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What We Know, Think We Know, or Are Starting to Know

That the brain may play a pivotal role in the regulation of energy balance in humans is not a new theory. In 1953, Kennedy proposed the "lipostatic theory" of obesity, which posited that some unidentified circulating factor released from fat tissue communicated with the hypothalamus to regulate energy balance [(1)]. Kennedy's theory was supported by other research at the time which showed that damaging the ventral medial hypothalamus of rats' lead to the rats being unable to control food intake and becoming obese [(2)].

Our understanding of the neurobiology of food intake and obesity began to accelerate over the past two decades, however, with the advent of functional magnetic resonance imaging [fMRI] to investigate brain responses to food and food cues [(3)]. fMRI scans provide an indirect measure of activity of neurons in particular brain regions, by measuring changes in blood flow in areas of the brain that are activated by different stimuli [(3)].

This allows researchers to examine responses to a variety of dietary exposures; visual images, taste, smell, palatability, energy density, and in different contexts of fed or fasted [(3)]. In the neurobiology of eating, one specific aspect of dietary behaviour that is of interest is "food craving", defined as a strong and conscious desire to consume a food [(4,5)]. Food cravings are considered conditioned responses that develop from exposure to food cues [(4,5)].

Within the neurobiology of eating and obesity, there are two systems that have commonly been referred to: the "homeostatic" and "hedonic" systems [(6)]. Homeostatic systems regulate eating relative to energy balance, e.g., increasing motivation to eat when energy stores are depleted [(6)]. Conversely, hedonic systems are reward-based and may promote eating in the absence of energetic need [i.e., overconsumption] [(6)].

Previous fMRI research has shown greater activation of reward-associated brain regions in individuals with obesity compared to normal weight individuals [(7)]. However, many fMRI studies use visual or image-based food cues, which may not fully test the influence of nutrients, e.g., glucose, on food cravings and reward pathways. The present study investigated the influence of glucose infusion on these interactions.

The Study

25 female participants with obesity [classified as Body Mass Index (BMI) >30kg/m^2 to <40kg/m^2] were matched for age and education status with 25 female participants classified by BMI as normal weight [>19kg/m^2 to <25kg/m^2]. All participants underwent two fMRI test sessions:

- **Glucose Infusion**: Participants underwent a baseline fMRI scan before administration of 75g glucose in 300ml water through a nasogastric tube, which was followed by a further fMRI scan and the completion of food craving tests.
- **Water Control**: The control condition involved the exact same protocol as described above, only 300ml of water alone was administered through the nasogastric tube.

The food craving test for both glucose and water conditions involved participants selecting 8 images from a profile of 85 images of high-calorie foods that they experienced most craving for. 8 non-food images were then matched as a control.

For the food craving tests, two conditions were tested:

- **Attentive Viewing**: In this condition, participants were asked to look attentively at the 8 high-calorie food images and 8 non-food images, respectively. Participants then rated their craving for the food displayed in the image.
- **Distracted Viewing**: In this condition, participants were asked TO complete a maths equation while the 8 high-calorie food images and 8 non-food images, respectively, were being displayed. Participants then rated their craving for the food displayed in the image.

Both the attentive and distracted image viewing conditions were completed after each of the glucose and water infusions, respectively.

Results: The final analysis included 22 women with obesity and 24 normal weight controls. The average age in women with obesity was 27yrs compared to 25yrs in normal weight controls. Mean BMI was 35.5kg/m^2 in women with obesity compared to 21.1kg/m^2 in normal weight controls. Women with obesity exhibited higher baseline scores in depression and in disordered eating, compared to controls.

Food Craving Ratings: Craving ratings did not differ between weight status of participants, or between either glucose or water infusion. When all participants were analysed together, craving ratings were lower during the distracted viewing image condition compared to the attentive viewing image condition.

***fMRI Results – Glucose vs. Water*:** In participants with obesity, there were no differences in brain region activations between either glucose or water infusions during either attentive or distracted viewing. In normal weight participants, activation of brain regions associated with reward anticipation increased following the glucose infusion and during the distracted viewing condition.

***fMRI Results – Attentive vs. Distracted*:** In participants with obesity, there were significant increases in the activity of brain regions associated with self-regulation and appetite regulation during the distracted viewing condition compared to the attentive viewing condition.

Conversely, in normal weight participants there was significant activation in a brain region associated with evaluating rewarding stimuli during the attentive viewing condition compared to the distracted viewing condition. These findings are discussed further under ***Interesting Finding***, below.

***fMRI Results – Differences in Craving Ratings*:** In normal weight controls, there were no associations between brain activation and craving ratings during either viewing condition, following either glucose or water infusion.

In participants with obesity, there was no association between brain activations and craving ratings after glucose infusion. However, following water infusion activation of a brain region associated with attentional processing was associated with lower craving ratings in participants with obesity.

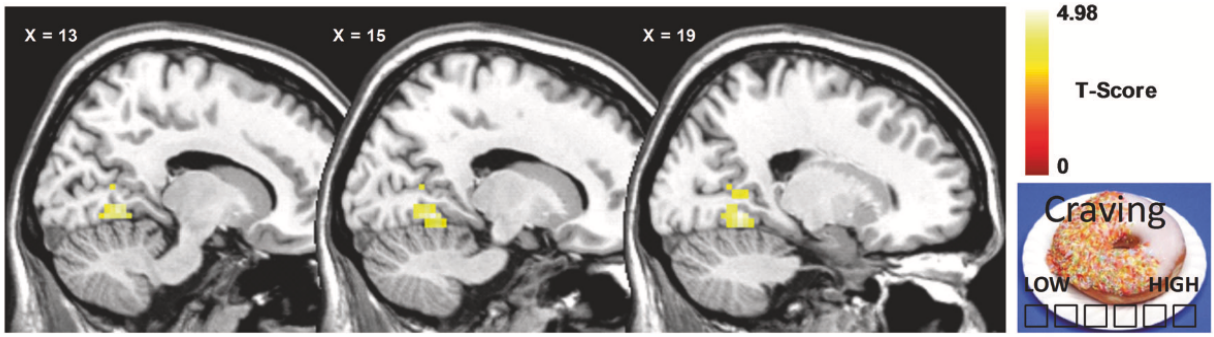

Figure *from the paper illustrating the fMRI scans from three participants with obesity; the activated brain region is highlighted in yellow, and depicts the lingual gyrus region that is involved in attentional processing. Higher levels of this brain region in response to visual food cues have been shown in participants with binge eating disorder*

The Critical Breakdown

Pros: The study aims and hypothesis were clearly stated, and the study design extended previous research by incorporating the glucose infusion to determine whether metabolic status interacted with visual food cues to influence craving ratings. The order of fMRI session for glucose or water infusion was randomised, and counterbalanced [i.e., equal numbers of participants completed the two fMRI sessions in one order or the other, e.g., glucose>water and water>glucose]. Participants remained unaware of whether they had received the glucose or water infusion. The use of fMRI scans allowed for the analysis to correlate brain region activation to measured food cravings. The administration of glucose or water with a nasogastric tube bypassed the potential influence of eating-related cognitive influences on responses.

Cons: The study sample was all-female, and sex differences in brain regional responses according to bodyweight status have previously been demonstrated [(8)]; thus, the findings should not be generalised outside of the study sample characteristics. Despite the fact that participants were screened at baseline for depressive and disordered eating symptoms, these were not included as covariates in the statistical analysis and could influence the outcomes. Only one strategy for dealing with cravings, namely the attentive vs. distracted viewing conditions, was tested. The nature of the analysis was cross-sectional, and consequently we cannot infer whether any differences observed between the weight status of participants reflect a cause or consequence of food exposures and behavioural patterns.

Key Characteristic

The design of the present study extended some previous research by investigating the regulation of food craving in the presence of a glucose load compared to water as a non-caloric control. fMRI research paradigms may often use visual stimuli, but another common method is to provide a milkshake compared to water [(9,10)]. However, the actual processes of consumption may trigger cognitive and related neural responses [(3)]. By using nasogastric administration of glucose, the present study was able to experimentally provide a metabolic stimulus that would bypass the act of ingestion [i.e., drinking, chewing, etc.].

This was a useful approach because glucose – sugar – would be expected to elicit some neural responses [11]. One theory within the neurobiology of obesity is that brain reward sensitivity to palatable foods is dampened, resulting in a positive feedback loop where anticipation for a reward, coupled with lack of satisfaction from the reward, promotes overconsumption [12,13].

While the present study did not investigate actual food intake, the findings from the glucose infusion indicate differences between women with obesity and normal weight controls. For example, in normal weight women the glucose infusion activated brain regions associated with anticipation of a reward, i.e., indicating signals from glucose were integrated into the brain. However, no such responses were observed in women with obesity, which suggests some degree of decreased brain sensitivity to glucose potentially mediated by weight status.

Interesting Finding

In addition to testing any potential influence of metabolic signals comparing glucose to water, the study also combined a test of cravings regulation, i.e., distracting from the presence of a food cue image. This allowed for insight into the neural demands associated with attempting to regulate cravings after exposure to high-calorie food images.

And what was interesting in this analysis was the levels of brain activation relative to craving regulation in participants with obesity. Recall that in this experimental design, the maths equation was presented as an overlay on the high-calorie food image, to distract the participant. And in participants with obesity, the distracted condition led to significant increases in brain activation in specific regions associated with executive function and self-regulation. These regions are activated during *conscious effort* to suppress a desire to consume palatable, unhealthy foods [3].

In layman's terms, the researchers put a pink elephant in the room with participants and asked them not to look at it, and the brain regions that showed increased activation suggest that the participants with obesity had to try really hard to not look at the pink elephant.

Relevance

What do brain region correlates really tell us? Two important questions arise when we try to think about this area of research. The first is whether any such brain activations and correlations with cravings or other hedonic responses lead to clinical outcomes such as obesity. The second is whether fMRI are reliable in the context of repeated measures over time, in order to be confident of any potential cause-effect relationship.

Let's take the first question; do fMRI studies prospectively demonstrate clinical outcomes related to neural characteristics? Although limited, the largest research to date conducted in normal weight BMI participants at baseline suggested that higher reward responsiveness at baseline was associated with greater subsequent weight gain over 3yrs [14,15].

The second question now becomes important; can we rely on these associations? This is where things get a little more ambiguous. In order to be confident that we can relate the

results of an fMRI scan to a clinical outcome like weight gain, we need to be confident that an fMRI would generate reproducible results over time.

However, the body of evidence on this question suggests that the reliability of fMRI brain activation patterns to food-related exposures from test to test may be poor [10,15,16]. A recent 26-week study in patients preparing for bariatric surgery did, however, demonstrate good reliability in patterns of brain activation of food cravings over three fMRI sessions [17]. It is possible that differences between this recent study and previous research could be that previous research analysed selected brain regions, while the more recent study used whole-brain fMRI.

Until this question is more conclusively resolved, however, we are left to hold that the reliability of fMRI for prospective associations is debated, and therefore requires caution against overextrapolation.

What about the effects of cravings, specifically? A comprehensive meta-analysis found that cravings induced by food cues was associated with subsequent eating and weight gain, with a moderate strength of effect [4]. Overall, craving reactivity explained about 11% of the eating and weight related outcomes, highlighting that cravings and reactivity to food cues are not solely explanatory, and multiple other factors are involved. This is indicative of the complex neurobiology of eating and bodyweight regulation.

Application to Practice

While the fMRI data provides us with fascinating insights into this complexity, we are left with the most important question: how does this apply in real life? There is very little to draw on specifically related to diet and lifestyle, as almost all fMRI research investigating associations between brain activations and weight loss is in the context of bariatric surgery [3].

And the dietary interventions that have utilised fMRI provide insights into brain activations related to weight loss, not strategies that may influence those very regions to aid weight loss [18,19]. However, as we covered in a previous Deepdive, there is evidence that for individuals who exhibit low satiety responsiveness, emphasising low energy density foods with high food volume may be an effective strategy to promote appetite regulation and facilitate weight loss. This may be the most prudent application we can

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