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Impact of Intensive Lifestyle Intervention on neural food cue-reactivity: Action for Health in Diabetes Brain Ancillary Study

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Abstract

Objective: Look AHEAD was a randomized trial comparing the effects of an intensive lifestyle intervention (ILI) vs. a diabetes support and education (DSE) control group in adults with type 2 diabetes and overweight/obesity. We used functional magnetic resonance imaging (fMRI) to determine if neural food cue-reactivity differed for these groups 10 years after randomization.

Methods: 232 participants (ILI n=125, 72% female, DSE n=107, 64% female) were recruited at 3 Look AHEAD sites for fMRI. Neural response to high-calorie foods compared to non-foods was assessed in DSE vs. ILI. Exploratory correlations were conducted within ILI to identify regions where activity was associated with degree of weight loss.

Results: Voxel-wise whole-brain comparisons revealed greater reward-processing activity in left caudate in DSE compared to ILI and greater activity in attention/visual processing regions in ILI

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than DSE ($p<0.05$, Family Wise Error Corrected). Exploratory analyses revealed greater weight loss among intervention participants from baseline was associated with brain activation indicative of increased attention/visual processing and cognitive control in response to high-calorie food cues ($p<0.001$, uncorrected).

Conclusions: These findings suggest there may be legacy effects of participation in a behavioral weight loss intervention, with reduced reward-related activity and enhanced attention/visual processing in response to high-calorie foods.

Keywords

obesity; intervention; weight loss; brain; imaging

INTRODUCTION

Brain imaging, specifically functional magnetic resonance imaging (fMRI), has been used to identify brain regions that are active in response to food cues. Patterns of brain activity associated with presentation of food cues differ between individuals of normal weight and those with obesity. Previous studies have demonstrated that when viewing food cues individuals with obesity have increased activity in reward-processing regions, such as striatum, orbitofrontal cortex, insula, amygdala, and hippocampus(1, 2, 3, 4, 5, 6), and decreased activity in regions involved in cognitive control or inhibition such as lateral prefrontal cortex(2, 7, 8). These studies have typically been cross-sectional, and few have explored effects of participation in a behavioral weight loss (BWL) program. Thus it is unclear if different patterns of food cue-reactivity persist following treatment. Understanding how the brain responds to food cues and how that may change as a function of weight loss or a BWL program may help identify underlying neural mechanisms supporting successful weight loss and guide future treatment for overweight/obesity.

Successful weight loss maintainers who have kept weight off for at least 1 year exhibit increased activity in superior frontal cortex, a control-related region, relative to both lifetime normal-weight individuals and those with obesity(9). Two studies that investigated prospective changes in food cue-reactivity revealed decreased reward-related responsivity to food cues shortly following BWL programs(10, 11). In contrast, a third study found increased cue-reactivity in a reward-processing region (i.e., ventral pallidum) following an in-hospital induced 10% weight loss(12). These findings suggest reward- and control-related activity can be altered with treatment. In particular, behavioral treatments may reduce reward-related responses and sustained weight loss maintenance may require enhanced inhibitory control. However, these studies had small sample sizes, and differences in methods and degree of weight loss may have contributed to differing results.

Research has also begun investigating responses to food cues in individuals with diabetes and/or metabolic syndrome. One study comparing BMI-matched individuals with and without type 2 diabetes found those with diabetes had relatively greater responsivity in emotion- and reward-processing regions(13). Another more recent study observed relatively decreased reward-processing activity for individuals with more components of metabolic syndrome and/or prediabetes(14). The same group found that, among individuals with

diabetes, those with obesity demonstrated less activation in salience and reward-related regions when fasted(15). When fed, these individuals had relatively greater amygdala activity than those without obesity(15). Although these studies have relatively small samples, these data suggest neural food cue-responsivity may also differ as a function of diabetes and related symptoms and highlight the need for more research in this area.

The Look AHEAD (Action for Health in Diabetes) study and the Look AHEAD Brain Magnetic Resonance Imaging (MRI) Ancillary Study provide the opportunity to examine the long-term impact of participation in a BWL program relative to a control condition on neural reactivity to food cues in a much larger sample. The Look AHEAD study was a large multicenter randomized controlled trial of individuals with type 2 diabetes that investigated the effects of an intensive lifestyle intervention (ILI), compared to a diabetes support and education (DSE) control group, on cardiovascular morbidity and mortality. The randomized intervention was stopped in September 2012 because of a lack of significant differences between groups on the primary outcome, but the study has continued as an observational cohort study(16). At the conclusion of the trial all living Look AHEAD participants were invited to join the observational study aimed at determining longer-term effects of the intervention on a number of outcomes.

In the Look AHEAD Brain Ancillary study participants from three of the Look AHEAD centers (Brown University, University of Pennsylvania, and University of Pittsburgh) underwent MRI ~10 years following randomization. Previous work has detailed structural brain differences (including total brain, ventricle, and white matter lesion volume), functional connectivity, and cognitive function in this sample(17, 18, 19, 20). The current study assessed neural food cue-reactivity 10 years after randomization to ILI or DSE. It was hypothesized that participation in ILI would be associated with decreased activity in reward-processing regions (e.g., ventral/dorsal striatum, substantia nigra, ventral tegmental area, orbitofrontal cortex) and increased inhibitory control-related activity (e.g., lateral prefrontal, inferior frontal, cingulate cortices) relative to DSE.

METHODS

Participants.

Active Look AHEAD participants from the three Look AHEAD Brain ancillary study clinics (N=875) were approached for participation. Participants were eligible if they consented to MRI scanning, were compatible with scanner bore size (operationalized as BMI<=45), and were free of standard MRI contraindications (e.g., pacemakers, ferrous metallic fragments in soft tissue, or severe claustrophobia). A total of 321 participants met these criteria and were scanned. As reported previously, compared to the 554 individuals who did not complete the MRI scan, this sample was slightly younger, had lower BMI, was more likely to be female and less likely to be white(20). fMRI cue-reactivity scans were conducted on 306 of these participants. Data from 302 participants were complete (Philadelphia n=117, Pittsbugh n=100, Providence n=85) and data from 242 participants met standard motion artifact criteria (Philadelphia n=97, Pittsbugh n=75, Providence n=70). Of these 242, 10 participants were excluded due to bariatric surgery, thus 232 participants were included in the current sample (Philadelphia n=93, Pittsbugh n=71, Providence n=68; total DSE: N=107, ILI

N=125). On average, these participants were approximately 10 years post-randomization (range= 9.93–12.45 years; mean±SD DSE=10.38±0.48, ILI=10.35±0.46, p=0.63)

Look AHEAD Study Intervention.

Detailed descriptions of the Look AHEAD intervention have been published previously(21, 22). In brief, ILI participants were assigned a calorie, fat gram, and physical activity goals designed to produce 10% weight loss. Further details are available in supplemental materials.

MRI Parameters:

Details of the structural MRI parameters have been published previously(20) and further detail is available within the supplemental material section. Scanning and assessment procedures were standardized across the three sites. All MRI scans were conducted on Siemens 3-Tesla scanners utilizing the same software platform and 32- channel head coils. Quality assurance protocols using MRI phantoms to regularly assess scanner performance in mulit-site studies were employed before and throughout this study in order to assess and ensure scanner performance across the three sites. In addition to structural anatomical scans, the imaging protocol included one run of food cue-reactivity (described below). For this food cue paradigm, a total of 204 functional images were acquired using a gradient-echo echo-planar sequence (TR=2000ms; TE=30 ms; flip angle=90°; 40 axial slices, 3×3×3mm voxel size). Padding was placed around each participant's head to minimize motion during scanning. Visual stimuli were presented via E-prime 2.0 Professional software (Psychology Software Tools, Inc., Sharpsburg, PA) projected onto a screen at the back end of the scanner bore, and viewed through a mirror attached to the head coil. Participants requiring eyeglasses for visual correction were fitted with MRI-compatible lenses.

Food Cue paradigm:

This block-design food cue-reactivity task is adapted from work by Killgore and colleagues(9, 23) and is similar to those used in several studies. Images of high-calorie foods (e.g., French fries, ice cream), low-calorie foods (e.g., broccoli, rice cakes), and neutral non-food images (e.g., furniture, flowers) were presented pseudo-randomly in blocks separated by 20-seconds of fixation baseline. Blocks consisted of 12 images presented for 2 seconds each, followed by a prompt for participants to rate their current urge to eat on a four-point scale (very low –very high) using MRI-compatible four-button response pads. Participants were not asked to fast prior to scanning but were asked to limit consumption (≤2 servings) of alcoholic or caffeinated beverages for 24 hours before their appointment. Upon arrival to the MRI facility all participants were queried on their last intake. Participants were given instructions (standardized across all sites) to simply view the images/crosshair and respond to all prompts using the keypad. No feedback was provided to participants on these responses.

Data Analytic Plan

Preprocessing and data analysis were performed using Statistical Parametric Mapping Software (SPM8; Wellcome Trust Centre for Neuroimaging, University College London,

UK; http://www.fil.ion.ucl.ac.uk/spm/) and a suite of processing scripts developed by researchers at Dartmouth College (available at http://github.com/ddwagner/SPM8w). This processing was centralized at the Providence site (more details available in supplemental materials).

A general linear model was run for each participant with regressors for each condition of interest (i.e., high-calorie foods, low-calorie foods, and neutral non-foods) as well as covariates of non-interest (e.g., ratings trials, six motion parameters derived from realignment corrections, and linear trend). Fixation periods were not explicitly specified in the model and comprise the baseline for comparison. Models were convolved with SPM8's canonical hemodynamic response function and were then used to generate contrast images comparing task conditions (e.g., high-calorie vs. non-food images).

A whole-brain voxel-wise random effects analysis was conducted for all participants comparing activation during presentation of high-calorie foods vs. fixation baseline to neutral non-food items vs. baseline (high calorie > non-food), thresholded with a family-wise error rate (FWE) of $p>0.05$, $k=10$. To directly identify any regions showing differential response for ILI vs. DSE, a voxel-wise independent samples t-test was conducted using cluster-wise false discovery rate (FDR) corrections. Baseline BMI and site were included as covariates to control for an observed group difference in baseline BMI. Although this work focuses on responses to high calorie food vs. non-food, other contrasts were analyzed and presented in supplemental material. Secondary post-hoc exploratory whole-brain voxel-wise analyses were conducted within ILI to examine correlations between percent weight loss from baseline and food cue-reactivity correcting for baseline BMI, site, age, and number of days between scan date and the date of most proximal weight measure. Correlations were also performed including the entire sample (ILI and DSE). MNI coordinates are reported for all fMRI analyses.

RESULTS

Demographics

A summary of baseline (i.e., when participants enrolled in Look AHEAD, 2001–2004) demographics for the sample in this sub-study is presented in Table 1. Overall, this sample was ~68% female with a mean age of ~60 years at the time of the scan. There were no differences between ILI and DSE in gender, age, ethnicity, education, CVD history at baseline, or duration of diabetes (all p's>0.1). There was, however, a significant difference in baseline BMI between the two groups in this sub-study (mean±SD BMI DSE=36.03±5.06, ILI=34.54±5.43, $p=0.03$).

Figure 1 shows percent weight loss from baseline. The greatest difference in weight loss between ILI and DSE was seen at Year 1. Following the large initial weight loss, participants in ILI regained weight but differences in weight loss between groups remained significant at all subsequent years up to year 9 (all p's<0.05). In this sample, year 10 weight losses did not differ significantly between groups (ILI=−7.18±9.06%, DSE=−5.11±9.95%; $p=0.11$).

Participants were not required to fast prior to the MRI; however, on average they reported having no food or caloric beverages for 3.8(±3.4) hours prior to the start of the session. There was no difference between groups in self-reported time since last intake (mean time DSE=3.7±3.2 hrs, ILI=3.9±3.5 hrs, p=0.61).

fMRI Results

Comparison of ILI vs. DSE—A whole brain t-test revealed a region of the right caudate (8, 2, 26), extending into cingulate, that was more responsive to high-calorie food>fixation baseline (compared to non-food>fixation baseline) in DSE vs. ILI (Table 2, Figure 2). By contrast, the ILI group showed greater reactivity in a region of the left angular gyrus (–30, –66, 32) extending into left middle temporal and superior occipital cortices relative to DSE (Table 2, Figure 2; other contrasts in supplement).

Secondary post-hoc correlation analyses—Within ILI, regions displaying positive or negative correlations with percent weight loss (calculated from baseline to the assessment most proximal to MRI) at the level of $p<0.001$, uncorrected, with FDR-corrected values <0.5 are listed in Table 3 (see Fig. 3 for visualization). Food cue-responsivity in bilateral anterior cingulate /medial frontal gyrus was positively correlated with percent body weight loss such that greater activity was associated with greater percent weight loss. Activity in the left superior and middle temporal gyri as well as a region of right middle frontal gyrus was similarly correlated with weight loss. In exploring correlations in the opposite direction (i.e., regions in which activity was associated with *less* weight loss), a region of right middle temporal lobe (BA 21) was identified. The association between weight loss and cue-reactivity is attenuated in right frontal gyrus and right middle temporal lobe with removal of a potential outlier.

Across the entire sample (ILI and DSE) similar regions of ACC and left middle temporal gyrus were associated with greater weight loss, however the association with right middle frontal gyrus did not reach statistical significance. Activity in right BA 21 was similarly associated with less weight loss.

DISCUSSION

The current study investigated neural activity in response to food cues in a subset of participants from the Look AHEAD trial ~10 years after randomization to either an intensive lifestyle intervention or a diabetes support and education control group. At the time of this assessment, the ILI group had a mean weight loss of 7.1kg from baseline vs. 6.2kg in the DSE (control group). A whole-brain analysis of responses to high-calorie food cues compared to non-food images revealed DSE had greater activity than ILI in the right caudate and right cingulate. By contrast, ILI exhibited greater activity in left angular gyrus/middle temporal cortex extending into occipital cortex. Although limited by the lack of baseline data on cue-reactivity, these unique patterns of brain activity for ILI vs. DSE suggest that responses to high-calorie food cues differ for individuals who participated in a BWL intervention compared to those who did not and may help to identify the mechanisms through which BWL treatment can impact how individuals process food cues in the environment and ultimate eating behavior.

The observation of relatively greater activity in the caudate for those in DSE relative to those in the intervention suggests greater reward-related processing of high calorie food cues in DSE vs. ILI. The caudate lies within the dorsal striatum of the basal ganglia and is part of the mesolimbic dopaminergic reward-processing network. Activity within this network, including the caudate, typically increases in response to rewarding or pleasurable stimuli across a variety of domains (e.g., food, money, drugs).(24) Previous research has suggested individuals with obesity exhibit even greater reward-related food cue-reactivity in the dorsal striatum than normal weight individuals.(4) The caudate in particular is thought to be involved in motivation for food(25) as well as motor planning(26). Thus increased activity in this region signals a heightened level of motivation or expectation/preparation for rewards. Therefore, our finding of relatively greater responsivity to high-calorie food cues in this region for individuals who did not undergo the BWL intervention is consistent with previous research on obesity, suggesting the behavioral lifestyle intervention may be associated with a reduction in reward-related or motivational response to high-calorie foods.

In contrast, ILI group exhibited greater food-cue responsivity in regions involved in attention and visual processing. Previous studies have indicated the occipital cortex of normal weight individuals is more active when viewing food pictures compared to non-food pictures(23, 27), especially high calorie foods(28), suggesting visual sensory information for food cues is processed differently than non-food items. Moreover, this response is attenuated after eating a meal(28). Studies have also shown differing responsivity in visual/attention processing regions in persons with obesity compared to normal weight individuals.(4, 9, 29) Successful weight loss maintainers exhibited greater visual and attention-related activity compared to both individuals with obesity and lifetime normal weight participants(9) and other work employing a food-based Stroop task which measures response inhibition towards food words (e.g., “pizza”, “ice cream”) has shown relatively longer reaction times to high-calorie food words in both successful weight loss maintainers(30) and individuals immediately following a BWL intervention(31). The finding herein, that ILI had greater responsivity in visual/attention-related regions, is consistent with this previous work on weight loss maintainers and suggests the possibility of heightened vigilance to high-calorie food cues among those who have participated in a BWL intervention. This is additionally supported by the correlation observed between percent weight loss and activity in similar attention/visual-processing areas.

Interestingly, a dissociation was observed between different visual processing areas (i.e., secondary visual-processing/attention vs. primary visual cortex). While activity in left secondary visual processing and attention-related regions was greater in ILI vs. DSE, and also greater in individuals who had lost more weight in ILI, activity in right primary visual cortex was associated with less weight loss. This may reflect differences in the level of visual processing for food images, as neurons in primary visual cortex respond to more basic features while neurons further along the processing pathway are fine-tuned and respond to more complex features, however more research is necessary to determine the nature of this dissociation and the relationship between increased secondary vision processing/attention activity and weight loss.

Identifying patterns of activity associated with weight loss may point toward targets for future treatment and may assist in identification of individuals susceptible to weight re-gain. Associations observed in exploratory correlations further suggest the possibility that inhibitory control-related activity in response to high calorie foods may be related to greater weight loss. At an uncorrected threshold, greater activity in bilateral anterior cingulate cortex (ACC) was associated with greater percent weight loss from baseline within ILI. ACC has been implicated in a host of executive and cognitive control-related functions such as conflict monitoring, problem solving, and decision-making. It has been posited that the dorsal ACC plays a key role in allocation of control, specifically integrating information about the expected value of exerting control (costs/benefits of using self-control and amounts of control needed)(32). Thus the potential relationship between ACC activity and weight loss may be indicative of cognitive control processing used, or required, by individuals who have lost weight and is consistent with the high levels of restraint typically observed in successful weight loss maintainers.(33) These findings, which suggest there may be a need to continue to actively exercise self-control in response to food for nearly a decade after initial weight loss, have implications for further refining BWL programs. For example, treatment strategies that make it easier to exert self-control long-term are needed. This may be accomplished by further reducing exposure to food cues or providing training in specific self-control skills. It is important to note these post-hoc correlations were exploratory in nature and future research may more directly examine the role of ACC in weight loss. Moreover, although this correlation was conducted only within ILI, it is possible that unintentional weight loss, which has been shown to occur in 15–20% of older adults(34), is likely not supported by the same cognitive mechanisms as intentional weight loss and may be increasingly relevant for both Look AHEAD groups as they continue ageing.

Strengths of this study include the randomized control design, relatively large sample size, use of a simple, commonly employed food cue-reactivity paradigm, and a range of weight loss success between groups. To date this is the largest study of its kind and provides a unique opportunity to investigate neural food cue-reactivity in a large population of older adults with overweight /obesity and type 2 diabetes whose weight and medical history has been well documented for an extended period of time.

Despite these strengths, there are limitations to consider. For instance, fMRI data were not collected at baseline. Thus the current study cannot directly assess prospective changes in food cue-reactivity, however, that participants were randomly assigned to ILI or DSE theoretically mitigates many of the potential confounds of other cross-sectional work. Moreover, the time point at which differences in functional neuroanatomical response to food cues may peak is unknown. The most pronounced weight loss differences between ILI and DSE were observed in the first year, thus it is possible more potent differences in food cue-reactivity may have existed earlier and were not captured here. Alternatively, cumulative years of exposure to the intervention may be a driving mechanism to alter participants' cue-reactivity, in which case the current data may represent a peak in differences.

Another potential limitation is that this study includes a subset of the total Look AHEAD sample willing and eligible to undergo MRI. This may have limited the sample to relatively healthier individuals across both groups compared to the complete sample (e.g., there are no

baseline BMI differences between groups in Look AHEAD however there were differences observed in the current sample, and there are significant weight loss differences in the full sample(35) that were not observed in this subset). Although in previous manuscripts Look AHEAD investigators have reported no overall group differences in cognitive function or rates of cognitive impairment(18, 19, 36), there may be an interaction effect between BMI and intervention on cognitive function. Specifically, among individuals with lower BMI, those in ILI performed better on cognitive function assessments than those in DSE, while among those with higher BMI the opposite pattern was observed(18). Therefore, it is possible that differences in cognitive function may contribute to the results herein. Additionally, structural neuroanatomical differences were identified between ILI and DSE, and it is not known if those differences have any impact on functional responses to food. For instance, it is possible that increased white matter lesion volumes and ventricle volumes observed in DSE relative to ILI may have an effect on vascular components of fMRI as well as cognitive processing of food cues. Moreover, structural differences may give rise to partial volume effects, wherein different types and amounts of tissues (e.g., grey vs. white matter and cerebrospinal fluid) may contribute differentially to observed signal, thus increasing potential for false positive errors. Further research is necessary to explore impacts of partial volume effects and how neuroanatomical differences between ILI and DSE in particular, and ageing brains more generally, may contribute to patterns of functional activation. Another limitation is that weights were not obtained at the scan. Due to potential differences in accuracy of self-reported weight resulting from differences in self-weighing frequency, objectively measured weights from participants' most recent assessments were used. The number of days between these measures was covaried to account for variability.

Although these limitations must be considered, the current study assesses the impact of BWL intervention on how the brain processes food cues in the largest sample to date. Findings from this study suggest there was a legacy effect of participation in the BWL intervention that led to reduced reward-related activity and enhanced attention/visual processing in response to high calorie food cues. Correlations between weight loss and brain activity in executive function as well as attention processing areas highlight key regions of the brain and neural processes that may be implicated in long-term weight loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Clinical Sites

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DATA SHARING

De-identified MRI and cognitive data, extensive other data from the Look AHEAD trial, and full documentation will be publicly available at the NIDDK Data Repository (https://repository.niddk.nih.gov/home/).

These de-identified data are for general use. Information on how to request these data appears on the Repository website.

Considerable data from the Look AHEAD trial are currently available. Cognitive data will be available later in 2018. MRI data will be made available in 2019.

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What is already known about this subject?

- Patterns of brain activity in response to food cues differ between individuals with obesity and those with healthy BMI.
- Individuals with obesity typically exhibit enhanced reward-related neural activity in response to food cues.
- Individuals who have successfully maintained weight loss exhibit increased control-related activity in response to food cues.

What does this study add?

- The current study assesses the impact of a behavioral weight loss intervention oh how the brain processes food cues in a large sample of individuals.
- Group comparisons revealed individuals in the intervention exhibited relatively greater activity in attention/visual processing regions and relatively less reward-related brain activity, and both within the intervention group and the entire sample as a whole, greater weight loss was associated with greater activity in regions associated with cognitive control and attention/visual processing.
- These findings are significant as they the suggest there may be legacy effects of participation in a behavioral weight loss intervention that led to reduced reward-related activity and enhanced attention/visual processing in response to high-calorie foods and correlations highlight key regions of the brain and neural processes that may be implicated in long-term weight loss.

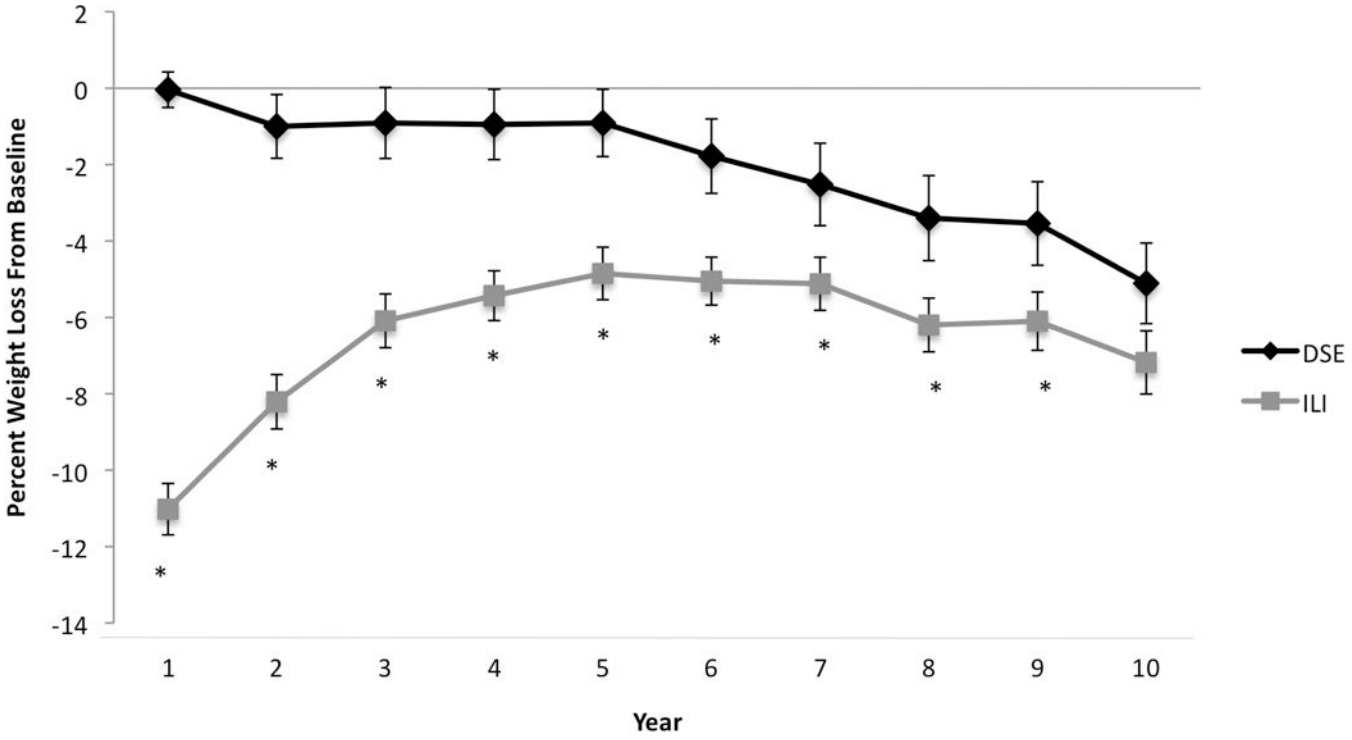

Fig. 1.

Mean percent weight loss from baseline for each year by group (ILI vs. DSE). Error bars represent standard error of the mean. Asterisk (*) denotes significant difference ($p < 0.05$) in weight loss between groups (year 10 $p = 0.1$).

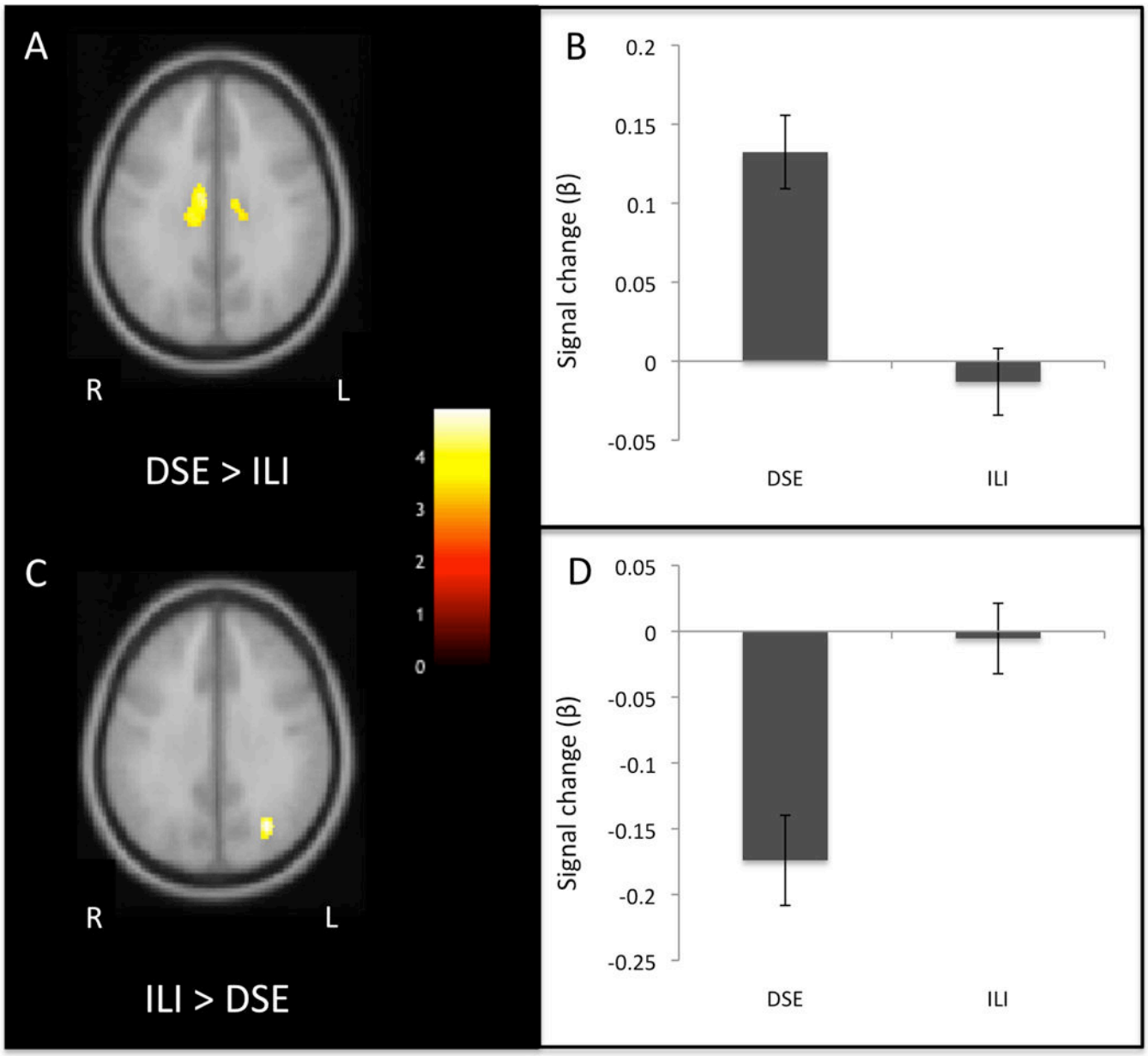

Fig. 2.

Statistical maps representing differences between groups in response to high-calorie food cues compared to neutral images. A whole-brain voxel-wise independent samples t-test revealed greater activation for DSE relative to ILI in regions of caudate (A) and greater activation for ILI relative to DSE in angular gyrus (C). For visualization purposes bar graphs display mean Beta weights for each group in the caudate (B) and angular gyrus (D). Error bars represent standard error of the mean.

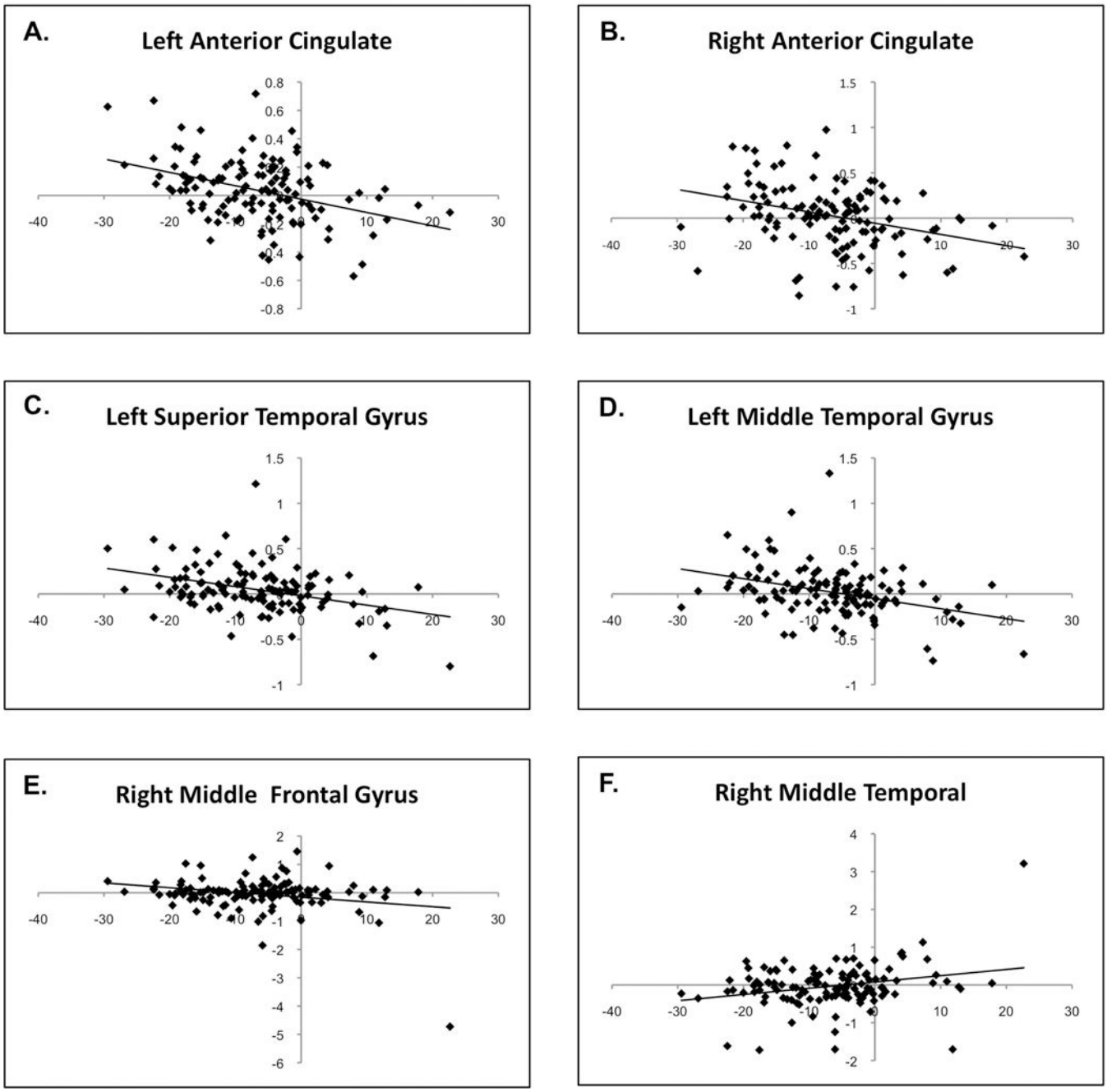

Fig. 3.

For visualization purposes, scatterplots depicting the relationship between food cue-reactivity and percent weight loss in each of the areas noted in Table 3 are displayed. Regions in which greater activity is associated with greater percent weight loss are presented (A, B, C, D, and E) and the one region in which greater activity is associated with less weight loss is plotted (F). The strength of the association between percent weight loss and activity in right middle frontal gyrus (E) and right middle temporal lobe (F) is attenuated when a potential outlier is removed.

Table 1.

Participant Demographics

	DSE (n=107)	ILI (n=125)	*p-value*
Female, *n (%)*	77 (71.96)	80 (64.0)	0.16
Baseline Age (years)	57.80 (6.2)	58.39 (6.9)	0.5
Ethnicity, *n (%)*			0.21
African American (Non-Hispanic)	24 (22.43)	25 (20)	
American Indian/Alaskan Native	0 (0)	2 (1.6)	
Asian/Pacific Islander	0 (0)	2 (1.6)	
Non-Hispanic White	77 (71.96)	94 (75.2)	
Hispanic/Latino	2 (1.87)	2 (1.6)	
Education, *n (%)*			0.44
High school degree or less	12 (11.21)	23 (18.4)	
Post high school	44 (41.12)	41 (32.8)	
College graduate or more	46 (42.99)	58 (46.4)	
CVD history at baseline, *n (%)*	10 (9.35)	7 (5.6)	0.32
Diabetes duration at baseline (years)	6.18 (5.69)	6.87 (7.44)	0.44
Baseline BMI (kg/m^2)	36.03 (5.06)	34.54 (5.43)	0.03*
Years in study at time of scan	10.38 (0.48)	10.35 (0.46)	0.63
Percent (%) Weight Loss from baseline to time of scan	4.90 (10.01)	6.79 (9.14)	0.14

Values presented are Mean (SD) unless otherwise noted.

Table 2.

Whole brain voxel-wise t-Test

	Brodmann Area	Peak Coordinates (x y z)	Cluster k	FDR-corrected cluster q value
DSE > ILI				
R Caudate	---	8, 2, 26	325	0.0001
R Cingulate	24	8,−10,30	---	---
R Caudate	---	−14, −18, 30	---	---
ILI > DSE				
L Angular Gyrus	39	−30, −66, 32	186	0.0001
L Middle Temporal	39	−40, −74, 16	---	
L Superior Occipital	19	−32, −76, 20	---	

Table 3.

Post-hoc Secondary whole brain voxel-wise correlations with percent weight loss from baseline to time of scan among ILI participants

	Brodmann Area	Peak Coordinates (x y z)	Cluster k	FDR-corrected cluster q value	Uncorrected cluster p value
Regions significantly associated with greater weight loss					
L Anterior Cingulate	25	−4, 14, −6	83	0.21	0.006
R Anterior Cingulate/Medial Frontal Gyrus	25	4, 30, −20	46	0.46	0.03
L SuperiorTemporal G	41	−52, −34, 8	40	0.52	0.04
L Middle Temporal Gyrus	19	−42, −64, 14	86	0.23	0.005
R Middle Frontal Gyrus	46	64, 26, 26	52	0.42	0.02
Regions significantly associated with less weight loss					
R Middle Temporal	21	70, −2, −12	40	0.3	0.04