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Body Mass is Positively Associated with Neural Response to Sweet Taste, But Not Alcohol, Among Drinkers

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Abstract

Obesity is a large and growing public health concern, presenting enormous economic and health costs to individuals and society. A burgeoning literature demonstrates that overweight and obese individuals display different neural processing of rewarding stimuli, including caloric substances, as compared to healthy weight individuals. However, much extant research on the neurobiology of obesity has focused on addiction models, without highlighting potentially separable neural underpinnings of caloric intake versus substance use. The present research explores these differences by examining neural response to alcoholic beverages and a sweet non-alcoholic beverage, among a sample of individuals with varying weight status and patterns of alcohol use and misuse. Participants received tastes of a sweet beverage (litchi juice) and alcoholic beverages during fMRI scanning. When controlling for alcohol use, elevated weight status was associated with increased activation in response to sweet taste in regions including the cingulate cortex, hippocampus, precuneus, and fusiform gyrus. However, weight status was not associated with neural response to alcoholic beverages.

Keywords

obesity; weight; alcohol; reward; fMRI

Obesity is a large and growing public health crisis, with over two-thirds [1] of American adults classified as overweight or obese. An estimated 19% of all-cause mortality in North America is due to excess weight [2]. Notably, research in both preclinical and human models has begun to identify neurobiological factors associated with weight status and weight change. Knowledge of these neural predictors and correlates is of critical importance to the understanding of the pathophysiology of obesity as well as to the development of biological and behavioral approaches to treatment and prevention [3].

Several areas of research have made critical contributions to the understanding of cognitive and neurobiological processing patterns that are related to obesity in humans (see [4]). One

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key topic of research has been the neural response to visual and gustatory food stimuli, which has highlighted that obesity is not merely a disorder of poor impulse control in the eating domain, but rather is associated with differential neurobiological response to these stimuli that may elicit such impulses. For example, compared to healthy weight women, obese women display more robust activation of reward-relevant brain regions, including nucleus accumbens, medial prefrontal cortex, insula, anterior cingulate cortex, orbitofrontal cortex, hippocampus, caudate, and putamen when viewing images of high energy density foods [5]. Additionally, such sensitivity to food cues is not attenuated following a meal; when compared to healthy weight individuals, those with higher weight and/or predisposition for obesity fail to display decreased activation of the medial prefrontal cortex, interior prefrontal cortex, and insula when sated as compared to when fasted [6]. Evidence of altered neural responses may be present relatively early in the developmental trajectory; in a sample of adolescents, increased body mass index (BMI) was associated with decreased activity in the ventromedial prefrontal cortex, anterior cingulate cortex, and precuneus when watching food commercials as compared to non-food commercials [7].

Additionally, other studies have examined neural responses to the anticipation and consumption of caloric substances during neuroimaging. For example, when consuming a milkshake, overweight individuals display decreased activity in the caudate and increased activity in the putamen, suggesting a potential difference in habitual, rather than goal-directed, processing of food reward [8]. Additionally, as compared to healthy weight women, obese women display increased activity in regions including the posterior cingulate, caudate, hippocampus, parahippocampal gyrus, ventromedial PFC, and Rolandic operculum when anticipating the consumption milkshakes, suggesting increased sensitivity to the reward value and pleasant nature of the anticipated food [10]. Taken together, these findings suggest that the brains of overweight and obese individuals react differently than those of normal weight individuals in response to food stimuli, especially in regions associated with reward value.

Obesity and eating behaviors are not the only public health concerns that are associated with neural reward and control circuitry; various psychiatric and behavioral disorders, including substance abuse and dependence, are also associated with altered function in these brain regions. In both eating and substance use pathologies, a normative behavior pattern becomes biologically and behaviorally dysfunctional. Notably, these neural and behavioral parallels between obesity and addiction have inspired a vast literature. Addiction models of obesity rely upon commonalities between consumptive behaviors (i.e., substance use and eating behaviors) as well as their associated pathologies, including in altered dopamine signaling as well as the cognitive processing and neural circuitry associated with reward, motivation, decision-making, and inhibition [11,12]. While such models have provided invaluable insights on the neurobiology of eating and weight status, there are crucial differences between substance abuse/dependence and obesity. These include the biological necessity of homeostatic eating behaviors, as well as the fact that substance use disorders are behaviorally specified, whereas weight status is an anthropomorphically defined variable that is influenced by eating and but also by other behaviors (e.g., sedentary time, physical activity). Moreover, while substance misuse and obesity *can* co-occur within individuals (e.g., [13]) they often do not, as evidenced by their disparate prevalence rates. Thus,

substance use and elevated weight status may have separable effects on neural function. It remains necessary to explore potential distinctions between excess weight (and pathological eating) and substance abuse and dependence. Despite their similarities in certain key neurobiological correlates (e.g., function and dysfunction of reward circuitry) these distinct behavioral and anthropomorphic phenotypes should exhibit somewhat separable neural substrates, and this information would inform the development of and potential differences in treatment and prevention of the two behavioral risks. The present investigation represents a key step in this area of research, by examining separable neural responses to caloric liquids that do and do not contain alcohol (namely, fruit juice and alcoholic beverages), among individuals of varying weight status and levels of alcohol use and misuse.

Method

Participants

Participants were adults who participated in larger parent trials of alcohol and other substance use, in which participants were recruited on the basis of their alcohol use. Inclusion in the present analysis required usable fMRI scan data from the Taste Cue Paradigm (described below), completion of the Alcohol Use Disorders Identification Test (AUDIT) [14], as well as clinically recorded height and weight, in order to permit calculation of body mass index (BMI). A total of 28 subjects, from an original sample of 444, were excluded for excessive motion during the scan (greater than 3mm translational or 0.053 radians rotational). The final sample thus included 416 participants (n=145 female), with a mean age of 31.84 (SD = 9.68).

Procedures

All research procedures were conducted in accordance with the Declaration of Helsinki. The trials were each approved by the university human research review committee, and participants provided written informed consent to participate.

While specific visit procedures varied among the parent trials, all participants completed a baseline assessment including the AUDIT[14] and a scan visit that included clinical measurement of height and weight and an fMRI scan, conducted on a 3T Siemens Trio scanner with a 12-channel phased array-coil. The fMRI scan included a high-resolution structural scan protocol for the registration of functional images and tissue classification. Following the structural scan, participants completed two runs of the Taste Cue task during functional MRI scanning (TR: 2.0 s, TE: 27ms, α : 70°, matrix size: 64 × 64, 32 slices, voxel size: 3 × 3 × 4 mm³). Full details of the Taste Cue paradigm have been described previously [15]. Briefly, participants received tastes of litchi juice, a sweet, non-alcoholic, fruit-based beverage and an alcoholic beverage (selected based upon participants' drinking preferences), delivered during fMRI scanning via Teflon tubing controlled by a computerized system. Each taste cue trial involved delivery of 1 mL of the beverage delivered over the course of 24 seconds, which minimizes participants' head movement during the trial. A 16-second washout period followed each taste cue delivery trial. These rest periods served as control trials for the calculation of fMRI contrasts.

Analyses were conducted in SPM8 for MATLAB (Wellcome Trust). Whole-brain analyses were conducted with a height threshold of $p < .001$ and an extent threshold of $p < .05$ to correct for multiple comparisons [16]. To test for relationships between elevated body mass and neural activation during receipt of litchi juice, the primary contrast of interest was Litchi > Rest, with exploratory analyses conducted for Alcohol > Rest. Analyses were conducted in a multiple regression framework, with regressors for age, gender, AUDIT score, and BMI. The primary predictor of interest was BMI, which was entered as a continuous measure (i.e., not as a weight status category, given that category boundaries are arbitrary). Additionally, to assess whether gender or alcohol use moderated the relationships between BMI and neural activation, interactions between these factors and BMI were calculated and included as additional regressors in follow-up analyses.

Results

As assessed by the AUDIT, participants' drinking habits ranged from social drinking to abuse and dependence (AUDIT range 3-39, mean = 16.91, SD = 8.07). Their BMI ranged from 15.82 to 41.71, with a mean of 25.90 (SD = 4.63). The weight status distribution of the sample was: 1.4% underweight, 48.3% normal weight, 30.5% overweight, and 19.7% obese. AUDIT score and BMI were significantly positively correlated, but there was nonetheless a large degree of unshared variance between these two metrics ($r = .162$, $p < .001$), highlighting the value in understanding their differential associations with neural activity.

Whole-brain analyses on the Litchi > Rest contrast indicated significant positive relationships between BMI and neural activation during receipt of litchi juice in four clusters after controlling for age, gender, and AUDIT score¹ (Table 1, Figure 1). When receiving and consuming this sweet beverage as compared to resting, individuals with higher BMI demonstrated increased activation of diverse brain regions, including the cingulate cortex, hippocampus, precuneus, and fusiform gyrus. No significant negative relationships emerged between BMI and neural activity. No notable relationships emerged between BMI and neural activity on the Alcohol > Rest contrast (Table 1).

Additional analyses examined gender and AUDIT score as factors that could plausibly moderate relationships between weight status and neural activation. First, given prior evidence of sexual dimorphism in neural response to food cues (e.g. [6,17]) as well as the inclusion of only a single gender (usually women) in a number of neuroimaging studies of obesity (e.g., [5,18]), we examined the possible moderating influence of gender on the relationship between BMI and neural response to sweet taste. There were no significant clusters associated, either positively or negatively, with the BMI $\times$ gender interaction in the Litchi > Rest contrast, demonstrating that gender did not moderate the relationship between body mass and neural activation to litchi juice. In terms of the effects of quantity and frequency of alcohol use and signs of alcohol dependence (measured by the AUDIT), whole-brain analyses for the contrast Alcohol > Rest found no significant clusters associated, either positively or negatively, with the BMI $\times$ AUDIT interaction. This analysis further

¹AUDIT was included as a covariate because parent trials recruited participants based upon their substance use, and the sample included participants whose patterns of alcohol were indicative of abuse or dependence, which can affect brain function. However, when AUDIT score is not included as a covariate, the overall pattern of results does not differ from the one presented here.

demonstrates a lack of evidence in the present sample for a relationship between weight status and neural response to alcoholic beverages when accounting for alcohol consumption tendencies.

Discussion

Identification and understanding of the neural correlates of weight status stands to contribute meaningfully to our understanding of the etiology of obesity as well as its successful prevention and treatment. To date, a wealth of literature has examined how elevated weight status is associated with various aspects of neurobiological function, with a particular focus on neural reward responses[19], especially to visual and gustatory food stimuli. The philosophy underlying many of these investigations, as well as much scientific discussion of the neurobiology and behavioral aspects of obesity, has borrowed largely from the literatures on substance use and addiction [11,12]. Such research has elucidated the common dopaminergic reward circuitry that drives these consumptive behaviors, which can become maladaptively responsive in both pathological substance use and obesity. Nevertheless, these overlapping neural mechanisms do not explain the totality of these disorders, especially given that weight status and pathological eating behaviors (e.g. disinhibited eating) are separable in ways that substance abuse/dependence and substance use are not. Moreover, a pure emphasis on the shared neural correlates of weight status and substance use does not provide key information regarding the distinct biological and behavioral phenotypes of obesity and substance use disorders.

The present investigation begins to fill this gap, by examining distinctions between weight status and substance use pathology at the neurological level. Notably, the alcohol and litchi cues in this study were roughly equivalent in volume and caloric content. Thus, the present findings can be interpreted as a dissociation in the neural responses to sugary, sweetened beverages as compared to alcohol as a substance, accounting for their shared biologically reinforcing value of energy content. The findings demonstrate that, when controlling for alcohol use patterns and pathology, increasing body mass index is associated with greater neural activation in response to sweet, sugary non-alcoholic beverages, but not to alcoholic beverages, and that this relationship did not vary by gender.

Key brain regions implicated in these results include the cingulate cortex, hippocampus, precuneus, and fusiform gyrus. While these regions are not constituents of characteristic circuitry associated with reward processing or homeostatic eating, prior research examining neural response to the oral receipt of caloric substances (e.g., [5,10,20,21]) has also identified these regions as being related to weight status. Notably, these regions are implicated in diverse aspects of stimulus processing, including control, self-related processing, memory, and salience. Previous research has identified that hippocampal responsiveness may be associated with emotional eating and memory-related processes associated with prior consumptive experience [22]. However, despite the consistency of findings highlighting relationships between weight status and activation in these brain regions in response to visual or gustatory food cues, extant research has yet to determine the direction of causality in these relationships, and further study is required to fully develop a mechanistic account of the specific functions of these brain regions in the processing of

food-related stimuli. Continued research is warranted to understand how these distinct neural responses may be associated with cognitive, affective, and behavioral responses to eating behaviors, as they may present targets for prevention and intervention efforts.

Limitations

While several features of the present sample, including its notable size for fMRI research as well as its composition of community-dwelling young and middle-aged men and women (as compared to undergraduate or single-gender samples), contribute to the strengths of this research, the sample nonetheless presents a key limitation of this study. Specifically, all participants were recruited for the parent research trials on the basis of their alcohol consumption. Thus, although we had a broad range of alcohol use and dependence status, these findings may not generalize to segments of the population that abstain from alcohol completely, or whose consumption is modest. In addition, while the litchi juice stimulus was selected as a sugary liquid that could provide equivalent energy content to the alcoholic stimuli, it is nonetheless a limitation that litchi juice was likely unfamiliar to the participants, whereas the alcohol stimuli were selected to be familiar.

In sum, these findings demonstrate a relationship between weight status and neural response to sweet tastes that is separable from that of oral receipt of caloric content, as weight status was not associated with neural response to isocaloric alcoholic beverages. Importantly, these effects emerged when controlling for alcohol consumption patterns, indicating independent contributions of weight status to neural response to primary reinforcers, beyond those accounted for by substance use history. Moreover, these relationships were identified using a continuous measure of body mass index, and not merely comparisons of obese individuals or individuals with eating pathology to healthy weight individuals, demonstrating that this increase in neural responsiveness to a sweet beverage occurs across the weight status spectrum. These distinct neural responses associated with elevated weight status, separable from response to the delivery of alcohol, continue to highlight the importance of neurobiological circuitry underlying the onset and maintenance overweight and obesity, and they also indicate potential for early identification and intervention to prevent obesity and its deleterious health consequences.

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Highlights

- Alcohol drinkers were given tastes of sweet juice and alcohol during fMRI scanning
- Elevated weight status is associated with greater neural activation to sweet juice
- Neural response to alcohol exposure is not associated with weight status

Figure 1. Positive correlations between BMI and BOLD signal response to litchi juice cue were evident in multiple regions, including cingulate cortex and hippocampus, after controlling for AUDIT score, gender, and age.

Table 1

Positive correlations between BMI and BOLD signal response to taste cues, controlling for AUDIT score, gender, and age.

Contrast	MNI Regions in cluster	Size	MNI coordinates		t-value	p-value
Litchi > Rest	Bilateral anterior cingulate cortex; right posterior and midcingulate cortex	362	15	-30	24	4.41
	Right hippocampus; right precuneus; right fusiform gyrus	141	33	-45	6	4.04
	Left inferior temporal gyrus	33	-39	-42	-15	3.76
	Left calcarine sulcus; left precuneus	33	-24	-51	9	3.42
Alcohol > Rest	None	36	12	-9	33	3.37

Size: number of voxels in cluster; t- and uncorrected p-value for peak voxel in cluster.