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Short communication

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.

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 Ref. [4]). One 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

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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.

1. Method

1.1. 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 3 mm translational or 0.053 rad rotational). The final sample thus included 416 participants (n = 145 female), with a mean age of 31.84 (SD = 9.68).

1.2. 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: 27 ms, α: 70°, matrix size: 64 × 64, 32 slices, voxel size: 3 × 3 × 4 mm^3). 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 s, which minimizes participants' head movement during the trial. A 16-s 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 $p < 0.001$ and an extent threshold of $p < 0.05$ 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.

2. 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 ($r = 0.162$, $p < 0.001$), 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 score[1] (Table 1, Fig. 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 a 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 x gender interaction in the Litchi > Rest contrast, demonstrating that gender did not moderate

[1] AUDIT 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.