


ORIGINAL ARTICLE

Obesity Biology and Integrated Physiology

Longitudinal relationship of baseline functional brain networks with intentional weight loss in older adults

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Abstract

Objective: The goal of this study was to determine whether the degree of weight loss after 6 months of a behavior-based intervention is related to baseline connectivity within two functional networks (FNs) of interest, FN1 and FN2, in a group of older adults with obesity.

Methods: Baseline functional magnetic resonance imaging data were collected following an overnight fast in 71 older adults with obesity involved in a weight-loss intervention. Functional brain networks in a resting state and during a food-cue task were analyzed using a mixed-regression framework to examine the relationships between baseline networks and 6-month change in weight.

Results: During the resting condition, the relationship of baseline brain functional connectivity and network clustering in FN1, which includes the visual cortex and sensorimotor areas, was significantly associated with 6-month weight loss. During the food-cue condition, 6-month weight loss was significantly associated with the relationship between baseline brain connectivity and network global efficiency in FN2, which includes executive control, attention, and limbic regions.

Conclusion: These findings provide further insight into complex functional circuits in the brain related to successful weight loss and may ultimately aid in developing tailored behavior-based treatment regimens that target specific brain circuitry.

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INTRODUCTION

The US population aged 65 years and older was 54.1 million in 2019 and is projected to reach 94.7 million by 2060 (1). Of concern is that, in 2018, the prevalence of obesity was 40.2%, a figure that varied little as a function of age (2). Given the vulnerability of older adults to chronic disease and physical disability, coupled with the increasing risk that obesity poses to healthy aging (3), there is an urgent need to increase our understanding of success with weight-loss interventions.

As noted in a 2016 review (4), most obesity-related studies in neuroscience have been cross-sectional, examining specific brain regions of interest (ROIs). This approach is limited by the use of static group designs and the fact that eating behavior involves communication between multiple ROIs (5). In reviewing evidence for the dynamic vulnerability theory of obesity (4), Stice and colleagues identified incentive sensitization and reward valuation as key processes in food choice and overeating. Donofry and colleagues echoed this position, with emphasis on a third process: executive function (5). A limitation of this research is that the bulk of evidence reviewed has not involved weight loss, and very few studies have involved older adults. The lack of attention on aging is a critical gap because, within the field of network science, a consistent observation has been that there is a decrease in the functional connectivity of brain networks with aging (6,7).

The current study addresses these shortcomings by collecting baseline functional magnetic resonance imaging (fMRI) data on a subset of older adults with obesity within a randomized clinical trial (NCT02923674) that involved 6 months of intensive weight loss (8). In a previous predictive study (9), the top two functional networks (FNs), FN1 and FN2, that explained variance in weight loss at 18 months captured communication between key brain regions important in reward valuation, incentive sensitization, and executive function. This original discovery of these networks did not examine features such as connectivity strength or network topology. Here, we evaluated the generalizability of these two networks to a completely unique sample, hypothesizing that FN1 and FN2 would exhibit significant relationships in their brain network connectivity and topology during both the resting state and task-evoked imagery of food cues with 6-month weight loss.

METHODS

Participants

A sample ($n = 71$) of older adults with obesity were recruited from a weight-regain study, Empowered with Movement to Prevent Obesity and Weight Regain (EMPOWER; ClinicalTrials.gov identifier: NCT02923674) (8). All eligible and willing participants without contraindications for an MRI scan completed an in-person screening visit and a 45-minute MRI scan after an overnight fast. MRI data were collected at baseline before participants initiated treatment. Of

Study Importance

What is already known?

- ▶ Obesity is associated with deleterious health effects in older adults.
- ▶ There is evidence that functional brain networks are important in weight loss.

What does this study add?

- ▶ In a sample of older adults with obesity undergoing a weight-loss intervention, we found significant relationships between amount of weight loss and topology within two previously discovered brain circuits.
- ▶ In the resting state, significant relationships between weight loss and network topology were observed within a set of brain regions that include the visual cortex and sensorimotor processing areas.
- ▶ During a food-cue condition, significant network topological relationships with weight loss existed in a different set of brain regions that include areas of the attention network and limbic circuitry.

How might these results change the direction of research or the focus of clinical practice?

- ▶ Two distinct brain network biases are related to the degree of success with weight loss: within the resting state, there is a sensorimotor motivational bias to pursue food, whereas, when processing food cues, there is a deficit in the executive control/attention network.
- ▶ These findings support interventions that directly counter these nonconscious brain network biases, such as implementation intentions coupled with mindfulness-based training and daily weigh-ins coupled with adaptive, personalized treatment.

the 71 participants who consented, 4 participants were removed because of excessive head motion, and 4 were removed owing to lack of 6-month weight-loss data. Therefore, the final sample included 63 participants. This study protocol was approved by the Wake Forest School of Medicine Institutional Review Board.

Overview of the EMPOWER study

Inclusionary criteria for EMPOWER included the following: age = 65 to 85 years; BMI = 35 to 45 kg/m²; and low activity, defined as <20 min/d of exercise (8). Participants were excluded if they had evidence of cognitive impairment (10). See Fanning and colleagues (8) for detailed descriptions of the methods.

Procedure for the MRI ancillary study

Initial in-person visit

Documented consent was obtained for this ancillary study, and MRI compatibility information was gathered. Participants also named their four favorite foods for use in the MRI scanning protocol.

MRI scanning visit: resting and food-cue states

Participants arrived in the morning after at least 8 hours of fasting. The MRI scan session included two conditions: resting state and a food-cue visualization task. During the resting state, participants were instructed to keep their eyes open and focus on an on-screen fixation cross for 6 minutes. During the food-cue visualization task, participants viewed the words of their favorite food items. As each word was presented in 30-second intervals for a total of 6 minutes, participants were instructed to imagine the taste, the smell, and the satisfaction of consuming the food.

MRI scanning protocol

See online Supporting Information.

FNs of interest

This study examined the generalizability and network properties of two FNs, FN1 and FN2, that we had found in prior research to be predictive of 18-month weight loss in older adults with obesity (9). These FNs were identified using machine-learning techniques. The two FNs captured key regions that play a role in incentive sensitization, reward valuation, and executive function (4,5). FN1 and FN2 were chosen from several possible FNs because they were the top two predictive networks and because they had a priori scientific credence (5,11) and theoretical importance (9,12) within the context of a hypothesis-based study design. These FNs were based on regions within the Shen functional atlas (Supporting Information Figure S1 and Table S1) (13). For FN1, the nodes in the most posterior area are in the visual cortex, and the nodes in the more anterior locations occupy lateral motor and somatosensory regions, the anterior cingulate and posterior insula. The nodes located in the inferior posterior aspect of the brain occupy the cerebellum. For FN2, the nodes located in the superior aspect of the brain are part of the attention-processing circuit. The nodes in the inferior aspect of the brain localize to the amygdala, temporal pole, hippocampus, fusiform gyrus, and inferior insula. On an a priori basis, we chose clustering coefficient (CC) and global efficiency (GE) to examine the small-world network properties (14) of FN1 and FN2 because they are the hallmark metrics of functional segregation (specialized/local neural processing) and integration (fast integration of specialized neural processing) in the brain (15).

It is important to note that, although FN1 and FN2 were the top two networks ranked by captured population variance in the original study, there were actually 21 networks used to perform the predictions. We limited the analyses here so that focused hypotheses could be tested with limited multiple comparisons. Testing all 21 networks for significant topological associations with weight loss would be more of a data-driven study design rather than a hypothesis-based design. It remains possible/probable that some of the other predictive networks exhibit topological properties essential for a more complete mechanistic understanding of the neural processes underlying weight loss that may emerge from future studies.

Statistical analysis by mixed-regression framework and associated covariates

We used a mixed-modeling framework for our analyses on FN1 and FN2. Absolute weight loss in kilograms was the continuous covariate of interest in our models. A two-part model examined the probability (presence or absence) of network connections as well as the strength of existing connections (16,17). Negative correlations (connection strengths) were set to zero because of the challenge of defining CC and GE in networks containing negative edges (18) and because the positive and negative edges lead to very different interpretations (19). This framework quantified the relationship between strength and probability as the outcome (dependent) variable and network and non-network covariates (including interactions between the two sets) as the independent variables. The model included average CC and average GE as network variables (20). Age, sex, race, and baseline weight were included in the model as covariates. For a summary of the covariate uses, see Supporting Information Tables S2 and S3. To account for potential effects of participants' brain sizes, the spatial euclidian distance and squared distance between network nodes were included as confounding variables (21). For a discussion of statistical power for this approach, see the online Supporting Information.

Planned post hoc analyses

In post hoc analyses, we estimated appropriate contrast statements of already estimated residuals (from fitted mixed models) for corresponding parameters to obtain inference about whether and how the relationship between brain connectivity and network metrics (i.e., clustering and GE) was modified by 6-month weight loss. The contrast statements for continuous variables were made through a unit change in that variable. For more detail, see Bahrami and colleagues (17).

Population average networks

To aid in visualizing the results from our analyses, we generated representative group networks. Owing to the noneuclidean nature of complex

brain networks, it is not possible to generate group mean networks without affecting topological variables (22). Therefore, to generate meaningful visualizations, representative group networks were estimated with respect to the observed modification effect of the 6-month weight loss (our covariate of interest) on the brain connectivity-network metric associations. For simplicity, we simulated group representative networks for low (minimum) and high (maximum) 6-month weight-loss groups. For more detail, see online Supporting Information.

RESULTS

Table 1 displays relevant demographic information. Participants' mean (SD) age was 70.4 (4.6) years, with an average baseline weight of 95.1 (1.6) kg. The average weight change (baseline weight – 6-month weight) was –7.4 (5.0) kg. Figure 1 shows the histogram of 6-month weight loss for the 63 participants.

Mixed-regression results

To examine the associations between weight loss with GE and CC for the two FNs during two independent conditions (i.e., resting state and food cues), we conducted four separate analyses, with each analysis modeling both the probability and strength of brain connections within a two-part, mixed-effects regression framework. Table 2 presents the statistical summary of the significant findings.

Bold values in Table 2 show significant weight-loss-related inferential results for both models. In summary, during the resting condition, the baseline relationship between brain network clustering and connectivity in FN1 was associated with 6-month weight loss, whereas for FN2, it was network GE and connectivity. Later in this article, we provide more specific explanations, with estimates for other parameters fully presented in Supporting Information Tables S4 to S7.

Resting state data

- The relationship between baseline **connection probability** and **CC** in **FN1** was significantly associated with 6-month weight

loss. Specifically, as CC increased, participants with greater (more successful) 6-month weight loss were less likely to have connections between highly clustered nodes within this FN compared with those who lost less weight.

- The relationship between **connection strength** and **CC** in **FN1** was also significantly associated with 6-month weight loss. Within this FN, as CC increased, participants with greater (more successful) 6-month weight loss had stronger connections compared with those who lost less weight.

These significant effects are illustrated in Figure 2, which shows the relationships between both connection probability and strength with CC and their associations with 6-month weight loss. The surfaces are colored by the slope of the connection probability (or strength) and its relationship to clustering by the degree of weight loss. As the surface plots show, the relationship between connection probability and clustering in FN1 became more negative as weight loss increased (darker blue in Figure 2). However, for the relationship between connection strength and clustering, a reverse pattern was observed, supporting the conclusion that participants with greater weight loss had stronger connections for higher clustering in FN1. Also, in Figure 2, the findings detailed earlier in this article have been transformed back into brain space using representative group networks to illustrate differences in the topology of FN1, with respect to their association with weight loss. Nodes in this network are sized by their actual clustering values and colored by the sum of their connection probability-clustering slopes (top networks) and connection strength-clustering slopes (bottom networks). The more blue and red nodes in the top and bottom right networks for those with higher 6-month weight loss clearly demonstrate that they exhibited more negative and positive relationships at baseline with the relationship between connection probability and strength with clustering, respectively.

In addition to the slope differences, the brain maps also reveal spatial differences within FN1 that were associated with weight loss. Most notably, the cerebellum had a different topological relationship to weight loss in the low-weight-loss group relative to the rest of the FN. However, in the high-weight-loss group, the cerebellum's topology and slopes were more like the other regions in this FN.

TABLE 1 Participant demographics and measures

| Variable | Overall (n = 63) | Male (n = 13) | Female (n = 50) |
|---|------------------|---------------|-----------------|
| Age (y) | 70.4 (4.6) | 70.6 (5.2) | 70.3 (4.5) |
| Baseline weight (kg) | 95.1 (11.6) | 108.7 (7.1) | 91.6 (9.8) |
| Race, n (%) | | | |
| African American or Black | 18 (28.6) | 1 (7.7) | 17 (34.0) |
| White | 45 (71.4) | 12 (92.3) | 33 (66.0) |
| Weight change: baseline – 6 months (kg) | –7.4 (5.0) | –9.7 (5.6) | –6.8 (4.8) |

Note: Data given as mean (SD) or frequency (%).

Food-cue data

- The relationship between **connection probability** and **GE** in **FN2** at baseline was significantly associated with 6-month weight loss. Within this ROI, as GE increased, participants with greater (more successful) 6-month weight loss were more likely to have connections when compared with those who lost less weight.
- The relationship between **connection strength** and **GE** in **FN2** at baseline was significantly associated with 6-month weight loss. Within this FN, as GE increased, people with greater (more successful) 6-month weight loss had stronger connections when compared with those who lost less weight.

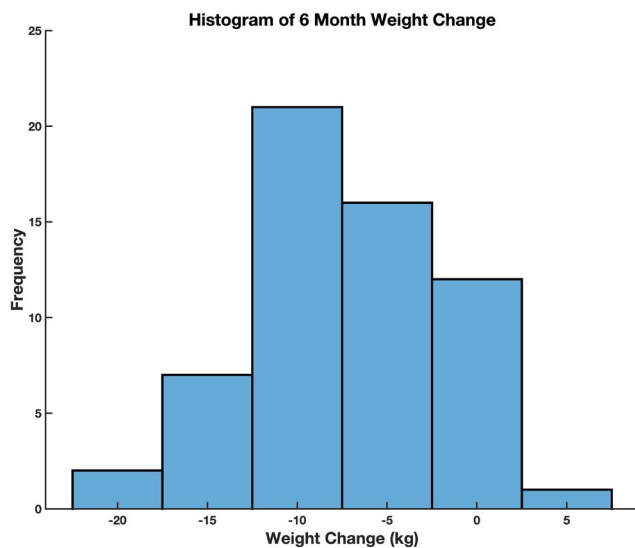


FIGURE 1 Histogram of 6-month weight change showing a normal distribution of weight loss [Color figure can be viewed at wileyonlinelibrary.com]

The significant findings are shown through surface plots and representative group networks in Figure 3. As shown, the relationship between connection probability (top) or connection strength (bottom) and GE in FN2 was significantly associated with 6-month weight loss, with a stronger effect observed for connection probability and GE in this FN. The relationship between both connection probability and strength and GE in FN2 became more positive as weight loss increased. The representative group networks support this effect as well. The nodes are sized by their actual GE values and colored by the sum of their connection probability (or strength)-GE slopes.

By mapping these relationships back into brain space (Figure 3), it is evident that the attention and limbic circuitry have different topological relationships with weight loss. Most notably, weight loss had a weaker association with network topology in the limbic circuitry than the nodes located in attention-processing regions. This was evident by the fact that the limbic nodes had slopes closer to zero (whether the slopes were negative or positive).

DISCUSSION

Using functional brain networks from 63 older adults and a mixed-regression framework, we examined how 6-month weight loss was associated with baseline network connectivity in two previously identified FNs of the brain that evolved from predictive analyses using machine learning: FN1 and FN2.

FN1 is dominated by interactions between the cerebellum, lateral sensorimotor areas (including the face, mouth, and throat), posterior insula, and mid-anterior cingulate cortex, as well as the early visual cortex (9). It is important to note that this network involves

TABLE 2 Parameter estimates and *p* value summaries of the contrast statements showing the modulating effects of 6-month weight loss (COI) on the interaction of the brain topological variables (CC and GE) and brain connectivity (strength and probability of connection) in FN1 and FN2

| Probability model | | | Strength model outputs | | |
|---|---------------|------------------|---|---------------|------------------|
| Parameter | Estimate | * <i>p</i> value | Parameter | Estimate | * <i>p</i> value |
| Resting | | | | | |
| $\beta_{r'} \text{ COI} \times \text{CC} + \beta_{r'} \text{ COI} \times \text{FN1} \times \text{CC}$ | -0.0741 | 0.0189 | $\beta_{s'} \text{ COI} \times \text{CC} + \beta_{s'} \text{ COI} \times \text{FN1} \times \text{CC}$ | 0.0117 | 0.0016 |
| $\beta_{r'} \text{ COI} \times \text{GE} + \beta_{r'} \text{ COI} \times \text{FN1} \times \text{GE}$ | 0.0597 | 0.0529 | $\beta_{s'} \text{ COI} \times \text{GE} + \beta_{s'} \text{ COI} \times \text{FN1} \times \text{GE}$ | -0.0041 | 0.3032 |
| $\beta_{r'} \text{ COI} \times \text{CC} + \beta_{r'} \text{ COI} \times \text{FN2} \times \text{CC}$ | 0.0081 | 0.8236 | $\beta_{s'} \text{ COI} \times \text{CC} + \beta_{s'} \text{ COI} \times \text{FN2} \times \text{CC}$ | 0.0010 | 0.8278 |
| $\beta_{r'} \text{ COI} \times \text{GE} + \beta_{r'} \text{ COI} \times \text{FN2} \times \text{GE}$ | 0.0382 | 0.3565 | $\beta_{s'} \text{ COI} \times \text{GE} + \beta_{s'} \text{ COI} \times \text{FN2} \times \text{GE}$ | 0.0069 | 0.1583 |
| Food cue | | | | | |
| $\beta_{r'} \text{ COI} \times \text{CC} + \beta_{r'} \text{ COI} \times \text{FN1} \times \text{CC}$ | -0.0002 | 0.9938 | $\beta_{s'} \text{ COI} \times \text{CC} + \beta_{s'} \text{ COI} \times \text{FN1} \times \text{CC}$ | 0.0057 | 0.1172 |
| $\beta_{r'} \text{ COI} \times \text{GE} + \beta_{r'} \text{ COI} \times \text{FN1} \times \text{GE}$ | -0.0339 | 0.2681 | $\beta_{s'} \text{ COI} \times \text{GE} + \beta_{s'} \text{ COI} \times \text{FN1} \times \text{GE}$ | -0.0001 | 0.9753 |
| $\beta_{r'} \text{ COI} \times \text{CC} + \beta_{r'} \text{ COI} \times \text{FN2} \times \text{CC}$ | -0.1210 | 0.0002 | $\beta_{s'} \text{ COI} \times \text{CC} + \beta_{s'} \text{ COI} \times \text{FN2} \times \text{CC}$ | -0.0051 | 0.1942 |
| $\beta_{r'} \text{ COI} \times \text{GE} + \beta_{r'} \text{ COI} \times \text{FN2} \times \text{GE}$ | 0.1186 | 0.0005 | $\beta_{s'} \text{ COI} \times \text{GE} + \beta_{s'} \text{ COI} \times \text{FN2} \times \text{GE}$ | 0.0134 | 0.0032 |

Note: Bold values show COI-related inferential results discussed here. Highlighted values show COI-related inferential results, which were significant for both probability and strength models and, therefore, are discussed in more detail in this study.

Abbreviations: CC, clustering coefficient; COI, covariate of interest; FN, functional network; GE, global efficiency.

*Adjusted using the adaptive false discovery rate procedure described in Benjamini and Hochberg (39).

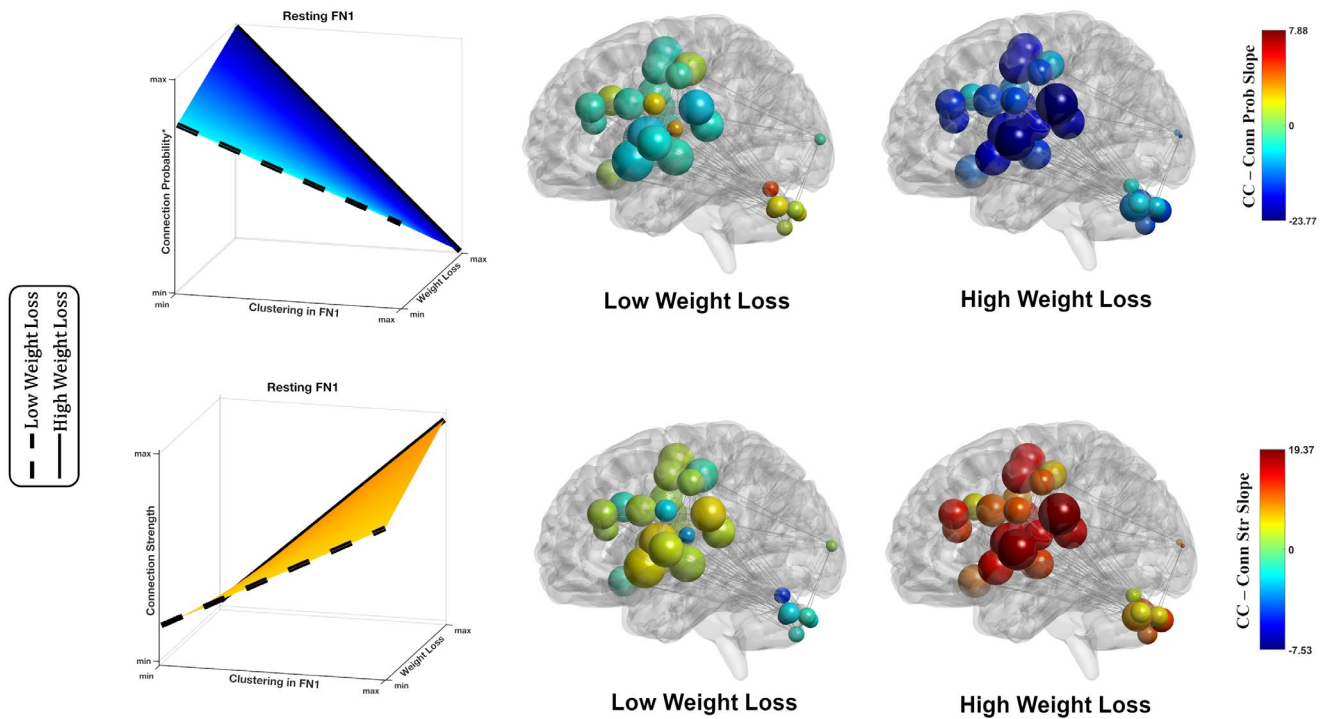


FIGURE 2 Connection probability and strength as functions of CC and 6-month weight loss in FN1. The surface plots show how the relationship between connection probability (top) and connection strength (bottom) and clustering in FN1 changes with 6-month weight loss. The surfaces are colored by the slope of connection probability (or strength)-network metric (clustering) relationships at each weight-loss value. The more blue and yellow colors demonstrate the more negative and positive relationships for the connection probability-clustering and connection strength-clustering, respectively, as the weight loss increases. The corresponding representative group networks for the adults with minimum (dashed line) and maximum (solid line) are shown as well. The nodes are sized by their actual network metric (clustering) and colored by the sum of the connection probability (or strength)-network metric (clustering) slopes. The representative group networks clearly show the significant effect of 6-month weight loss on the connection probability (and strength)-clustering relationships. The y-axis in this figure and in Figure 3 is the log odds of connection probability. Because changes in the log odds of connection probability reflect similar change in the connection probability, we labeled the y-axis as connection strength for simplicity. CC, clustering coefficient. FN, functional network

both unconscious sensory, motor, cognitive, and affective processes that are likely responsible for the intrusive quality of food craving, and conscious cognitive and affective processes that serve to elaborate on these intrusive cues fueling the desire for food consumption, a position consistent with Kavanagh's Elaborated Intrusion Theory of Desire (12). Within this network, we observed a significant association of 6-month weight loss with brain connectivity-clustering relationships during the resting state. As weight loss increased, the probability that brain regions in FN1 with higher clustering would become connected to each other decreased (a negative slope); however, the strength of existing connections increased. This implies that, for older adults who lost more weight, higher-clustered regions in FN1 were less likely to be connected to each other yet established strong connections when they were connected. In other words, for older adults who lost more weight, FN1 contained pools or groups of highly clustered, strongly connected nodes that are relatively isolated from each other. In participants who lost less weight, the pools of clustered nodes are more likely to be interconnected but have weaker connections. Therefore, for participants who lost the least weight, the results for FN1 imply the existence of an independent big clique "talking" to itself but not to the rest of the network; that

is, it is segregated from the rest of the brain. Interestingly, portions of the cerebellum are included in FN1, but, as shown in Figure 2, the cerebellum's network topology is different from the rest of FN1 among those who lost less weight but was similar to the rest of the FN1 subnetwork in those who lost more weight. These cerebellar findings warrant further study to determine whether there are unique properties of this structure as related to weight loss.

From a clinical perspective, the strong sensorimotor dynamics inherent to FN1 imply that, when the brain is in a resting state, those who are more successful at weight loss segregate the motivational influence of these brain structures from the remainder of the brain. By contrast, those who lost less weight exhibited sensorimotor dynamics that are integrated with other areas of the brain, a quality that implies that they are more broadly susceptible to the influence of food cues. It is worth pointing out that the pattern of connectivity within FN1 for those who struggled to lose weight is consistent with dysfunction in interoceptive awareness and the integration of these body and sensory cues into personal identity that has been observed in individuals with eating disorders (12,13). Within the context of weight loss, we would argue that connectivity within this network is a manifestation of reward valuation and incentive sensitization

that have been emphasized by Stice and Burger as central theories in obesity and overeating (11). This interpretation is supported, in part, by prior cross-sectional data on this cohort that we have published previously, in which FN1 was found to be related to self-reported ratings on the Power of Food Scale (23).

A bilateral interacting pattern between the executive attention network and hedonic/goal-directed network, including the amygdala, hippocampus, and inferior insula, was found to serve as the core for FN2, with results supporting a significant association between 6-month weight loss and brain connectivity within this FN-GE relationship during the food-cue condition. As weight loss for the older adults increased, the probability that brain regions with higher GE in FN2 become connected and the strength of existing connections also increased. These findings suggest that, during the food-cue condition, older adults who had greater weight loss exhibited high efficiency in FN2, with nodes that were tightly and strongly connected to each other. In essence, those participants who lost more weight have an FN2 that is behaving like a so-called “Rich Club” of highly efficient nodes sharing information, especially within the attention circuit, which is functioning as a superhighway (24). In these individuals, the executive attention circuit appears to act as an intermediary between the rest of the brain and the limbic circuitry. On the other hand, in those who lost less weight, the limbic portions of FN2 likely interact with the rest of the brain without using the attention network as an intermediary superhighway. One could argue

that, in effective weight loss, the executive attention network helps optimize what the more primal limbic regions attend to rather than allowing the limbic regions to communicate freely with the rest of the brain.

As we have previously postulated, FN2 captures top-down control that the attention network projects onto limbic regions known to be important in goal-oriented behavior (25,26). Prior research has shown that these limbic regions are implicated in the obesity epidemic (27). Droutman and colleagues (28), consistent with work by others (29,30), have argued that the anterior insula is an integrative interoceptive site connecting autonomic, affective, and cognitive processing. Therefore, within the context of weight loss, FN2 highlights the importance of executive function, as recently emphasized in a review by Donofry and colleagues (5); however, it would appear that elements of reward valuation and incentive sensitization are also integrated with FN2. In combination with the data from FN1, our findings suggest that concepts important to weight loss are distributed throughout the brain, as opposed to being associated with specific regions of the brain. Of note is that, in cross-sectional analysis on this cohort mentioned earlier in this article, we also found that connectivity within both FN1 and FN2 was significantly associated with a measure of self-efficacy that assesses people’s ability to resist consuming favorite foods when exposed to internal states, environmental cues, and social contexts that pose a risk for promoting hedonic eating (23).

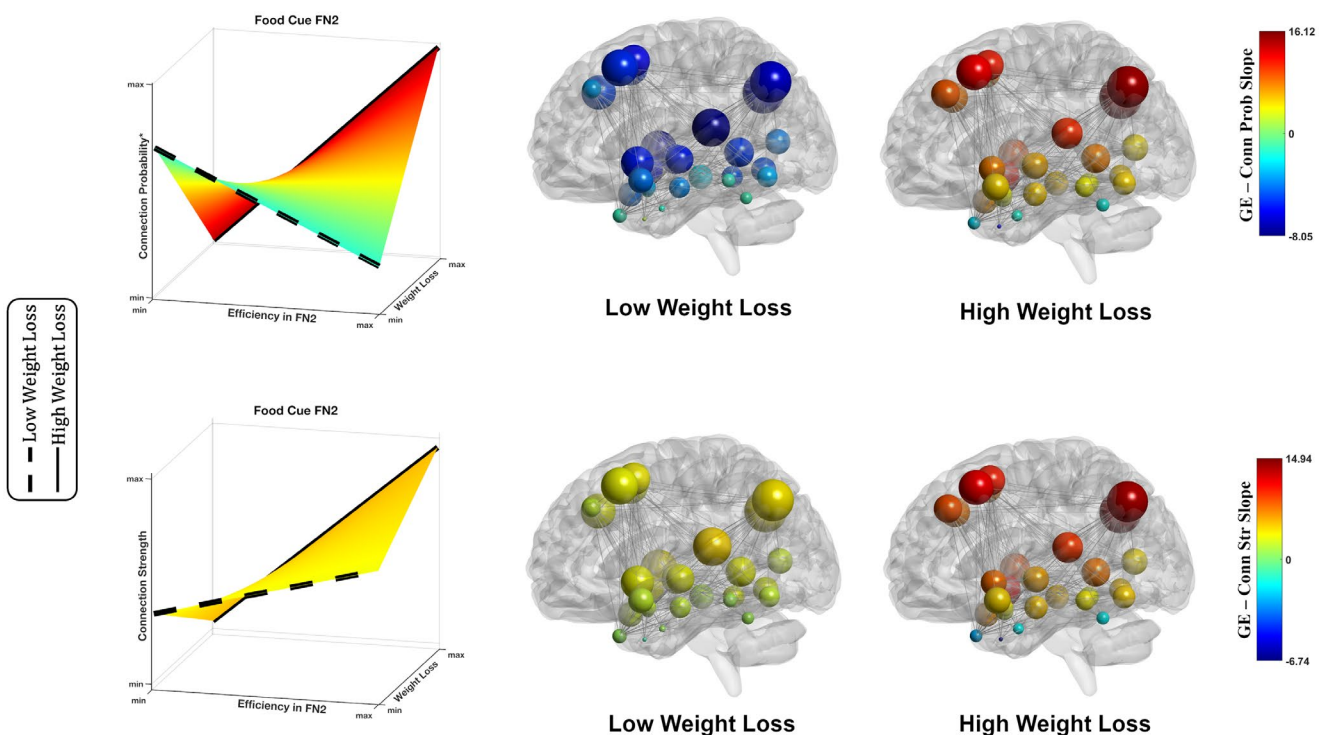


FIGURE 3 Connection probability and strength as functions of GE and 6-month weight loss in FN2. The surface plots show how the relationship between connection probability (top) and connection strength (bottom) and efficiency in FN2 changes with 6-month weight loss. The surface plots and the representative group networks show that the relationship between both connection probability and strength and efficiency in FN2 becomes more positive as the 6-month weight loss increases. For the surface color and node size and color, see Figure 2 caption. FN, functional network; GE, global efficiency


Clinically, these findings underscore two distinct biases that many older adults with obesity confront when embarking on a program of weight loss. First, within the resting state, there is the existence of a nonconscious sensorimotor motivational bias to pursue food. Second, when processing food cues, there is a deficit in the attentional network that optimizes processing goals of the more primal, limbic regions of the brain. From the perspective of behavior change, nonconscious processes play a central role in self-regulatory failure (31) that warrants the design of interventions that directly target these biases, a clinical perspective suggested by Stice and Burger (11) and reinforced by the current findings. It is possible that a mechanism underlying participants' use of electronic scales to communicate daily weights to clinics in real time for the purpose of enhancing self-monitoring and for implementing just-in-time treatment (32) is that it uses the FN2 to help override attentional deficits through top-down self-regulatory processes. Of interest is a pilot study of response and attention training by Stice and colleagues (33) that produced significant reductions in the responses of reward and attention regions to high-calorie food images. Also, in a weight-maintenance study, Chumachenko and colleagues (34) found that mindfulness-based stress reduction improved functional connectivity between the prefrontal cortex and the amygdala compared with a control group. Although the sample size was underpowered to detect change in weight, the mindfulness-bases-stress-reduction group remained weight stable, whereas the control group increased their BMI by 3.4%.

As mentioned in the introduction, within the field of network science, a consistent observation has been that there is a decrease in the connectivity of brain networks with aging (6,7). Interestingly, although fMRI studies of older adults with obesity have been limited and results have been mixed (35-37), in the current study, both resting and task-evoked responses to food cues are consistent with observations in young and middle-aged adults (5,11); however, because we did not have a middle-aged group for comparison, it is not possible to know whether the effects on our network metrics were influenced by age. Because Morley (38) has provided strong evidence that food intake decreases with aging, an effect that is multifactorial involving both central and peripheral mechanisms, future research is warranted on adults across the lifespan.

This study is not without limitations. First, although the data are longitudinal by design and are superior to cross-sectional analyses, they do not determine cause and effect. Randomized, controlled clinical trials are needed on behavioral and/or pharmacological treatments that target control over conditioned behavior to determine whether these networks can be altered and their effect on weight loss. Second, these data can only be generalized to older adults with obesity who are free of cognitive impairment. Third, there are some limitations imposed by the sample size, such as not permitting a deeper exploration into brain network differences as a function of either sex or race. Fourth, it would have been ideal to have included behavior-inhibition tasks such as the Stroop food-cue

task to further assess the clinical relevance of these networks, and this would be a valuable addition to subsequent research. Fifth, none of the analyses used here was predictive in a nature that was comparable to our original study (9). Therefore, we do not know how the most-predictive networks in this population compare with the original study population. We also do not know how well the original networks would perform in predicting weight loss in this new population. Given the strong associations that were observed between network topology and weight loss, we anticipate that such future studies will further support the role of these (and other networks) in successful weight loss. Finally, a related issue is that we chose a hypothesis-driven approach to the selection of the two FNs employed in this study that were supported by both research and theory. However, some readers might object to this choice and would have preferred a data-driven approach searching for significant topological associations and using all available networks uncovered in our prior predictive study (9).

CONCLUSION

To our knowledge, this is the first study to link key concepts that have been identified as important in understanding obesity and overeating to success with behavioral weight loss among older adults with obesity. The significant association between 6-month weight loss and hallmark network metrics in two critical FNs of the brain suggests the existence of differential segregation and integration of neural processing in these networks with respect to the amount of weight lost. These are complex functional circuits in distributed regions of the brain that are known to be responsible for the intrusive quality of food craving and goal-oriented behavior. 

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Jonathan H. Burdette, Barbara J. Nicklas, Jason Fanning, and W. Jack Rejeski designed the experiments. Jonathan H. Burdette, Barbara J. Nicklas, Jason Fanning, and W. Jack Rejeski performed the research. Jonathan H. Burdette, Paul J. Laurienti, Sean L. Simpson, and Mohsen Bahrami analyzed the data, and Jonathan H. Burdette, Paul J. Laurienti, Mohsen Bahrami, and W. Jack Rejeski wrote the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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