjects came to the laboratory twice, before and after the intervention. Test sessions started at 11:00 AM or 12:30 PM. Pre-measurements were performed in the month prior to the start of the intervention. Post-measurements were performed in the month following the last group session. Subjects were instructed to abstain from eating foods and drinking anything else than water four hours prior to the start of the test sessions. Subjects were encouraged to have a light breakfast before fasting. Furthermore, subjects were instructed to abstain from drinking alcohol 24 hours before the test session. Before scanning, physical measurements were taken (weight, waist and hip circumference), digit span was assessed (Groth-Marnat, 2009), and the following self-report questionnaires were administered: the Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991) to assess smoking and nicotine dependence; the Positive And Negative Affect Scale (Watson et al., 1988) to assess positive and negative affect before scanning; the Barratt Impulsiveness Scale-11 (Barratt and Patton, 1995) to assess impulsivity; the Behavioral Inhibition System / Behavioral Approach System questionnaire (Carver and White, 1994) to assess punishment and reward sensitivity; the Kirby questionnaire (Kirby, 2009) to assess delayed reward discounting; the Food Frequency Questionnaire, Dutch Healthy Diet (van Lee et al., 2013) to assess the degree to which subjects eat according to the national guidelines for a Dutch healthy diet; a shortened version of the Food Behavior Questionnaire to assess behaviour towards food; the Dutch Eating Behaviour Questionnaire (van Strien et al., 1986) to assess emotional, external and restraint eating behavior; the Five Facet Mindfulness Questionnaire – Short Form (Baer et al., 2006) to assess degree of mindfulness; the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) to assess levels of anxiety and depression; a Treatment Credibility Questionnaire (TCQ) to assess how much subjects believed the intervention would work for them. Note that the pre-training TCQ was filled out at the first training session, not on the pre-training test session, as subjects were unaware of the contents of their training at that time. Subsequently, subjects underwent a one hour MR scanning session in which they performed an incentive delay task.

Paradigm: Incentive Delay task

We adapted the original incentive delay task (Knutson et al., 2001) to assess reward anticipation to monetary as well as caloric cues. For task details see **Figure 2**. In short, on each trial subjects were cued as to which of four rewards they could win (monetary: 1 or 50 cents;

caloric: a sip of water or a high-caloric drink of their choice (orange juice, chocolate milk or regular cola)). As soon as a white star (target) appeared on the screen subjects were to press a button with their right index finger as fast as possible. If subjects responded within an individually-determined time-window they won and the reward was added to their cumulative gain. After scanning, subjects received and drank their total caloric gain. Their total monetary gain was added to their financial reimbursement. Subjects received instructions for the incentive delay task before going into the scanner, and were aware they would receive their gain following scanning. Before scanning, subjects rated how much they *wanted* and *liked* each reward on a Visual Analogue Scale (VAS). To expose subjects to the reward outcomes, they were provided with the actual coins, and one sip (5 mL) of water and one of the chosen drink while rating the VAS.

Interventions

Subjects were randomly assigned to one of two intervention programs: mindful eating (ME) or educational cooking (EC; active control), using minimization with respect to age, gender, BMI and experience with meditation and yoga. Subjects were assigned through minimization (Scott et al., 2002), which guarantees that groups are balanced in terms of certain *a priori* determined minimization factors. An algorithm randomly assigned subjects to one of the groups by taking into account the minimization factors: age (categories: 18-25, 26-35, 36-45, 46-55), gender (categories: male, female), BMI (categories: 19 – 24.9 normal weight, 25 – 29.9 overweight, 30 – 35 moderately obese) and experience with meditation and yoga (categories: never, 0 – 2 years, 2 – 5 years, 5 – 10 years, > 10 years). Experience with meditation and yoga was assessed by means of an in-house self-report questionnaire.

The programs were matched in terms of time, effort, and group contact, but differed significantly in terms of content. Both programs consisted of 8 weekly, 2.5 hour group sessions from 7PM-9:30PM, plus one day dedicated (6 hours) to the intervention goals. Subjects were asked to spend 45 minutes per day on homework assignments and to record the amount of time spent on homework forms. The intervention programs were described as "eating with attention" (ME) and "eating with knowledge" (EC) to prevent a selection-bias of subjects interested in mindfulness. Only after the first test session, subjects were informed about the intervention to which they were randomized, to ensure that baseline measurements were not influenced by intervention expectations. Because group size was set to 10 to 15 subjects per round, included subjects were divided across three rounds for each intervention (3xME, 3xEC). The final sample for analyses consisted of 32 subjects in the ME intervention and 26 subjects in the EC intervention (for a flow diagram see **Figure 1**). Between groups, the number of people excluded from analysis was not significantly different (ME: 28.8%, EC: 44.7%, $\chi^2(1, N = 92) = 2.461$, $p = .117$).

Mindful eating (ME)

The aim of the ME intervention was to increase experiential awareness of food and eating (e.g. being more aware of food taste and smell, thoughts and feelings during eating or cravings, and internal signals like satiety). The ME program was based on the original MBSR program developed by Kabat-Zinn et al. (1990) at the Stress Reduction and Relaxation Clinic, Massachusetts Medical Center. Subjects performed formal mindfulness practices (i.e. body scan, sitting meditation, walking meditation and mindful movement), aimed at increasing general mindfulness skills, which were similar to the original program. In addition, subjects performed informal mindfulness practices based on the Mindful Eating, Conscious Living program (MECL; Bays, 2009), which were mainly directed to mindful eating and not part of the original MBSR program. Sessions focused on themes, such as: the automatic pilot, perception of hunger and other internal states, creating awareness for boundaries in eating behavior, stress-related eating, coping with stress, coping with (negative) thoughts, self-compassion, and how to incorporate mindfulness in daily life. Towards the end of the program, subjects had a silent day. During this day, the whole group performed formal mindfulness exercises and ate a meal together in complete silence. Homework consisted of a formal mindfulness practice, using CDs with guided mindfulness exercises, and an informal mindfulness practice directed at one moment (e.g. a meal) a day. Time spent on homework was noted on homework forms every day. The ME intervention was developed and delivered by qualified psychologists/psychiatrists, who graduated from the post-graduate mindfulness teacher training at the Radboud University Medical Centre for Mindfulness.

Educational Cooking (EC)

The aim of the EC intervention was to increase informational awareness of food and eating. The program was based on the Dutch healthy diet guidelines (www.voedingscentrum.nl). The EC program was based on the Dutch healthy diet guidelines (voedingscentrum.nl). To establish similar group contact and activities (vs. passive listening) as in the ME, subjects were actively enrolled in cooking workshops during the group meetings of the EC. Sessions focused on healthy eating, healthy cooking of vegetables and fruit, use of different types of fat and salt for cooking, reading of nutrition labels on food products, healthy snacking, guidelines for making healthy choices when eating in restaurants, and how to incorporate healthy eating and cooking in daily life. Towards the end of the program, subjects had a balance day, during which the subjects adhered to all nutritional health guidelines for every snack and meal. Homework assignments entailed practicing cooking techniques, or grocery shopping with informational awareness (i.e. reading food labels for nutritional content), and counting the amount of calorie intake for one meal a day (to be noted in a homework diary). The EC intervention was developed and delivered by a qualified dietitian from Wageningen University and the cooking sessions were guided by a professional chef. Sessions took place at a large kitchen facility of the Nutrition and Dietetics faculty of the Hogeschool of Arnhem-Nijmegen.

Behavioral analyses

Between-group comparisons were analyzed using independent-samples t-tests, Fisher's Exact Tests, or Mann-Whitney U tests. Effects of training on physical and neuropsychological measurements were analyzed using repeated-measures ANOVA with Time (pre, post) as within-subject factor and Intervention (ME, EC) as between-subject factor. Mean latencies of the correct manual responses (i.e. when subjects pressed in time) were analyzed using repeated-measures ANOVA with within-subject factors Reward (high, low), Domain (caloric, monetary), Time, and the between-subject factor Intervention (ME, EC). Specific effects were tested with subsequent F-tests. All analyses were performed using two-tailed tests in SPSS (version 23.0, Chicago, IL). The significance level was set at an alpha of p=0.05.

fMRI acquisition and analyses

We acquired whole-brain functional images (multi-echo) on a Siemens 3T Skyra MRI scanner (Siemens Medical system, Erlangen, Germany) using a 32-channel coil to measure blood oxygen level dependent (BOLD) contrast. A multi-echo echo-planar imaging (EPI) sequence was used to acquire 34 axial slices per functional volume in ascending direction (voxel size 3.5x3.5x3mm; repetition time (TR) 2070 ms; TE 9ms, 19.25ms, 29.5ms, and 39.75ms; flip angle 90 □; field of view 224mm). This is a method that uses accelerated parallel imaging to reduce image artifacts (in plane acceleration 3) and acquire images at multiple TEs following a single excitation (Poser et al., 2006). Before the acquisition of functional images, a high-resolution anatomical scan was acquired (T1-weighted MPRAGE, voxel size 1x1x1mm, TR 2300ms, TE 3.03ms, 192 sagittal slices, flip angle 8 □, field of view 256 mm).

Data were pre-processed and analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm). The volumes for each echo time were realigned to correct for motion artefacts (estimation of the realignment parameters is done for the first echo and then copied to the other echoes). The four echo images were combined into a single MR volume based on 31 volumes acquired before the actual experiment started using an optimised echo weighting method (Poser et al., 2006). Combined functional images were slice-time corrected by realigning the time-series for each voxel temporally to acquisition of the middle slice. Subject-specific structural and functional data were then coregistered to a standard structural or functional stereotactic space (Montreal Neurological Institute (MNI) template). After segmentation of the structural images using a unified segmentation approach, structural images were spatially coregistered to the mean of the functional images. The resulting transformation matrix of the segmentation step was then used to normalize the anatomical and functional images into Montreal Neurological Institute space (resampled at voxel size 2 x 2 x 2). Finally, the normalized functional images were spatially smoothed using an isotropic 8 mm full-width at half-maximum Gaussian kernel.

Statistical analyses of fMRI data at the individual subject (first) level were performed using an event-related approach and included 13 regressors-of-interest: four regressors for cue presentation (high and low caloric cues, high and low monetary cues), one regressor for target presentation, four outcome regressors for hits (high and low caloric hits, high and low monetary hits), and four outcome regressors for trials on which subjects responded too late (high and low caloric too late, high and low monetary too late). If subjects failed to respond on a trial (i.e. a miss), the trial was excluded from analyses. Onsets of the regressors were modeled as a stick function (duration=0) convolved with a canonical hemodynamic response function (Friston et al., 1998). Twelve rigid-body transformation parameters (three translations and rotations, and their linear derivatives) obtained during realignment and a constant term were included as regressors of no-interest. 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.

We ran two general linear models (GLMs) at the second level: one for reward anticipation with high minus low reward cue contrast images, and one for reward receipt with hit minus too late contrast images. Analysis of variance (ANOVA) was performed in a full-factorial design, with between-subject factor Intervention and within-subject factors Time and Domain, resulting in 8 cells. Effects were considered statistically significant when reaching a threshold of $p<0.05$, family wise error (FWE) corrected for multiple comparisons at the peak level, whole brain or in the *a priori* defined regions of interest (see below). Interaction effects of interest are also reported at $p<.001$ (uncorrected for multiple comparisons at the peak level).

To further investigate the effects of intervention on reward anticipation and receipt, region-of-interest (ROI) analyses were performed for midbrain and striatum using *a priori* defined ROIs for midbrain and striatum. ROIs were anatomically defined based on the Hammersmith atlas (Hammers et al., 2003): bilateral substantia nigra for *midbrain* (74;75; Gousias et al., 2008), and bilateral caudate nucleus (34;35), nucleus accumbens (36;37) and putamen (38;39) for *striatum* (Hammers et al., 2003). Mean beta weights were extracted from all voxels in both ROIs separately using MarsBar (Brett et al., 2002). The regionally averaged beta-weights were analyzed using ANOVA with the same factors as in the whole-brain analyses. As two ROIs were tested, effects were considered significant when reaching a threshold of $p<.025$ (Bonferroni corrected for multiple comparisons).

Results

Behavioral results

Characterization of intervention groups

The mindful eating (ME) and educational cooking (EC) groups were well matched in terms of the minimization factors age, gender, body mass index (BMI) and experience with meditation and yoga (**Table 1**). Note that the groups differed marginally significantly in terms of educational level. However, *post hoc* correlation analyses revealed no correlations between educational level and the neural effects described below and is therefore unlikely to drive these effects. Furthermore, the total time subjects spent on the intervention, and the number of sessions subjects attended did not differ significantly between the two groups (**Table 1**).

Anthropometric and neuropsychological measures

The interventions had differential effects on the anthropometric measures as indicated by a significant Time x Intervention interaction (**Table 2**), i.e. BMI and waist were decreased following EC (main Time: BMI: $F(1,25)=6.2$, $p=.020$; waist circumference: $F(1,25)=17.9$, $p<.001$), but not following ME (main Time: BMI: $F(1,31)<1$, $p=.647$; waist circumference: $F(1,31)<1$, $p=.504$). Furthermore, we found that EC subjects reported closer compliance to the Dutch guidelines for healthy eating (main Time: $F(1,25)=12.8$, $p=.001$) than ME subjects (main Time: $F(1,31)=1.4$, $p=.244$) as substantiated by a significant Time x Intervention interaction for FFQ-DHD scores (**Table 2**). EC subjects also showed a significant increase in knowledge on healthy eating following the intervention (main Time; $F(1,25)=48.8$, $p<.001$), whereas ME subjects did not (main Time: $F(1,31)<1$, $p=.394$) as evidenced by a significant Time x Intervention interaction for FBQ scores (**Table 2**). Analysis of the other neuropsychological measurements revealed no significant interactions between Time and Intervention (**Table 2**).

Response times

On average, 59.6% (SD: 10.0) of the trials were hit trials. Subjects responded faster on high rather than low reward hit trials (main Reward: $F(1,56)=25.0$, $p < .001$), thus revealing a reward benefit. In addition, subjects responded faster to monetary relative to caloric reward cues (main Domain: $F(1,56)=17.4$, $p<.001$). We observed a reward benefit for both caloric ($F(1,115)=5.8$, $p=.018$) and monetary trials ($F(1,115)=37.3$, $p<.001$), which was, however, larger in the latter trials (Reward x Domain interaction: $F(1,56)=9.0$, $p=.004$). Finally, subjects' mean response times were lower on post relative to pre test sessions (pre: 310.66 (SD: 21.3), post: 304.60 (SD: 20.8) ms; main Time: $F(1,56)=17.4$, $p<.001$). We found no significant 4-way interaction with Intervention ($F(1,56)<1$).

Neuroimaging results

Reward Anticipation

First, brain regions were identified that responded to reward anticipation (main effect of Reward condition: high>low). At our whole-brain corrected threshold (FWE<.05, peak-level), this contrast yielded significant responses in striatum (bilateral caudate nucleus) and bilateral midbrain regions, as well as in occipital, motor and frontal regions (**Figure 3a; Table 3**). In addition, striatal (left putamen and right caudate nucleus) and bilateral inferior occipital regions demonstrated greater responses for anticipation to monetary than caloric reward cues (i.e. interaction of Domain x Reward)(**Table 3**).

Second, we were interested in the effects of ME on reward anticipation in *a priori* defined regions-of-interest (ROIs: striatum and midbrain). When using our ROIs as small search volumes, we found a significant Reward x Domain x Time x Intervention interaction in bilateral midbrain (FWE<.05, SVC, peak-level; **Figure 3b**; **Table 3**), but not in the striatum. To disentangle the observed four-way interaction in the midbrain, we performed ROI analyses (**Figure 3c**) using a bilateral structural ROI (see **Materials and methods**). As expected, we found the same four-way interaction in the ROI betas ($F(1,56)=6.0$, $p=.018$, $\alpha=.025$). *Post hoc* analyses revealed that this effect was driven by a significant reduction in midbrain responses on post relative to pre measurement in anticipation of specifically caloric cues following the ME (Time x Reward: $F(1,31)=6.4$, $p=.016$, $\alpha=.025$), but not the EC intervention (Time x Reward: $F(1,25)=3.6$, $p=.070$). There was no significant difference for the monetary domain following either the ME (Time x Reward: $F(1,31)=1.9$, $p=.181$) or the EC intervention (Time x Reward: $F(1,25)<1$).

Because we observed significant pre-intervention differences in midbrain caloric reward anticipatory activity between the two groups ($t(56)=2.4$, $p=.021$)(**Figure 4**), we performed *post hoc* sub-group analyses to test whether the observed four-way interaction was the result of a potential floor effect in the EC group. For this analysis, we only included subjects with midbrain ROI betas for caloric reward anticipation larger than zero. This resulted in a sample of 20 ME, and 10 EC subjects. The same analyses as described previously were performed on this sample.

There were no between-group pre-differences on the midbrain caloric betas (t(56)=1.3, p=.213) in this sample. Importantly, the four-way interaction remained marginally significant (F(1,28)=3.5, p=.072), again driven by a significant post versus pre reduction in caloric reward anticipation in ME (Time x Reward: F(1,19)=10.5, p=.004, α=.025), but not in EC (Time x Reward: F(1,9)<1).

To rule out that the observed interaction effect in midbrain can be explained by the group difference in BMI and waist circumference, we added difference scores for BMI and waist circumference (post-pre) as covariates to the analyses of the midbrain ROI betas. The Reward x Domain x Time x Intervention interaction remained significant when correcting for BMI and waist circumference (4-way interaction with BMI covariate: F(1,55)=5.2, p=.026; with waist circumference covariate: F(1,55)=7.3, p=.009).

Reward Receipt

No significant main effects of Intervention or interactions with Intervention were found for BOLD responses to reward receipt in whole-brain analyses, nor in ROI analyses using *a priori* defined ROIs for striatum and midbrain. For main effects and other interaction effects of reward receipt see **Table 4**.

Discussion

The aim of this study was to investigate the effects of an 8-week mindful eating intervention on subcortical reward anticipation using an incentive delay task. Consistent with our hypothesis, we found that anticipatory midbrain BOLD responses to caloric reward cues were decreased following the mindful eating (ME), but not the educational cooking (EC; active control) intervention. Anticipatory sub-cortical BOLD responses to monetary reward cues were not affected by either intervention. The effects were specific to reward anticipation and did not extend to reward receipt. Physical measures of obesity (i.e. BMI and waist circumference) were decreased following the educational cooking intervention, but not following the mindful eating intervention.

Dopaminergic midbrain neurons are crucial for processing predicted reward value (Schultz, 2006; Haber and Knutson, 2010) and, in concert with striatum, modulate motivated behavior such as eating (Berridge, 2009). In line with this, Small et al. (2001) showed that midbrain activity as measured by positron emission tomography ($H_2{}^{15}O$) decreased with reduced self-reported reward value of chocolate while a sample of healthy individuals ate chocolate beyond satiety. In another study, midbrain BOLD responses to sips of palatable milkshake were found to positively correlate with subsequent *ad libitum* milkshake intake in a group of healthy-weight to moderately obese individuals (Nolan-Poupart et al., 2013). More specifically, previous studies have shown that reduced subcortical reward responses to caloric cues, particularly in striatum are associated with obesity (Rothemund et al., 2007; Stoeckel et al., 2008), with weight gain (Demos et al., 2012), and with increased snack food intake in healthy-weight to overweight individuals (Lawrence et al., 2012). Furthermore, both midbrain and striatal BOLD responses to palatable food pictures was found to correlate positively with self-reported reward drive in healthy individuals (Beaver et al., 2006). These (indirect) measures of motivated eating behavior are thus associated with greater subcortical responses when processing predicted food reward value. In this study we observed intervention effects on caloric reward anticipation (i.e. high caloric drink versus water) – in an, on average, overweight sample of subjects motivated to change their bad eating habits – only in the midbrain, and not in the striatum. This is in accordance with a study in healthy individuals by O'Doherty and colleagues (2002), who found significant responses to cues predicting the receipt of a glucose solution versus a neutral taste in midbrain only, whereas both midbrain and striatum were responsive to cues predicting the receipt of a sweet versus an aversive salty taste; the latter may be a larger contrast in terms of valence. Given the coding of predicted reward in the midbrain, the currently observed effect of the mindful eating intervention on anticipatory midbrain responses to caloric cues suggests that mindfulness may be able to affect overeating by reducing the impact of food cues on reward processing, as it has been shown to reduce subcortical amygdala responses to emotional stimuli (Tang et al., 2015).

Indeed, several studies have found that an intensive mindful eating intervention led to reduced measures of overeating such as consumption of sweets (Mason et al., 2015), binges, externally and emotionally driven eating (Alberts et al., 2012) and reductions in BMI (Tapper et al., 2009) in non-clinical populations, as well as number of binges in binge-eating disorder (Kristeller et al., 2013). However, in this study we did not find evidence for decreased overeating, as physical measures of obesity (i.e. BMI and waist circumference) were not affected in the month following the ME intervention. A reason for not finding ME intervention-related reductions in our secondary measures such as BMI or waist circumference is that it may take a few months before mindfulness manifests itself in an individual's behavior following a mindfulness-based intervention (Tapper et al., 2009; Mason et al., 2015). In addition, mindfulness is aimed at stimulating acceptance (Bishop et al., 2004) and has been found to decrease body image concern in healthy women with disordered eating behavior (Alberts et al., 2012). Although we did not measure body image concern, this may have reduced the explicit motivation to lose weight in part of our healthy subject sample. Alternatively, the heterogeneity of our sample in terms of motivation might explain the lack of mindfulness-mediated changes in eating behavior as measured in this study. Although all subjects were motivated to change their bad eating habits, some wanted to lose weight, whereas others aimed for a healthier or more regular eating pattern. Unfortunately, we did not systematically record individuals' motivations. Sampling from a more homogeneous population in terms of motivation or recording these data is advised for future studies.

In contrast, we did observe beneficial effects of the EC intervention on physical measures of obesity and self-reported eating behavior in the absence of effects on subcortical reward anticipatory responses. The beneficial effects might not be surprising for this group, since the EC intervention was explicitly aimed at more healthy food intake, with reduced intake of sugar, fats and salt as part of the homework assignments and, thus, more likely to result in reduced BMI and waist circumference, independent of subjects' motivation. However, it is unclear how the small reductions in physical measures of obesity that were observed in the current study translate to long-term health benefits, in particular considering the low success rate of weight loss maintenance following standard weight loss programs (Wing and Phelan, 2005), and the absence of changes in neurocognitive measures as measured here.

Our finding that reduced anticipatory midbrain responses were specific to the caloric domain is in line with a previous study showing that only a brief 50-min mindful eating workshop (versus an educational video) reduced subsequent impulsive choice patterns for food-, but not money-related outcomes (Hendrickson and Rasmussen, 2013). However, meditators have been found to exhibit reduced striatal BOLD responses to primary reward prediction errors (Kirk and Montague, 2015) as well as monetary reward anticipation (Kirk et al., 2014a) relative to non-meditating controls. In the latter study, Kirk and colleagues (2014a; 2015) compared meditators to non-meditators without a baseline measurement. The observed decrease in striatal reward processing could thus be due to pre-existing between-group differences (Mascaro et al., 2013). Since the present study is actively controlled including pre and post measurements, the current effects can be ascribed to the mindfulness intervention. Kirk and colleagues (2014b) recently also performed a randomized actively controlled study including pre and post measurements and found that vmPFC value signals were modulated by the mindfulness intervention for both primary (juice) and secondary (monetary) rewards. These general reward effects versus our specific caloric effects might be due to both the type of intervention (general MBSR in Kirk et al. (2014b) versus mindful eating presently) as well as the study sample. Specifically, in our study, subjects were highly motivated to change undesired eating habits and their mindfulness practice was targeted at overcoming those. Note that we did not observe any effects of either intervention on neural responses at the time of caloric or monetary reward receipt. One might expect reductions in vmPFC BOLD responses following the mindfulness-based intervention as was recently reported by Kirk et al. (2014b) for juice delivery. However, another important difference with the current study is that we used promised (i.e. delivered after scanning) instead of actual rewards (delivered during scanning). Moreover, our design was optimized for reward anticipation, with perhaps not enough successful reward receipt trials (i.e. approximately 33% of all anticipated rewards were missed). Together, our results suggest that a targeted mindfulness-based intervention – including homework practices such as resisting impulsive eating behaviors – may have highly specific effects on (here, food) reward anticipation.

In conclusion, we found that an intensive mindful eating intervention reduced midbrain food anticipation. Future studies are required to demonstrate the clinical relevance of mindfulness-mediated reductions in food anticipation for counteracting reward cue-driven overeating, particularly in our obesogenic environment with food cues everywhere. Given the success of mindfulness-based programs in reducing symptoms of other reward-related disorders such as substance use (Brewer et al., 2011; Witkiewitz et al., 2014) and problem gambling (Toneatto et al., 2014), these interventions may also act by reducing anticipatory reward responses to the target of abuse and thereby reducing consumption and relapse rate.

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Tables

Table 1 Between-group (ME, EC) comparisons.

	mindful eating (ME)			educational cooking (EC)			*p*-value	*test-statistic*
n	32			26				
Gender (Male:Female)	5 : 27			5 : 21			.740	na [a]
Age (yrs)	32.3	±10.8	20-52	30.6	±11.3	19-51	.546	.607 [b]
Education (NLV)	6.5	±0.6	5-7	6.2	±0.7	5-7	.053	304.0 [c]
Digit span (total score)	15.6	±3.5	9-23	14.1	±3.5	9-22	.120	1.577 [b]
Smoking (FTND score)	0.19	±1.1	0-6	0.04	±0.2	0-1	.902	413.5 [c]
Body mass index (kg/m^2)	26.6	±4.1	19-35	25.5	±3.4	20-33	.296	1.054 [b]
Waist circumference (cm)	89.6	±12.8	72-122	86.5	±11.7	70-117	.338	.967 [b]
Yoga/meditation experience (yrs)	1.0	±2.6	0-14	1.9	±4.3	0-19	.334	-.974 [b]
Time on training (hrs)	31.0	±14.4	2.5-47.8	23.9	±21.2	0-77.7	.135	1.518 [b]
Attendance < 4 sessions (n)	5			5			.740	na [a]
Attendance (number of sessions)	6.5	±2.5	1-9	6.3	±2.8	1-9	.738	0.336 [b]

If not otherwise stated, values denote mean±SD, and min-max.

NLV: the Dutch version of the National Adult Reading Test was administered to assess education ; *FTND*: Fagerstrom Test for Nicotine Dependence .

[a] Based on Fisher's Exact Test, [b] Independent samples t-test (degrees of freedom: 56) [c] Mann-Whitney test

Table 2 Means and standard deviations, pre- and post-training, for each group (ME, EC) separately, and Time (pre, post) x Intervention (ME, EC) statistics.

	mindful eating (ME)				educational cooking (EC)				*p*	*test-statistic*[a]
	pre		post		pre		post			
Physical measurements										
BMI (kg/height(m)^2)	26.6	±4.1	26.6	±4.2	25.5	±3.4	25.2	±3.5	.023	5.5
Waist (cm)	89.6	±12.8	89.3	±13.2	86.5	±11.7	84.4	±11.7	.026	5.2
Neuropsychological measurements / self-report										
Digit Span (total score)	15.6	±3.5	15.2	±3.6	14.1	±3.5	13.5	±3.7	.689	< 1
PANAS										
Positive Affect	31.8	±6.5	30.0	±6.1	31.4	±4.8	29.8	±5.1	.772	< 1
Negative Affect	12.7	±2.8	13.9	±4.3	12.7	±2.6	13.4	±3.6	.602	< 1
FTND (smoking score)	0.19	±1.1	0.19	±1.1	0.04	±0.2	0.04	±0.2	1.000	416[b]
BIS-11	62.0	±9.3	62.1	±9.0	64.5	±8.7	63.7	±8.3	.492	< 1
BIS	20.8	±3.3	20.3	±3.2	19.8	±3.3	19.6	±3.3	.671	< 1
BAS	41.5	±3.3	42.3	±4.0	43.2	±4.1	42.7	±4.1	.101	2.8
Kirby	0.013	±0.023	0.015	±0.023	0.020	±0.045	0.011	±0.017	.094	2.9
FFQ – DHD	52.2	±10.4	54.2	±10.0	51.6	±12.0	59.5	±10.8	.036	4.6
FBQ – short version	64.0	±7.0	62.8	±5.6	62.1	±4.8	62.7	±6.3	.264	1.3
Knowledge	15.6	±1.5	15.8	±1.3	14.9	±1.5	16.7	±0.8	<.001	19.6
Temptation	15.0	±3.2	14.4	±3.3	14.8	±3.3	14.5	±4.0	.729	< 1
DEBQ										
Restraint	2.8	±0.6	2.9	±0.6	2.9	±0.7	2.9	±0.6	.814	< 1
Emotional	2.8	±0.8	2.8	±0.8	2.8	±0.7	2.7	±0.9	.728	< 1

External	3.2	±0.4	3.2	±0.5	3.4	±0.5	3.1	±0.5	.120	2.5
FFMQ-SF[c]	78.1	±7.7	76.8	±7.4	76.5	±8.6	75.7	±7.9	.671	< 1
HADS										
Anxiety	4.4	±2.4	6.0	±2.5	4.8	±2.5	6.2	±3.9	.902	< 1
Depression	2.6	±2.4	2.8	±2.4	2.4	±2.3	2.7	±2.6	.864	< 1
TCQ[d]	30.0	±7.4	27.8	±8.4	32.7	±4.8	32.8	±8.1	.215	1.6
Wanting										
Low caloric reward	4.5	±2.8	4.6	±2.8	4.5	±3.1	4.6	±2.8	.987	< 1
High caloric reward	6.3	±2.0	5.8	±2.4	5.4	±3.0	5.6	±2.4	.330	< 1
Low monetary reward	1.9	±2.4	1.5	±2.0	2.2	±2.5	2.4	±2.6	.318	1.0
High monetary reward	5.2	±2.8	5.4	±2.7	5.0	±3.2	5.4	±2.4	.840	< 1
Liking										
Low caloric reward	6.4	±2.3	6.1	±2.2	6.2	±2.7	6.6	±2.2	.187	1.8
High caloric reward	7.2	±1.6	6.7	±2.1	6.8	±2.9	6.4	±2.7	.783	< 1
Low monetary reward	2.2	±2.4	2.2	±2.2	2.8	±2.4	2.8	±2.3	.967	< 1
High monetary reward	5.1	±2.5	5.2	±2.4	4.4	±2.7	5.3	±2.2	.143	2.2
Response Times										
Low caloric reward	313.7	±41.0	312.4	±33.8	322.5	±51.6	312.6	±43.8	.319	1.0
High caloric reward	303.4	±33.8	299.1	±31.5	322.2	±50.0	311.8	±48.4	.471	< 1
Low monetary reward	313.0	±47.0	311.2	±44.2	317.4	±44.8	313.3	±49.6	.834	< 1
High monetary reward	294.7	±26.2	285.1	±32.5	302.3	±41.5	293.9	±43.0	.874	< 1
Hunger[b]	5.9	±2.6	5.9	±2.7	5.9	±3.0	5.6	±2.9	.835	< 1
Thirst[b]	5.7	±2.6	5.9	±2.8	6.0	±2.4	5.5	±2.4	.273	1.2
Satiety[b]	2.3	±2.1	2.1	±0.9	1.9	±1.1	2.1	±1.2	.345	< 1

If not otherwise stated, values denote mean±SD.

PANAS: Positive And Negative Affect Scale; *FTND*: Fagerstrom Test for Nicotine Dependence ; *BIS-11*: Barratt Impulsiveness Scale-11; *BIS/BAS*: Behavioral Inhibition System / Behavioral Approach System questionnaire; *Kirby*: delayed reward discounting questionnaire; *FFQ-DHD*: Food Frequency Questionnaire, Dutch Healthy Diet; *FBQ*: Food Behavior Questionnaire, a shortened version; *DEBQ*: Dutch Eating Behaviour Questionnaire; *FFMQ-SF*: Five Facet Mindfulness Questionnaire – Short Form; *HADS*: Hospital Anxiety and Depression Scale; *TCQ*: Treatment Credibility Questionnaire. Note that the pre-training TCQ was filled out at the first training session, not on the pre-training test session, as subjects were unaware of the contents of their training at that time.

[a]If not otherwise stated, the reported test-statistic is the F-value (degrees of freedom: 1,56)

[b]Mann-Whitney U

[c]FFMQ-SF: N = 48 (N_{ME} = 22, N_{EC} = 26; degrees of freedom: 1,46)

[d]TCQ, Hunger, Thirst, Satiety: N = 55 (N_{ME} = 29, N_{EC} = 26; degrees of freedom: 1,53).

Table 3 Summary of brain regions exhibiting main effects of reward, domain and/or interactions with domain, intervention, and time at the time of reward anticipation.

Label	Side (Left/Right)	MNI-coordinates x, y, z (mm)			Size (number of voxels)	*pFWE* (peak-level)	*t*-value[a] (peak)
Main effect of Reward: high > low[b]							
Inferior occipital lobe	R	24	-94	-4	1319	< .001	12.99
Cerebellum	R	36	-58	-20		< .001	5.96
Inferior occipital lobe	L	-22	-96	-4	1459	< .001	11.47
Caudate nucleus	R	10	10	-2	1145	< .001	7.70
Caudate nucleus	L	-8	10	-4		< .001	7.49
Thalamus	L	-4	-18	8		.003	5.48
Superior motor area	L	-6	-2	58	2134	< .001	6.32
Precentral	L	-38	-14	52		< .001	6.23
Superior motor area	R	6	6	56		< .001	6.23
Precentral	R	52	0	50	25	.012	5.13
Premotor cortex	R	42	0	58		.037	4.85
Insula	L	-32	28	4	2	.026	4.94
Midbrain	R	8	-28	-8	1	.043	4.81
Midbrain	L	-6	-28	-8	2	.044	4.80
Insula	L	-30	28	0	2	.050	4.77
Main effect of Reward: low > high reward [b]							
Frontal superior lobe	R	18	26	50	7	.023	4.97
Interaction effect of Reward x Domain: monetary (high > low reward) > caloric (high > low reward)[b]							
Inferior occipital lobe	L	-20	-96	-4	1511	< .001	19.96

Inferior occipital lobe	R	24	-92	-6	1349	< .001	18.71
Putamen	L	-20	22	-8	1	.037	4.85
Caudate nucleus	R	12	10	4	1	.047	4.79
Interaction effect: Reward x Domain x Time x Intervention[c]							
Midbrain	R	12	-18	-12	8	.005	3.64
Midbrain	L	-10	-22	-12	13	.005	3.64
Midbrain	L	-12	-18	-12		.006	3.54
Midbrain	L	-8	-18	-14		.010	3.40

[a] Degrees of freedom: 1, 224; [b] $p < .05$, whole brain family wise error (FWE) corrected; [c] $p < .05$, small volume, FWE corrected.

Table 4. Summary of brain regions exhibiting main effects of reward, domain and/or interactions with domain, training, and time at the time of reward receipt.

Label	Side (Left/Right)	MNI-coordinates x, y, z (mm)			Size (number of voxels)	*pFWE* (peak-level)	*t*-value [a] (peak)
Main effect of receipt: hits (high > low) > too lates (high > low) [b]							
Temporal inferior lobe	L	-52	-48	-14	36815	< .001	13.32
Striatum	L	-14	6	-12		< .001	12.08
Caudate	R	12	10	-8		< .001	11.27
Frontal medial lobe	L	-20	24	50	1612	< .001	9.34
Frontal medial lobe	L	-30	18	54		< .001	8.95
Frontal superior lobe	R	22	30	48	318	< .001	6.16
Frontal medial lobe	R	30	12	52		< .001	6.08
Frontal superior lobe	L	22	6	48		.025	4.98
Frontal inferior lobe	R	46	38	16	63	.001	5.70
Thalamus	L	0	-14	18	5	.022	5.01
Temporal medial lobe	L	-62	-12	-22	3	.035	4.89
Main effect of receipt: too lates (high > low reward) > hits (high > low reward) [b]							
Temporal medial lobe	R	48	-28	-6	1183	< .001	11.47
Supramarginal	R	62	-46	32		< .001	9.15
Temporal medial lobe	R	62	-46	12		.004	5.43
Frontal inferior lobe	R	46	22	4	837	< .001	7.83
Frontal inferior lobe	R	56	24	16		.002	5.53
Insula	L	-32	20	-10	339	< .001	6.85
Insula	L	-36	20	8		< .001	6.83
Insula	L	-30	28	0		.001	5.75

Superior motor area	R	8	16	60	235	< .001	6.61
Supramarginal	L	-62	-44	28	144	< .001	6.61
Temporal medial lobe	L	-50	-28	-4	61	< .001	6.16
Frontal medial lobe	R	26	50	24	108	< .001	5.89
Anterior cingulate	R	8	26	32	41	.007	5.30
Anterior cingulate	R	10	16	38		.026	4.97
Midbrain	L	-6	-26	-2	6	.010	5.19
Midbrain	R	6	-26	-2	7	.011	5.18
Temporal medial lobe	L	-54	6	-16	6	.019	5.04
Interaction effect of domain x receipt x reward: monetary > (hits (high > low reward) > toolates (high > low reward)) > caloric (hits (high > low reward) > toolates (high > low reward)) [b]							
Lingual	R	18	-84	-4	116	< .001	7.02
Lingual	L	-14	-88	-4	1	.023	5.01

[a] Degrees of freedom: 1,224; [b] $p < .05$, whole brain FWE corrected.

Figures

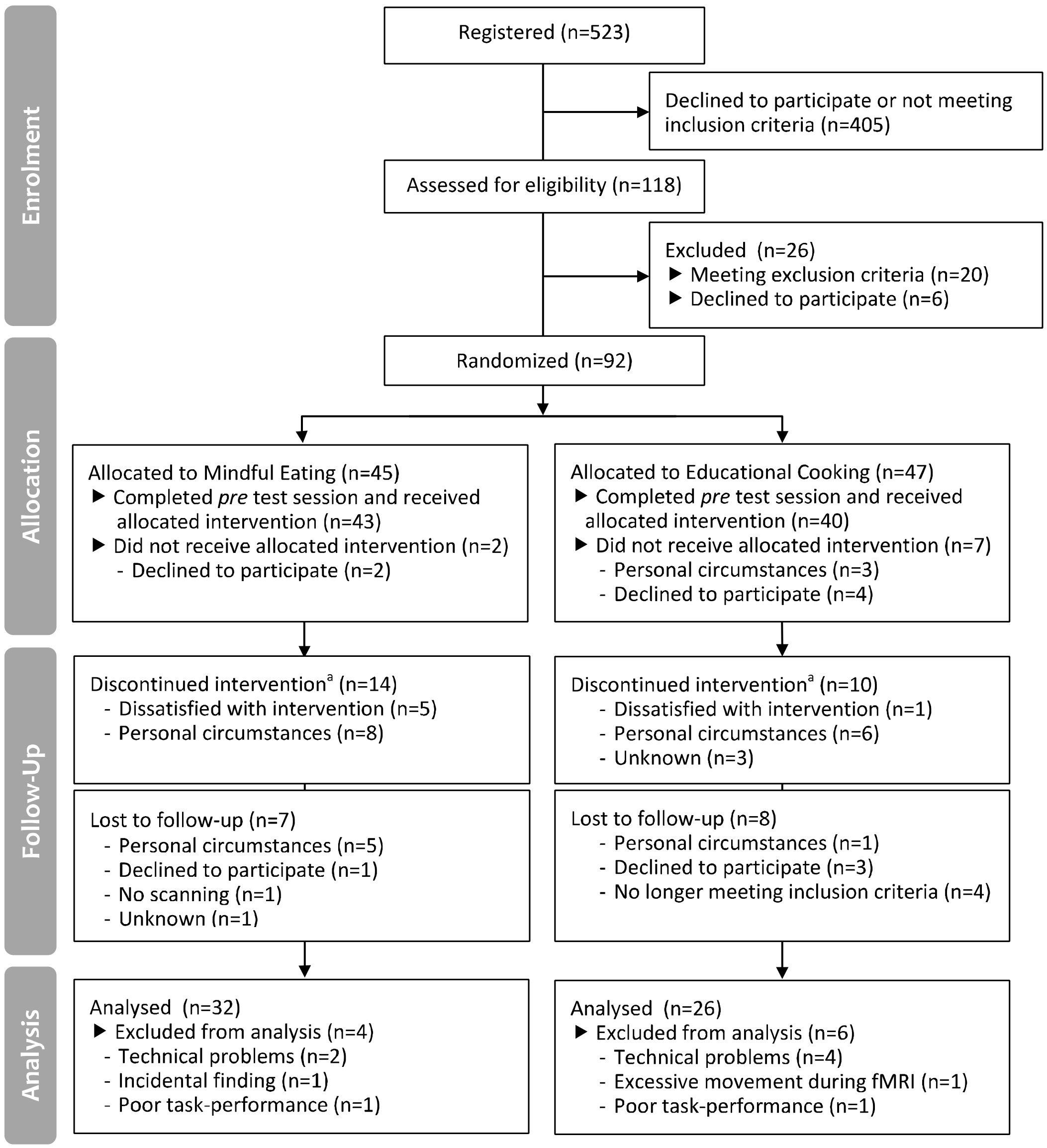

Figure 1. CONSORT flow diagram.

[a] Attended <4 sessions of the intervention program. Note that these subjects were invited back to the laboratory for the *post* test session

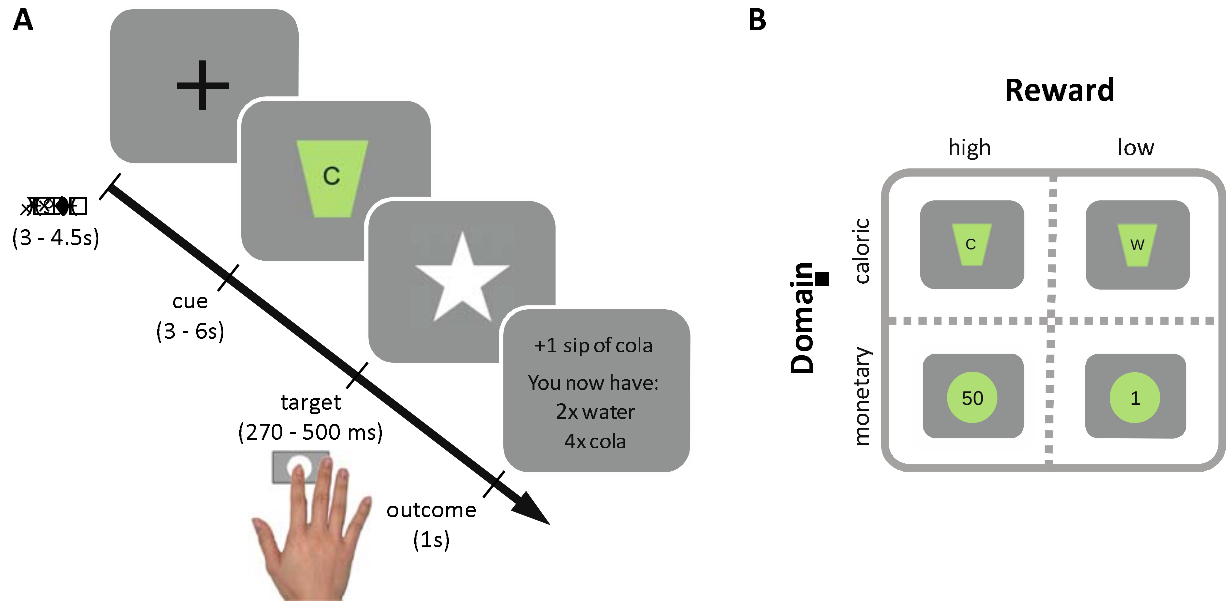

Figure 2. Incentive delay task. **A)** Each trial started with a fixation cross, followed by a cue signaling which reward could be earned on that trial. Subsequently, a white star (i.e. target) appeared for a brief period and subjects were instructed to press a button as fast as possible upon detection using their right index finger. If subjects pressed before the response deadline (hit trial), the target remained on the screen, informing subjects of the successful registration of their key press. Subsequently, a brief feedback image informing the subjects about the total gain was presented. If subjects pressed too late or failed to press at all (too late or miss trial, respectively), they were presented with the text message "you win nothing" plus the total gain so far. To ensure subjects won similar amounts of each reward (in ±2/3 of the trials), target presentation times were determined individually and adaptively: following hit trials the response deadline for that reward cue was decreased with 10 ms, following too late or miss trials it increased with 10 ms. **B)** Reward cues for high and low caloric cues (C: subject's choice from cola, orange juice or chocolate milk vs. W: water) and high and low monetary cues (50 cents vs. 1 cent). The task took between 20 – 25 minutes to complete. Subjects performed 4 blocks of 25 trials (a total of a 100 trials). A block contained either high/low monetary or high/low caloric trials. Each trial type was repeated approximately 25 times (M: 24.4, SD: 2.78). Block-presentation was pseudo-randomly distributed and counterbalanced across subjects (randomization scheme: ABBA or BAAB).

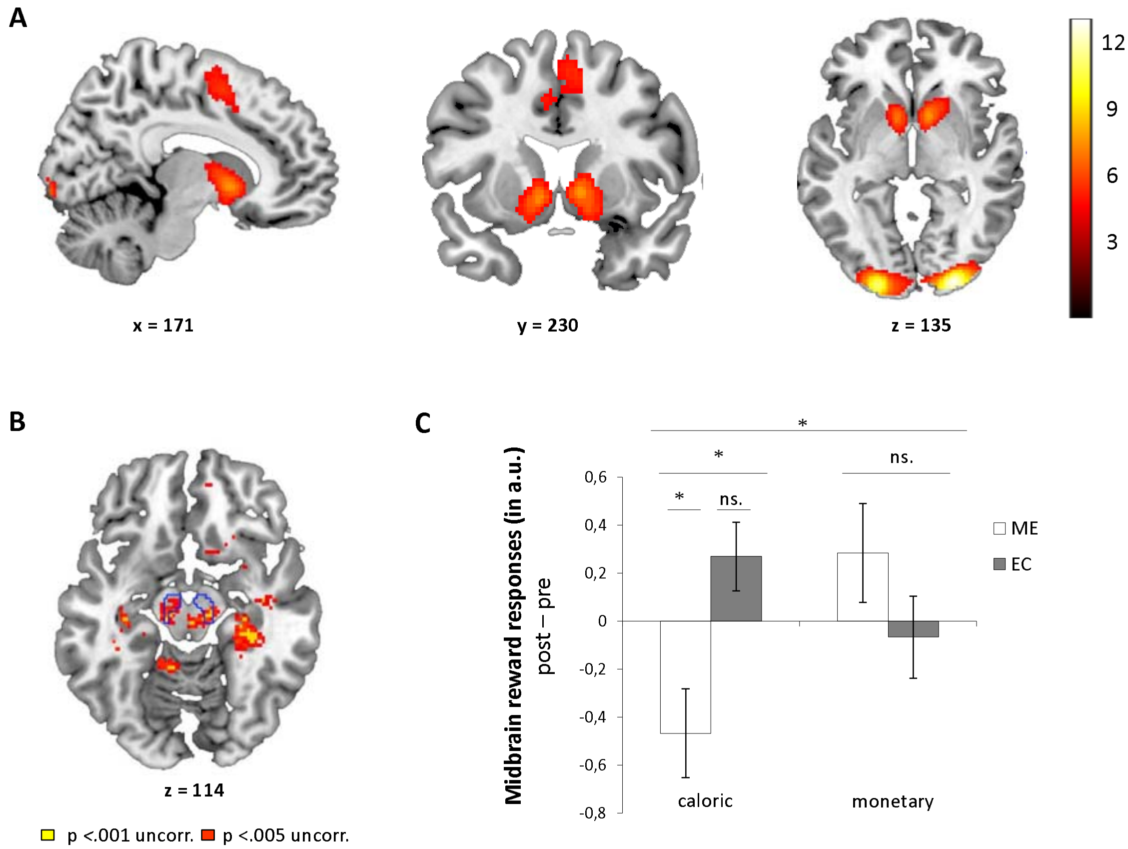

Figure 3. Summary of neuroimaging results. **A)** Main effect of reward. Contrast of high vs. low reward cue trials (high > low). Full brain statistical parametric maps were thresholded at p < .05 (FWE-corrected, peak-level). **B)** Axial slice of whole brain interaction effect of Domain x Time x Intervention for the Reward contrast (high > low). Statistical parametric maps were thresholded at p < .001 (yellow) and p < .005 (red) uncorrected for visualization purposes. Outlined regions are corrected for multiple comparisons within our small search volume, at peak pFWE < .05. **C)** Betas from the bilateral structural midbrain ROI (outlined in blue in panel B). Post- minus pre-intervention mean betas based on the high minus low reward contrast are presented for each domain (caloric, monetary) and for each intervention group (ME, EC) in arbitrary units (a.u.). Asterisks indicate p < .025 (Bonferroni corrected for multiple ROIs). All statistical parametric maps are overlaid onto a T1-weighted canonical image. Slice coordinates are defined in MNI152 space and images are shown in neurological convention (left=left).

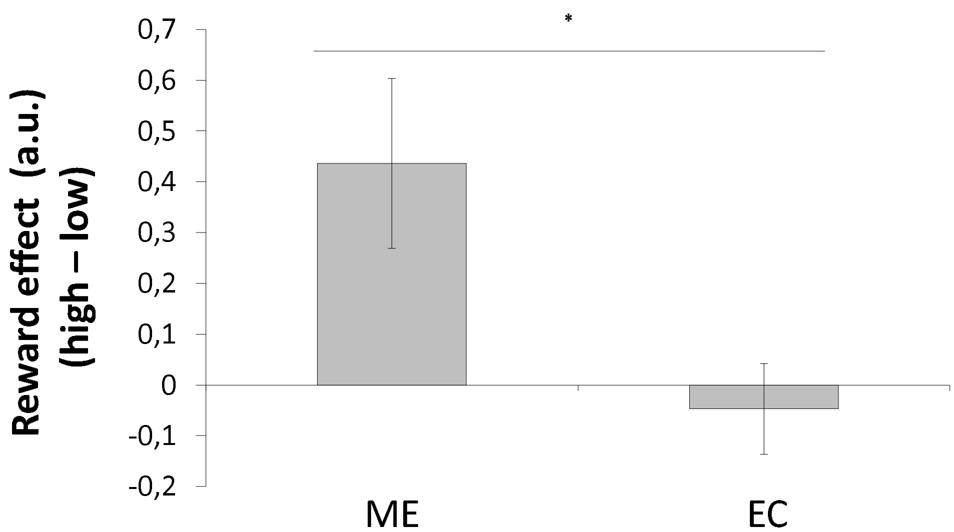

Figure 4. Midbrain caloric ROI betas are presented to indicate between-group pre-differences in midbrain reward (high – low) anticipatory activity. Asterisk indicates *p* = .021.