OBESITY SOCIETY

obesityweek℠ 2019 Vegas

LAS VEGAS, NV | NOVEMBER 3-7

Join TOS in Vegas

Come to the 37th Annual Meeting of The Obesity Society

Save the date Nov. 3 -7

WHAT:

TOS Annual Meeting at ObesityWeek™ 2019

WHEN:

November 3-7

WHERE:

Mandalay Bay Resort and Casino

Las Vegas, Nevada

- TOS 37th Annual Meeting includes sessions for all TOS committees and sections
- ObesityWeek features more than 4,000 attendees from 40+ countries
- Learn about scientific breakthroughs first hand from world-renowned experts
- Have vital interactions, make essential connections

Join TOS and get special discounts on your registration!

For more information call (301) 563-6526 or visit **https://obesityweek.com/**

Submit abstracts at **https://obesityweek.com/abstract-information/**

OBESITY SOCIETY

Research. Education. Action.

www.obesity.org

CONNECT WITH TOS

Impact of Intensive Lifestyle Intervention on Neural Food Cue Reactivity: Action for Health in Diabetes Brain Ancillary Study

Kathryn Demos McDermott [1], Samantha E. Williams[1,2], Mark A. Espeland[3], Kirk Erickson[4], Rebecca Neiberg[2], Thomas A. Wadden [5], R. Nick Bryan[5], Lisa Desiderio[5], Regina L. Leckie[4,6], Lucy H. Falconbridge [5], John M. Jakicic [7], Miguel Alonso-Alonso[8], and Rena R. Wing [1], for the Action for Health in Diabetes Brain Magnetic Resonance Imaging (Look AHEAD Brain) Ancillary Study Research Group

Objective: The Action for Health in Diabetes (Look AHEAD) research study was a randomized trial comparing the effects of an intensive lifestyle intervention (ILI) versus a diabetes support and education (DSE) control group in adults with type 2 diabetes and overweight or obesity. Functional magnetic resonance imaging was used to determine whether neural food cue reactivity differed for these groups 10 years after randomization.

Methods: A total of 232 participants (ILI, $n = 125$, 72% female; DSE, $n = 107$, 64% female) were recruited at three of the Look AHEAD sites for functional magnetic resonance imaging. Neural response to high-calorie foods compared with nonfoods was assessed in DSE versus ILI. Exploratory correlations were conducted within ILI to identify regions in which activity was associated with degree of weight loss.

Results: Voxel-wise whole-brain comparisons revealed greater reward-processing activity in left caudate for DSE compared with ILI and greater activity in attention- and visual-processing regions for ILI than DSE ($P < 0.05$, family-wise error corrected). Exploratory analyses revealed that greater weight loss among ILI participants from baseline was associated with brain activation indicative of increased cognitive control and attention and visual processing 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 or visual processing in response to high-calorie foods.

Obesity (2019) **27**, 1076-1084. doi:10.1002/oby.22496

[1] Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, The Miriam Hospital/Weight Control and Diabetes Research Center, Providence, Rhode Island, USA. Correspondence: Kathryn E. Demos McDermott (kathryn_demos@brown.edu) [2] Department of Psychology, Saint Louis University, St. Louis, Missouri, USA [3] Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA [4] Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA [5] Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA [6] Department of Psychology, Carnegie Mellon University, Pittsburgh, Pennsylvania, USA [7] Department of Health and Physical Activity, University of Pittsburgh, Pittsburgh, Pennsylvania, USA [8] Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.

Funding agencies: This ancillary study is supported by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH), Department of Health and Human Services (DK092237-01 and DK092237-02S2). Action for Health in Diabetes (Look AHEAD) is supported through the following cooperative agreements from NIH: DK57136, DK57149, DK56990, DK57177, DK57171, DK57151, DK57182, DK57131, DK57002, DK57078, DK57154, DK57178, DK57219, DK57008, DK57135, and DK56992. The following federal agencies have contributed support: National Institute of Diabetes and Digestive and Kidney Diseases; National Heart, Lung, and Blood Institute; National Institute of Nursing Research; National Institute on Minority Health and Health Disparities; Office of Research on Women's Health; the Centers for Disease Control and Prevention; and the Department of Veterans Affairs. This research was supported in part by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases. The Indian Health Service (IHS) provided personnel, medical oversight, and use of facilities. The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the IHS or other funding sources. Additional support was received from the University of Pittsburgh General Clinical Research Center (M01RR000056); the Clinical Translational Research Center funded by the Clinical and Translational Science Award (UL1 RR 024153) and NIH grant (DK 046204); and the Frederic C. Bartter General Clinical Research Center (M01RR01346). The following organizations have committed to make major contributions to Look AHEAD: FedEx Corporation; Health Management Resources; LifeScan, Inc., a Johnson & Johnson Company; OPTIFAST of Nestle HealthCare Nutrition, Inc.; Hoffmann-La Roche, Inc.; Abbott Nutrition; and Slim-Fast Brand of Unilever North America.

Disclosure: The authors declared no conflicts of interest.

Clinical trial registration: ClinicalTrials.gov identifier NCT00017953.

Additional Supporting Information may be found in the online version of this article.

Received: 26 July 2018; **Accepted:** 6 March 2019; **Published online 21 May 2019. doi:10.1002/oby.22496**

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 (1-6), and decreased activity in regions involved in cognitive control or inhibition, such as the 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 whether 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 and obesity.

Successful weight loss maintainers who kept weight off for at least 1 year exhibited increased activity in the superior frontal cortex, a control-related region, relative to both individuals with lifetime normal weight 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 that 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 had 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 Action for Health in Diabetes (Look AHEAD) study and the Look AHEAD Brain Magnetic Resonance Imaging (Look AHEAD Brain) 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 with 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 several outcomes.

In the Look AHEAD Brain Ancillary Study, participants from three of the Look AHEAD centers (Brown University [Providence, Rhode Island], University of Pennsylvania [Philadelphia], 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 (17-20). 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 previously reported, compared with 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 was 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; Pittsburgh, *n* = 100; Providence, *n* = 85), and data from 242 participants met standard motion artifact criteria (Philadelphia, *n* = 97; Pittsburgh, *n* = 75; Providence, *n* = 70). Of these 242, 10 participants were excluded because of bariatric surgery; thus, 232 participants were included in the current sample (Philadelphia, *n* = 93; Pittsburgh, *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 previously published (21,22). In brief, ILI participants were assigned calorie, fat gram, and physical activity goals designed to produce 10% weight loss. Further details are available in the online Supporting Information.

MRI parameters

Details of the structural MRI parameters have been previously published (20), and further detail is available within the online Supporting Information. Scanning and assessment procedures were standardized across the three sites. All MRI scans were conducted on Siemens 3-Tesla scanners (Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania) utilizing the same software platform and 32-channel head coils. Quality assurance protocols using MRI phantoms to regularly assess scanner performance in multisite studies were employed before and throughout this study across the three sites. In addition to structural anatomical scans, the imaging protocol included one run of food cue reactivity. For this food cue paradigm, a total of 204 functional images were acquired using a gradient-echo echo-planar sequence (repetition time [TR] = 2,000 milliseconds; echo time [TE] = 30 milliseconds; flip angle = 90°; 40 axial slices, 3 × 3 × 3 mm voxel size). Padding was placed around each participant's head to minimize motion during scanning. Visual stimuli were presented via E-prime version 2.0 software (Psychology Software Tools, Inc., Sharpsburg, Pennsylvania) 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 was adapted from work by Killgore et al. (9,23) and was 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 nonfood images (e.g., furniture, flowers) were presented pseudorandomly 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 4-point scale (very low to 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 or cross hair 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 (SPM version 8; Wellcome Trust Centre for Neuroimaging, University College London, UK) and a suite of processing scripts developed by researchers at Dartmouth College (GitHub, San Francisco, California, http://github.com/ddwagner/SPM8w). This processing was centralized at the Providence site (more details available in online Supporting Information).

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 nonfoods), as well as covariates of noninterest (e.g., ratings trials, six motion parameters derived from realignment corrections, linear trend). Fixation periods were not explicitly specified in the model and constitute the baseline for comparison. Models were convolved with the SPM8 canonical hemodynamic response function and were then used to generate contrast images comparing task conditions (e.g., high-calorie vs. nonfood images).

A whole-brain voxel-wise random effects analysis was conducted for all participants, comparing activation during presentation of high-calorie foods versus fixation baseline to neutral nonfood items versus baseline (high-calorie > nonfood), thresholded with a family-wise error rate of $P > 0.05$ ($k = 10$). To directly identify any regions showing differential response for ILI versus DSE, a voxel-wise independent samples *t* test was conducted using cluster-wise false discovery rate 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 foods versus nonfoods, other contrasts were analyzed and presented in the online Supporting Information. 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). Montreal Neurological Institute (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 substudy 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, cardiovascular disease history at baseline, or duration of diabetes (all Ps > 0.1). There was, however, a significant difference in baseline BMI between the two groups in this substudy (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 Ps < 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%; $P = 0.11$).

TABLE 1 Participant demographics

	DSE (*n* = 107)	ILI (*n* = 125)	*P* value
Female, *n* (%)	77 (71.96)	80 (64.00)	0.16
Baseline age (y)	57.80 (6.2)	58.39 (6.9)	0.5
Ethnicity, *n* (%)			0.21
African American (non-Hispanic)	24 (22.43)	25 (20.00)	
American Indian/Alaska Native	0 (0)	2 (1.60)	
Asian/Pacific Islander	0 (0)	2 (1.60)	
Non-Hispanic white	77 (71.96)	94 (75.20)	
Hispanic/Latino	2 (1.87)	2 (1.60)	
Education, *n* (%)			0.44
High school degree or less	12 (11.21)	23 (18.40)	
Post high school	44 (41.12)	41 (32.80)	
College graduate or more	46 (42.99)	58 (46.40)	
CVD history at baseline, *n* (%)	10 (9.35)	7 (5.60)	0.32
Diabetes duration at baseline (y)	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.

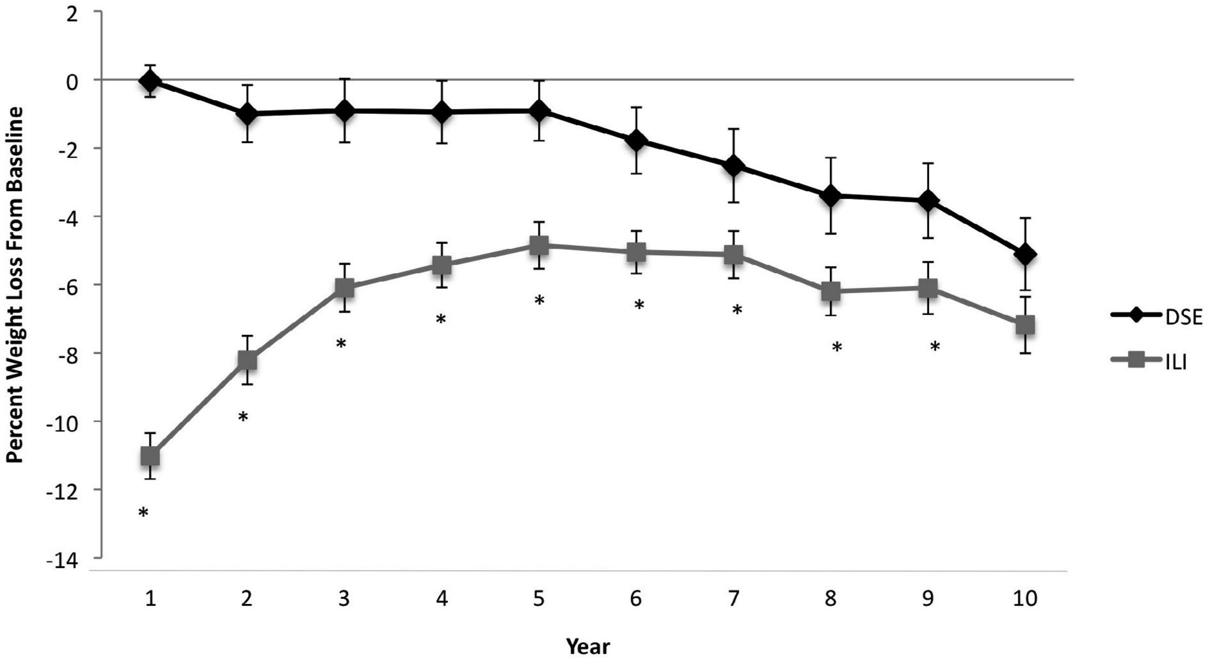

Figure 1 Mean percent weight loss from baseline for each year by group (ILI vs. DSE). Error bars represent SEM. *Significant difference ($P<0.05$) in weight loss between groups (year 10; $P=0.1$).

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 hours, ILI = 3.9 ± 3.5 hours; $P=0.61$).

fMRI results

Comparison of ILI versus DSE. A whole-brain *t* test revealed a region of the right caudate (*x*, *y*, *z* coordinates = 8, 2, 26), extending into cingulate, that was more responsive to high-calorie food > fixation baseline (compared with nonfood > fixation baseline) in DSE versus 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 the left middle temporal and superior occipital cortices relative to DSE (Table 2, Figure 2; other contrasts in online Supporting Information).

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 false discovery rate–corrected values < 0.5, are listed in Table 3 (Figure 3 provides a visualization). Food cue responsivity in bilateral anterior cingulate and medial frontal gyrus was positively correlated with percent of body weight lost, 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 the 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 the right middle temporal lobe (BA 21) was identified. The association between weight loss and cue reactivity was attenuated in the right frontal gyrus and right middle temporal lobe with removal of a potential outlier.

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	–	

L, left; R, right; FDR, false discovery rate.

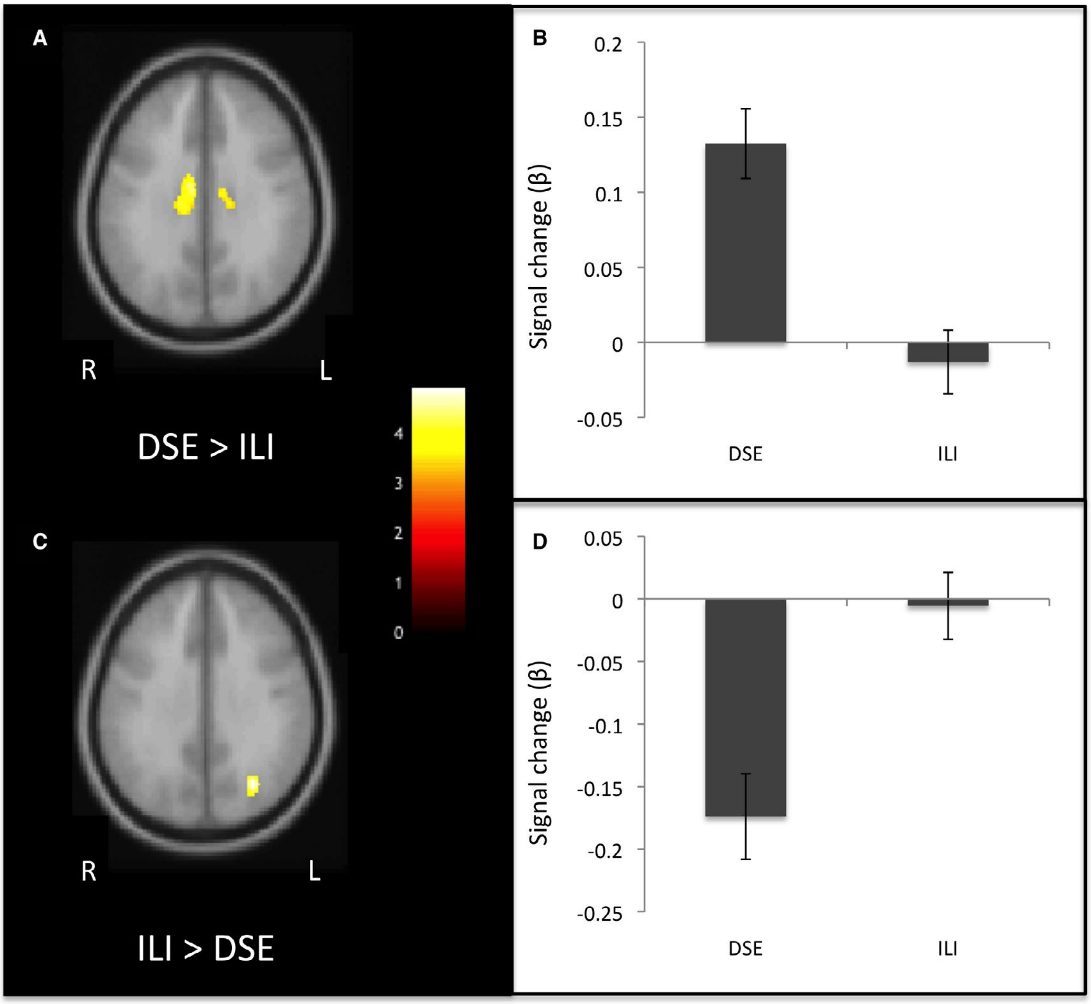

Figure 2 Statistical maps representing differences between groups in response to high-calorie food cues compared with neutral images. Whole-brain, voxel-wise, independent samples *t* test revealed (**A**) greater activation for DSE relative to ILI in regions of caudate (with mean beta weights for each group displayed for visualization purposes in panel B), and (**C**) greater activation for ILI relative to DSE in angular gyrus. Error bars represent SEM. [Colour figure can be viewed at wileyonlinelibrary.com]

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*
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 superior temporal gyrus	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

L, left; R, right; FDR, false discovery rate.

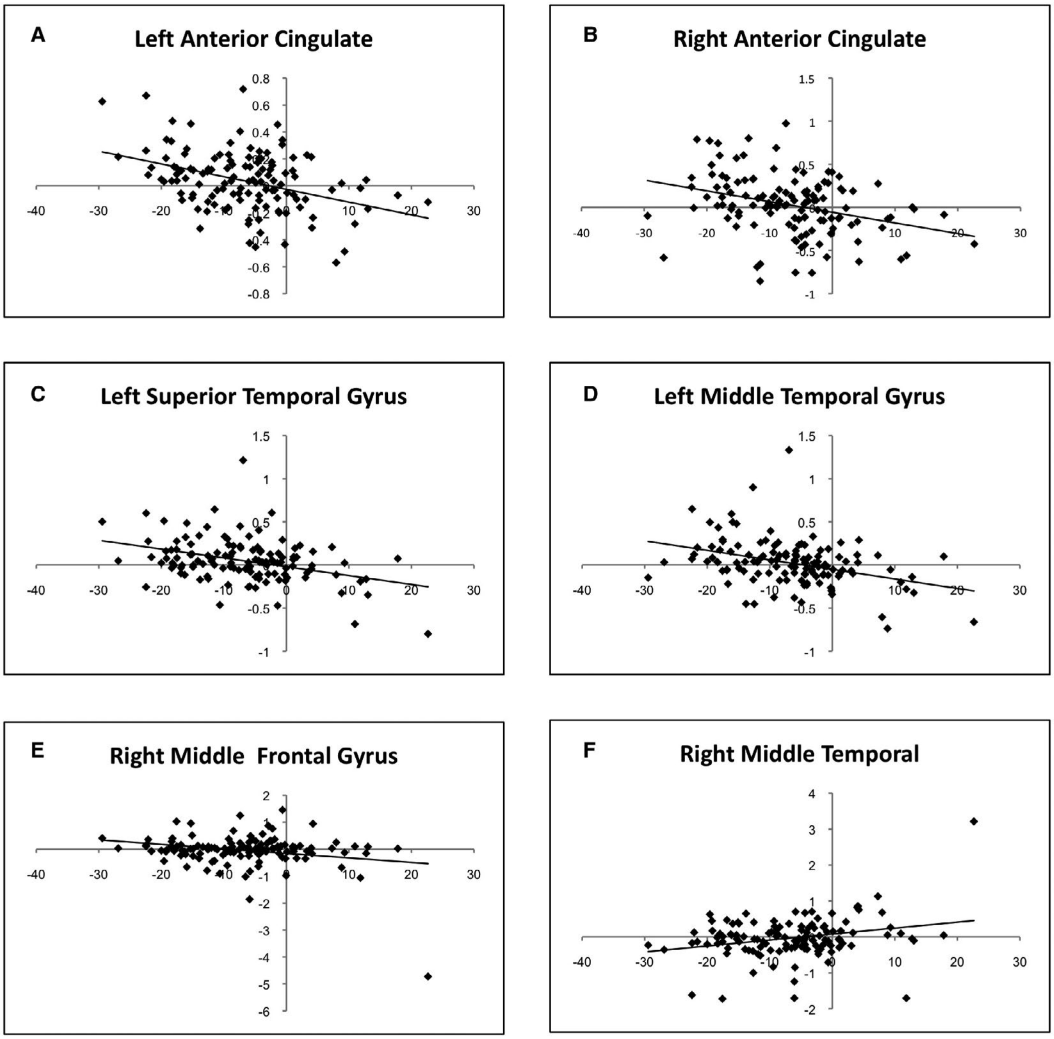

Figure 3 For visualization purposes, scatterplots depicting the relationship between food cue reactivity and percent weight loss in each of the areas noted in Table 3 are displayed. (**A-E**) Regions in which greater activity was associated with greater percent weight loss, and (**F**) the one region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

Across the entire sample (ILI and DSE), similar regions of the anterior cingulate cortex (ACC) and the left middle temporal gyrus were associated with greater weight loss; however, the association with the right middle frontal gyrus did not reach statistical significance. Activity in the 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 ILI or a DSE control group. At the time of this assessment, the ILI group had a mean weight loss of 7.1 kg from baseline versus 6.2 kg in DSE. A whole-brain analysis of responses to high-calorie food cues compared with nonfood images revealed DSE had greater activity than ILI in the right caudate and right cingulate. By contrast, ILI exhibited greater activity in the left angular gyrus and middle temporal cortex, extending into the occipital cortex. Although limited by the lack of baseline data on cue reactivity, these unique patterns of brain activity for ILI versus DSE suggest that responses to high-calorie food cues differ for individuals who participated in a BWL intervention compared with those who did not, and they may help to identify the mechanisms through which BWL treatment can impact how individuals process food cues in the environment and ultimately eating behavior.

The observation of relatively greater activity in the caudate for those in DSE relative to those in ILI suggests greater reward-related processing of high-calorie food cues in DSE versus 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 that individuals with obesity exhibit even greater reward-related food cue reactivity in the dorsal striatum than individuals with normal weight (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 and 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, the ILI group exhibited greater food cue responsivity in regions involved in attention and visual processing. Previous studies have indicated the occipital cortex of individuals with normal weight is more active when viewing food pictures compared with nonfood pictures (23,27), especially high-calorie foods (28), suggesting visual sensory information for food cues is processed differently than nonfood items. Moreover, this response was attenuated after eating a meal (28). Studies have also shown differing responsivity in visual- and attention-processing regions in individuals with obesity compared with those with normal weight (4,9,29). Successful weight loss maintainers exhibited greater visual- and attention-related activity compared with both individuals with obesity and lifetime normal weight participants (9). Other work employing a food-based Stroop task, which measures response inhibition toward 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- and 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 participated in a BWL intervention. This is additionally supported by the correlation observed between percent weight loss and activity in similar attention- and visual-processing areas.

Interestingly, a dissociation was observed between different visual-processing areas (i.e., secondary visual processing or attention vs. primary visual cortex). While activity in left secondary visual-processing and attention-related regions was greater in ILI versus DSE, and also greater in individuals who had lost more weight in ILI, activity in the 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 the 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 and 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 regain. 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 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 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% to 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 aging.

Strengths of this study include the randomized controlled 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 or obesity and type 2 diabetes, whose weight and medical history have 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; therefore, it is possible that 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 with the complete sample (e.g., there were no baseline BMI differences between groups in Look AHEAD; however, there were differences observed in the current sample, and there were significant weight loss differences in the full sample that were not observed in this subset) (35). 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 whether 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., gray vs. white matter, cerebrospinal fluid) may contribute differentially to the 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 aging brains more generally, may contribute to patterns of functional activation. Another limitation is that weights were not obtained at the scan. Because of 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 assessed 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 and 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.O

Acknowledgments

Clinical Sites, **University of Pennsylvania:** Thomas A. Wadden[1]; Barbara J. Maschak-Carey[2]; Robert I. Berkowitz[3]; Bernadette Bailey; Yuliis Bell; Norman Butler; Raymond Carvajal; Christos Davatzikos; Renee Davenport; Lisa Diewald; Mark Elliott; Lucy Faulconbridge; Barry Fields; Krista Huff; Mary Jones-Parker; Brendan Keenan; Sharon Leonard; Qing-Yun Li; Katelyn Reilly; Kelly Sexton; Bethany Staley; Matthew Voluck. **University of Pittsburgh:** John M. Jakicic, PhD[1], Jacqueline Wesche-Thobaben[2]; Kirk Erickson[3]; Andrea Hergenroeder[3]; Scott Kurdilla; Regina L. Leckie; Juliet Mancino; Meghan McGuire; Tracey Murray; Anna Peluso; Deborah Viszlay; Jen C. Watt. **The Miriam Hospital/Alpert Medical School of Brown University, Providence, Rhode Island:** Rena R. Wing[1]; Caitlin Egan[2]; Kathryn Demos[3]; Kirsten Annis; Ryan Busha; Casie Damore; Causey Dunlap; Lynn Fanella; Lucas First; Michelle Fisher, R.N.; Stephen Godbout; Anne Goldring; Ariana LaBossiere. **MRI Reading Center:** Nick Bryan[1]; Lisa Desiderio[2]; Christos Davatzikos; Guray Erus; Meng-Kang Hsieh; Ilya Nasrallah. **Coordinating Center, Wake Forest School of Medicine:** Mark A. Espeland[1]; Judy Bahnson[2]; Ramon Cassanova[3]; Satoru Hayasaka[3]; Denise Houston[3]; Paul Laurienti[3]; Robert Lyday[3]; Jerry M. Barnes; Tara D. Beckner; Delilah Cook; Michelle Gordon; Debra Hege; Amelia Hodges; Patricia Hogan; Ashley Morgan; Rebecca H. Neiberg; Ginger Pate; Jennifer Walker.

1. Principal Investigator

2. Program Coordinator

3. Coinvestigator

All other staff listed alphabetically by site.

Deidentified 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 deidentified 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.

© 2019 The Obesity Society

References

1. Bruce AS, Holsen LM, Chambers RJ, et al. Obese children show hyperactivation to food pictures in brain networks linked to motivation, reward and cognitive control. *Int J Obes (Lond)* 2010;34:1494-1500.
2. Dimitropoulos A, Tkach J, Ho A, Kennedy J. Greater corticolimbic activation to high-calorie food cues after eating in obese vs. normal-weight adults. *Appetite* 2012;58:303-312.
3. Grosshans M, Vollmert C, Vollstadt-Klein S, et al. Association of leptin with food cue-induced activation in human reward pathways. *Arch Gen Psychiatry* 2012;69:529-537.
4. Rothemund Y, Preuschhof C, Bohner G, et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage* 2007;37:410-421.
5. Scharmuller W, Ubel S, Ebner F, Schienle A. Appetite regulation during food cue exposure: a comparison of normal-weight and obese women. *Neurosci Lett* 2012;518:106-110.
6. Stoeckel LE, Weller RE, Cook EW 3rd, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage* 2008;41:636-647.
7. Nummenmaa L, Hirvonen J, Hannukainen JC, et al. Dorsal striatum and its limbic connectivity mediate abnormal anticipatory reward processing in obesity. *PLoS One* 2012;7:e31089. doi:10.1371/journal.pone.0031089
8. Batterink L, Yokum S, Stice E. Body mass correlates inversely with inhibitory control in response to food among adolescent girls: an fMRI study. *Neuroimage* 2010;52:1696-1703.
9. McCaffery JM, Haley AP, Sweet LH, et al. Differential functional magnetic resonance imaging response to food pictures in successful weight-loss maintainers relative to normal-weight and obese controls. *Am J Clin Nutr* 2009;90:928-934.
10. Deckersbach T, Das SK, Urban LE, et al. Pilot randomized trial demonstrating reversal of obesity-related abnormalities in reward system responsivity to food cues with a behavioral intervention. *Nutr Diabetes* 2014;4:e129. doi:10.1038/nutd.2014.26
11. Murdaugh DL, Cox JE, Cook EW 3rd, Weller RE. fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. *Neuroimage* 2012;59:2709-2721.
12. Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J Clin Invest* 2008;118:2583-2591.
13. Chechlacz M, Rotshtein P, Klamer S, et al. Diabetes dietary management alters responses to food pictures in brain regions associated with motivation and emotion: a functional magnetic resonance imaging study. *Diabetologia* 2009;52:524-533.
14. Farr OM, Mantzoros CS. Obese individuals with more components of the metabolic syndrome and/or prediabetes demonstrate decreased activation of reward-related brain centers in response to food cues in both the fed and fasting states: a preliminary fMRI study. *Int J Obes (Lond)* 2017;41:471-474.
15. Farr OM, Mantzoros CS. Obese individuals with type 2 diabetes demonstrate decreased activation of the salience-related insula and increased activation of the emotion/salience-related amygdala to visual food cues compared to non-obese individuals with diabetes: a preliminary study. *Diabetes Obes Metab* 2018;20:2500-2503.
16. Look AHEAD Research Group; Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145-154.
17. Casanova R, Hayasaka S, Saldana S, et al. Relative differences in resting-state brain connectivity associated with long term intensive lifestyle intervention. *Psychoneuroendocrinology* 2016;74:231-239.
18. Espeland MA, Luchsinger JA, Baker LD, et al. Effect of a long-term intensive lifestyle intervention on prevalence of cognitive impairment. *Neurology* 2017;88:2026-2035.
19. Rapp SR, Luchsinger JA, Baker LD, et al. Effect of a long-term intensive lifestyle intervention on cognitive function: Action for Health in Diabetes Study. *J Am Geriatr Soc* 2017;65:966-972.
20. Espeland MA, Erickson K, Neiberg RH, et al. Brain and white matter hyperintensity volumes after 10 years of random assignment to lifestyle intervention. *Diabetes Care* 2016;39:764-771.
21. Look AHEAD Research Group. The development and description of the comparison group in the Look AHEAD trial. *Clin Trials* 2011;8:320-329.
22. Look AHEAD Research Group; Wadden TA, West DS, Delahanty L, et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)* 2006;14:737-752.

23. Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Cortical and limbic activation during viewing of high- versus low-calorie foods. *Neuroimage* 2003;19:1381-1394.
24. Delgado MR. Reward-related responses in the human striatum. *Ann N Y Acad Sci* 2007;1104:70-88.
25. Volkow ND, Wang GJ, Fowler JS, et al. "Nonhedonic" food motivation in humans involves dopamine in the dorsal striatum and methylphenidate amplifies this effect. *Synapse* 2002;44:175-180.
26. Roland PE. Organization of motor control by the normal human brain. *Hum Neurobiol* 1984;2:205-216.
27. van der Laan LN, de Ridder DT, Viergever MA, Smeets PA. The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues. *Neuroimage* 2011;55:296-303.
28. Cornier MA, Von Kaenel SS, Bessesen DH, Tregellas JR. Effects of overfeeding on the neuronal response to visual food cues. *Am J Clin Nutr* 2007;86:965-971.
29. Cornier MA, Salzberg AK, Endly DC, Bessesen DH, Rojas DC, Tregellas JR. The effects of overfeeding on the neuronal response to visual food cues in thin and reduced-obese individuals. *PLoS One* 2009;4:e6310. doi:10.1371/journal.pone.0006310
30. Phelan S, Hassenstab J, McCaffery JM, et al. Cognitive interference from food cues in weight loss maintainers, normal weight, and obese individuals. *Obesity (Silver Spring)* 2011;19:69-73.
31. Demos KE, McCaffery JM, Cournoyer SA, Wunsch CA, Wing RR. Greater food-related Stroop interference following behavioral weight loss intervention. *J Obes Weight Loss Ther* 2013;3:187. doi:10.4172/2165-7904.1000187
32. Shenhav A, Botvinick MM, Cohen JD. The expected value of control: an integrative theory of anterior cingulate cortex function. *Neuron* 2013;79:217-240.
33. Phelan S, Liu T, Gorin A, et al. What distinguishes weight-loss maintainers from the treatment-seeking obese? Analysis of environmental, behavioral, and psychosocial variables in diverse populations. *Ann Behav Med* 2009;38:94-104.
34. McMinn J, Steel C, Bowman A. Investigation and management of unintentional weight loss in older adults. *BMJ* 2011;342:d1732. doi:10.1136/bmj.d1732
35. Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study. *Obesity (Silver Spring)* 2014;22:5-13.
36. Hayden KM, Baker LD, Bray G, et al. Long-term impact of intensive lifestyle intervention on cognitive function assessed with the National Institutes of Health Toolbox: the Look AHEAD study. *Alzheimers Dement (Amst)* 2018;10:41-48.