Genetic risk for obesity predicts nucleus accumbens size and responsivity to real-world food cues

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Obesity is a major public health concern that involves an interaction between genetic susceptibility and exposure to environmental cues (e.g., food marketing); however, the mechanisms that link these factors and contribute to unhealthy eating are unclear. Using a well-known obesity risk polymorphism (*FTO* rs9939609) in a sample of 78 children (ages 9–12 y), we observed that children at risk for obesity exhibited stronger responses to food commercials in the nucleus accumbens (NAcc) than children not at risk. Similarly, children at a higher genetic risk for obesity demonstrated larger NAcc volumes. Although a recessive model of this polymorphism best predicted body mass and adiposity, a dominant model was most predictive of NAcc size and responsivity to food cues. These findings suggest that children genetically at risk for obesity are predisposed to represent reward signals more strongly, which, in turn, may contribute to unhealthy eating behaviors later in life.

reward | obesity | fMRI | brain morphometry | genetic risk

The relationship between genes and sensitivity to environmental cues is elusive, yet it is paramount to understanding the development of potentially maladaptive human behaviors. The rising prevalence of obesity is a major public health concern that has been attributed to various factors, such as genetic susceptibility (1), and increases in the availability and marketing of calorie-dense foods (2). However, little is known about how genetic predisposition to obesity influences sensitivity to real-world food cues and contributes to the development of unhealthy eating behaviors.

Previous neuroimaging studies have demonstrated that responses to food cues in reward-related regions of the brain, such as the nucleus accumbens (NAcc), predict weight gain in adulthood (3) and giving in to food temptations in daily life (4). Furthermore, structural differences in NAcc volume have been positively associated with body mass index (BMI) in adults (5, 6). Because the development of the NAcc precedes the development of prefrontal control systems (7), this structure is suggested to play a key role in motivating and establishing unhealthy eating behaviors early in the lifespan. Importantly, genetic factors are a known contributor to brain development (8) and may influence risky behaviors during childhood and adolescence by biasing the early development of anatomical structures underlying reward-related brain function.

In addition, the notion that genes contribute to obesity has recently gained much attention. More specifically, the fat-mass and obesity-associated (*FTO*) rs9939609 polymorphism has been strongly related to increased BMI and adiposity across the lifespan, and is suggested to influence food intake and food choice, rather than energy expenditure (9–11). Those with two high-risk "A" alleles (AA) are at an enhanced risk for obesity compared with those with two low-risk "T" alleles (TT) or those who are heterozygous (AT) for the *FTO* rs9939609 polymorphism. Although the *FTO* gene is highly expressed in the brain (1), the mechanism by which this gene promotes unhealthy eating behaviors remains poorly understood. Previous studies have suggested that *FTO* alters dopaminergic midbrain circuitry (12, 13). Thus, one possibility is that the *FTO* gene influences the early development and responsivity of reward-related brain structures, thereby predisposing individuals to develop patterns of unhealthy eating. Prior neuroimaging studies examining the influence of variants in this gene on brain structure and function have primarily been reported in adults, and therefore may be missing important genetic associations that manifest early in development and predispose individuals to develop patterns of unhealthy eating. Indeed, findings in these adult studies are somewhat mixed, with gene-related effects reported across a number of brain regions not traditionally associated with reward, including the posterior cingulate, cuneus, precuneus, and fusiform gyrus (14, 15). Only one study thus far has reported a relationship between *FTO* rs9939609 and neural responses to food cues in a canonical reward region: the putamen (14). A separate study observed modulatory effects of physiological state (fed versus fasting) and metabolic state (circulating acetyl-ghrelin) on responses to food in reward-related brain regions (16). Here, we extend prior neuroimaging work on obesity and the influence of *FTO* rs9939609 by targeting reward responses to naturalistic food cues in a pediatric population.

To examine the relationship between genetic risk for obesity and sensitivity to real-world food cues, we used functional and structural MRI (fMRI and sMRI) to measure NAcc responsivity to food advertisements and NAcc volumes, respectively. Adapted from an fMRI paradigm previously used with adolescents (17), food and nonfood commercials were embedded into the natural breaks of an age-appropriate television show (Fig. 1*A*). Participants ($n = 78$; ages 9–12 y)

Significance

Genetic predisposition and sensitivity to environmental cues jointly give rise to maladaptive human behaviors, such as unhealthy eating. Despite the dramatic rise in obesity rates, the relationship between these factors is not well understood. Here we show that children genetically at risk for obesity exhibit stronger reward-related responses to real-world food cues (i.e., food advertisements) in the nucleus accumbens, a brain area canonically associated with reward processing. Additionally, this structure is larger in children at a higher risk for obesity. Taken together, these findings offer one explanation for how genetic risk for obesity may predispose individuals to engage in unhealthy eating behaviors and may inform strategies targeting early intervention.

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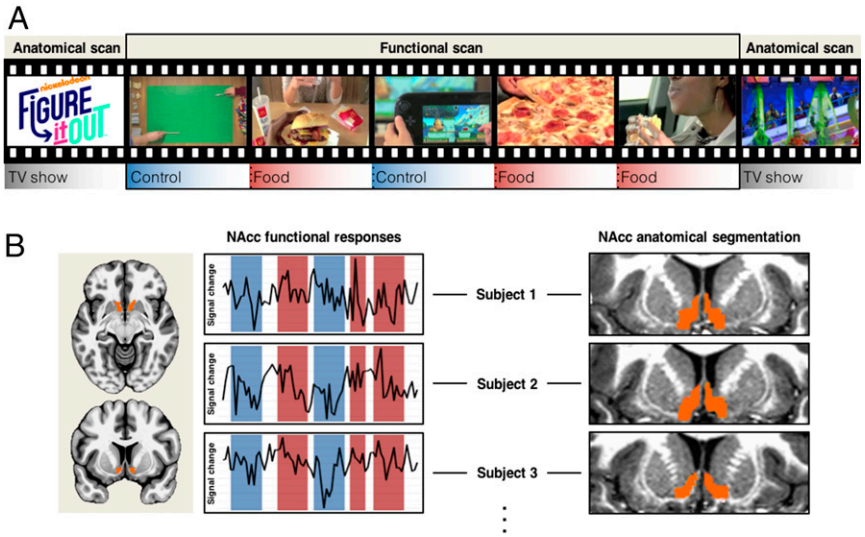

Fig. 1. Study design. (*A*) Participants passively viewed food and nonfood (control) commercials embedded within an age-appropriate television show (Nickelodeon's *Figure it Out*). fMRI images were acquired during commercial presentations and anatomical scans were collected during the television show. (*B*) Independently defined left and right NAcc masks were used to extract functional responses to food and control commercials for each subject. Blood-oxygen level-dependent (BOLD) signals were averaged within each condition and used to examine group differences across *FTO* genotype. Separately, high-resolution anatomical images were used to individually segment each participant's left and right NAcc. Subsequent volume estimates were compared across genotypes.

were genotyped for *FTO* rs9939609 (AA, TT, or AT) and were led to believe that we were interested in brain activity associated with watching television, thereby keeping participants naïve to the study purpose and increasing the ecological validity of our paradigm (see Table S1 for participant characteristics). In addition to examining differences in NAcc responsivity related to genetic risk for obesity, we extracted volumetric estimates of the NAcc for each subject to examine structural associations with *FTO* genotype (Fig. 1*B*). We hypothesized that children at a higher genetic risk for obesity would exhibit stronger NAcc activity to real-world food cues as well as exhibit larger NAcc volumes. Furthermore, we hypothesized that these relationships would be independent of current obesity status, thereby demonstrating specificity to genetic risk based on *FTO* genotype rather than risk based on early-life presence of overweight or obesity.

Results

Association Between Anthropometric Measures and Genetic Risk for Obesity. A one-way ANOVA accounting for age and sex demonstrated a differential effect of the *FTO* rs9939609 polymorphism on BMI [$F_{(2,\ 73)} = 7.1$; $P < 0.002$; $\eta_p^2 = 0.148$] and percent body fat measured via bioelectric impedance [$F_{(2,\ 73)} = 3.9$; $P < 0.05$; $\eta_p^2 = 0.090$] across AA ($n = 19$), AT ($n = 37$), and TT ($n = 22$) individuals (Fig. 2*A*). To examine the specific influence of the high-risk (A) allele on obesity in children, we considered additive (AA > AT > TT), recessive (AA > AT and TT), and dominant (AA and AT > TT) models of the *FTO* genotype. Because of the high collinearity of these models and the number of multiple comparisons reported throughout the manuscript, significance was determined using Šidák correction based on the effective number of independent variables (M_{eff}) identified using matrix spectral decomposition (18, 19) across all statistical tests performed ($n = 18$, six dependent variables × three candidate genetic models) (*Methods*). Here, the effective number of independent tests was determined to be 4.06 (19) and the adjusted threshold for significance 0.0125 (*SI Text*). The findings reported here were significant regardless of the multiple-comparison correction implemented, and other multiple-comparison correction approaches are reported in the *SI Text* when such approaches are standard for the field.

Planned contrasts demonstrated a recessive model of the *FTO* genotype to most strongly predict anthropometric phenotype, such that AA children were at a statistically greater risk for obesity than either AT and TT children, evidenced by higher BMI [$t_{(73)} = 3.5$; $P < 0.001$; $\eta^2 = 0.191$] and body fat percentages [$t_{(73)} = 2.6$; $P < 0.02$; $\eta^2 = 0.121$]. Consistent with previous studies (1), *FTO* genotypes also demonstrated a significant additive association with BMI [$t_{(73)} = 2.9$; $P < 0.05$]; however, this additive relationship was not significantly associated with percent body fat after correcting for multiple comparisons [$t_{(73)} = 2.1$; $P = 0.04$]. The dominant model of the *FTO* genotype was not significantly associated with BMI [$t_{(73)} = 1.7$; $P = 0.13$] or percent body fat [$t_{(73)} = 1.1$; $P = 0.29$] (see Table S2 for full regression models).

Association Between NAcc Responses to Food Cues and Genetic Risk for Obesity. Given our hypothesis that food commercials (relative to nonfood commercials) would engage the NAcc more strongly in individuals at a genetically higher risk for obesity, we performed a targeted region-of-interest (ROI) analysis in the left and right NAcc. A one-way ANOVA revealed differential effects of the *FTO* genotype on responses to food commercials in both the left [$F_{(2,\ 73)} = 3.9$; $P < 0.05$; $\eta_p^2 = 0.112$] and right [$F_{(2,\ 73)} = 4.1$; $P < 0.05$; $\eta_p^2 = 0.082$] NAcc (Fig. 2*B*). Similar to the analyses with body anthropometry reported above, neural responses were tested for genetic associations based on dominant, additive, and recessive models and significance was determined by Šidák correction based on M_{eff}. In contrast to the relationship between *FTO* genotypes and anthropometric phenotypes (i.e., BMI, percent body fat), neural responses to food commercials were best characterized by a dominant model of the polymorphism (AA and AT > TT), such that AT and AA children both exhibited heightened responsivity relative to TT children in both the left [$t_{(73)} = 2.8$; $P < 0.01$] and right [$t_{(73)} = 2.9$; $P < 0.01$] NAcc. An additive model of the *FTO* polymorphism failed to achieve significance in NAcc responses after Šidák correction [left: $t_{(73)} = 2.3$; $P = 0.03$; right: $t_{(73)} = 2.5$; $P = 0.01$]. A recessive model demonstrated no significant relationship with neural responses to food commercials [left NAcc: $t_{(73)} = 1.4$; $P = 0.21$; right NAcc: $t_{(73)} = 1.7$; $P = 0.13$]. A comparison of NAcc responses between high-risk individuals (AA and AT) and low-risk individuals (TT) suggested a moderate-to-large effect size bilaterally (left: $\eta^2 = 0.113$; right: $\eta^2 = 0.114$). Furthermore, these effects were consistent when controlling for either BMI or adiposity (Tables S3 and S4). In an analysis restricted to non-Hispanic

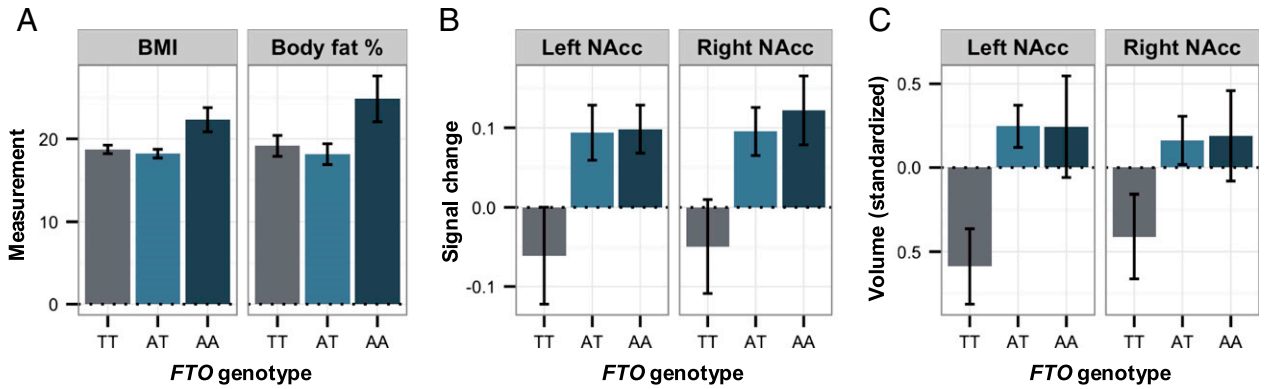

Fig. 2. Anthropomorphic and neural differences across *FTO* genotypes. (*A*) BMI [$F_{(2,\ 73)} = 7.1$; $P < 0.002$] and body fat percentages [$F_{(2,\ 73)} = 3.9$; $P < 0.05$] significantly differed across *FTO* genotype in 78 children (AA: $n = 19$; AT: $n = 37$; TT: $n = 22$). A recessive model of the genotype best-characterized differences in BMI [$t_{(73)} = 3.5$; $P < 0.001$] and body fat percentages [$t_{(73)} = 2.6$; $P < 0.02$]. Data are displayed as mean ± SEM. (*B*) Responses to food commercials relative to control commercials significantly differed across *FTO* genotype in the left [$F_{(2,\ 73)} = 3.9$; $P < 0.05$] and right [$F_{(2,\ 73)} = 4.1$; $P < 0.05$] NAcc. Functional responses were best described by a dominant model of the gene in both the left [$t_{(73)} = 2.8$; < 0.01] and right [$t_{(73)} = 2.9$; $P < 0.01$] NAcc. Data are displayed as mean ± SEM. (*C*) Volumetric estimates of the NAcc demonstrated a significant differences across *FTO* genotype in the left [$F_{(2,\ 62)} = 6.0$, $P < 0.005$] and a trending relationship in the right [$F_{(2,\ 62)} = 3.0$, $P < 0.06$]. A dominant model of the gene best described volumetric differences in the left [$t_{(62)} = 3.2$, $P < 0.005$] and right [$t_{(62)} = 2.3$, $P < 0.03$] NAcc. Volume estimates are centered around a mean of 0 and displayed as mean *z*-score ± SEM.

white participants ($n = 65$), the results were consistent and remained significant (Table S5).

To identify additional brain regions showing a relationship between food cue-reactivity and the *FTO* genotype, a whole-brain exploratory analysis was performed (Fig. 3*A*). A between-subjects comparison of at-risk (AA and AT) individuals to low-risk (TT) individuals identified a single cluster that was more responsive to food cues in at-risk children. The peak of this cluster was situated within the medial orbitofrontal cortex (–3, 27, –15) and extended posteriorly into bilateral ventral striatum ($P < 0.05$, cluster corrected).

Association Between NAcc Volume and Genetic Risk for Obesity. To further examine the influence of the *FTO* rs9939609 genotype on reward sensitivity in children, bilateral NAcc volumes were segmented from high-resolution T1-weighted anatomical images using FreeSurfer (20). Controlling for total brain volume as well as age and sex, a one-way ANOVA revealed a significant difference across *FTO* genotypes in the left NAcc [$F_{(2,\ 62)} = 6.0$, $P < 0.005$; $\eta_p^2 = 0.151$] and a trending relationship in the right NAcc [$F_{(2,\ 62)} = 3.0$, $P = 0.06$; $\eta_p^2 = 0.090$] (Fig. 2*C*) in 68 participants that passed quality assurance; however, similar relationships were observed in the full cohort ($n = 78$) (Fig. S1). Consistent with the previous analyses, additive, dominant, and recessive models of the *FTO* genotype were used to assess significant relationships between the risk allele and NAcc volumes across participants after Šidák correction based on M_{eff}. Planned contrasts demonstrated a dominant model of the *FTO* genotype to best predict the volumetric estimates in the left [$t_{(62)} = 3.2$, $P < 0.005$]; however, this model did not significantly predict volumetric estimates within the right NAcc after correction [$t_{(62)} = 2.3$, $P = 0.02$]. Similarly, NAcc volume demonstrated no significant relationships with the additive [left: $t_{(62)} = 2.5$, $P = 0.02$; right: $t_{(62)} = 1.7$, $P = 0.09$] or recessive [left: $t_{(62)} = 1.3$, $P = 0.22$; right: $t_{(62)} = 0.79$, $P = 0.43$] models of the *FTO* genotype after correction. Based on the dominant model of the *FTO* genotype, a comparison between high- and low-risk individuals revealed a large effect size in the left NAcc ($\eta^2 = 0.167$) and a moderate effect size in the right NAcc ($\eta^2 = 0.082$). In addition, there was no relationship between the genotype and a control structure, the left hippocampus [$F_{(2,\ 62)} = 0.73$, $P = 0.49$] or with total brain volume [$F_{(2,\ 63)} = 0.90$, $P = 0.41$] for any model. Accounting for body fat percentage or BMI did not change these relationships (Tables S3 and S4), and similar effects were observed in an analysis restricted to non-Hispanic white participants (Table S5).

Discussion

The present study examined the relationship between genetic risk for obesity and reward-related brain structure and responses to real-world food stimuli in children. Consistent with previous studies, we observed significant associations between the *FTO* rs9939609 polymorphism and BMI, as well as with adiposity. Independent of current obesity status, genetic risk for obesity was associated with both heightened responsivity to food commercials and larger volumes within the NAcc, a region prominently associated with reward processing. Importantly, we used a naturalistic paradigm that closely mimics what children are likely to encounter in a real-world setting, offering insight into the factors that contribute to real-world eating behaviors. The observed reward responsivity to food cues, in concert with greater structural volume, may provide a mechanism by which genetically at-risk individuals are more susceptible to engage in unhealthy eating behaviors early in life, a problem that could contribute to obesity throughout the lifespan.

These findings extend prior studies that have begun to identify relationships between neural responses to food cues in adults and the *FTO* rs9939609 polymorphism. In particular, studies have demonstrated heightened responsivity to food cues in regions associated with reward (e.g., the putamen) in adults at risk for obesity (14), as well as a modulatory role of *FTO* on the relationship between neural responses to food and circulating acyl-ghrelin (16). Furthermore, one recent study identified both structural and functional differences in the posterior fusiform gyrus associated with genetic risk for obesity (15), and another observed relationships between *FTO* rs9939609 and activity in the precuneus and cuneus (14). The whole-brain exploratory analysis reported here (Fig. 3*A*) did not replicate previously reported effects in adults. Moreover, none of these prior studies in adults reported effects in the ventral striatum of the kind that we observed in children, either because these effects were not present (14, 16) or the effects were not examined (15). As such, it is difficult to reconcile the current findings in children with those previously reported in adults. The differences between the present study and prior investigations may be attributable to population differences (i.e., children versus adults), paradigm differences (i.e., commercial videos of food versus static images of food), or statistical power given the relatively small sample sizes across studies (21). It is worth noting, however, that even within the cohorts of adults tested previously, there is little consistency in reported effects across studies. Moreover, with one exception (14), none of the prior work links *FTO* genotypic differences to neural differences in canonical reward

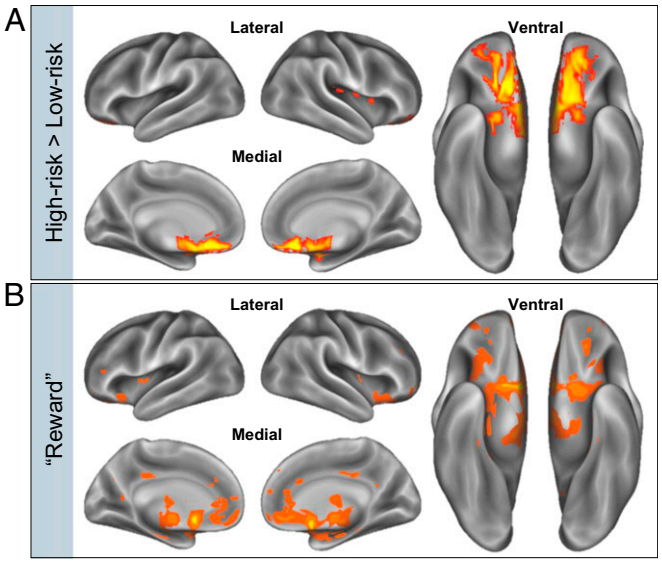

Fig. 3. Whole-brain comparison of at-risk (AA and AT) to low-risk (TT) individuals. (*A*) To identify additional areas that respond more strongly to food cues in individuals genetically at risk for obesity, a between-subjects whole-brain exploratory analysis was performed. Similar to previous studies [e.g., Kühn et al. (15)] and consistent with the ROI results, AT and AA genotypes were combined and compared with the low-risk TT individuals. In doing so, a single cluster (k = 308 voxels) was more responsive to food commercials (relative to nonfood commercials) in children at risk for obesity (AT and AA) than low-risk children (TT). The peak of this cluster was observed in the medial portion of the orbitofrontal cortex (MNI coordinates: −3, 27, −15) and extended posteriorly into the bilateral ventral striatum ($P < 0.05$, cluster corrected). (*B*) For comparison, a whole-brain map illustrating the term "reward" from a large-scale metaanalysis of neuroimaging studies using text mining (23) is provided.

regions despite the fact that previous studies have demonstrated a causal role of *FTO* in regulating dopaminergic transmission (12) and also in modulating mesocorticolimbic circuitry in adults (13). The effects reported here in children in ventral striatum function and structure, as well as the voxel-wise whole-brain exploratory analysis, constrain the *FTO* genotypic differences to canonical reward neurocircuitry. To highlight the overlap, Fig. 3*B* (22) depicts the results of an automated, large-scale meta-analysis of neuroimaging studies using text mining (23) on the term "reward." Although these investigations (including the present study) suggest that responses to food cues are altered in individuals at risk for obesity, future studies are needed to address these discrepancies and elucidate the impact of *FTO* rs9939609 on neural responses to food and perhaps other appetitive cues.

Although the current study presents initial evidence supporting a relationship between *FTO* and reward system structure and function, several limitations warrant caution in interpreting these findings. First, longitudinal studies are clearly needed to fully understand the relationship between *FTO* and brain development. For example, a recent study in older adults (70–82 years old) observed that the *FTO* risk allele was associated with lower NAcc volume (24). One possibility may be that the *FTO* gene influences the rate of neural development in reward-related structures during childhood as well as neural atrophy of these structures during late adulthood. Future studies should address the relationship between FTO and brain structure across the lifespan.

Second, previous studies have largely supported an additive effect of variants in *FTO* on obesity metrics (e.g., BMI) (1, 11, 25–27). More recent reports, however, have argued in support of exploring nonadditive models of obesity-associated genes (e.g., dominant, recessive) (28). Consistent with this idea, the present study observed a recessive model best predicted BMI and percent body fat, whereas a dominant model best predicted reward-related structure and functional responses to food cues. The critical difference among these genetic models is the relationship with heterozygous individuals. Here, children genotyped as heterozygous (i.e., AT) for the *FTO* rs9939609 polymorphism exhibited a dissociation between anthropometric (e.g., BMI) and neural phenotypes. These individuals demonstrated strongest similarity to the low-risk group (TT) in that they were not overweight or obese, yet their NAcc volumes and food cue-responsivity were statistically more similar to the high-risk (AA) individuals. The neural similarities between these genotypic groups suggest that the high-risk A allele may affect reward-related areas of the brain before anthropometric differentiation. In this way, an individual's obesity status may not independently drive reward-related responses to food cues; rather, these signals may additionally depend on dopaminergic reward pathways influenced by an individual's genetic background. Furthermore, these pathways may be more sensitive during childhood. Developmental evidence suggests that the ventral striatum matures earlier than prefrontal regions associated with self-control (7). Thus, childhood may represent a critical period for establishing reward-related circuitry motivating appetitive behaviors. In addition to implications for brain development, this distinction may in part explain the differences observed in the present study in comparison with prior *FTO* neuroimaging studies conducted in adults.

Although speculative, one possibility is that *FTO* may influence the development of reward system circuitry, such that this system matures earlier in higher-risk than low-risk individuals. When combined with slowly maturing control systems, the effect of the higher-risk genotypes may serve to open a time window during which enhanced reward signals reinforce and maintain unhealthy eating habits early in life. Future studies will need to consider longitudinal approaches to investigating the role of brain development on the interaction between genetic and environmental factors associated with obesity.

Third, the sample size reported here may be underpowered to fully capture all relationships between the *FTO* genotype and brain structure and function. More specifically, the neural effects observed here are driven by differences between a sample of 22 low-risk participants (TT genotype) relative to 56 at-risk participants (AT and AA genotypes). Button et al. (21) argued that studies reporting significant effects using low sample sizes or low statistical power are less likely to detect true effects and may also overestimate the likelihood that observed effects are true (false positives) and their associated effect sizes accurate. In their analyses, the median statistical power for more than 450 neuroimaging studies was 8%. In contrast, the effect sizes reported here were moderate to large, with post-hoc statistical power ranging from 60 to 91%. That said, future work replicating these findings in larger sample sizes will still be needed in addition to studies that examine *FTO* gene effects across the lifespan.

Fourth, the present study did not observe any relationships between NAcc responsivity and BMI status in children. This finding, however, is consistent with our prior work in another pediatric population using an identical behavioral paradigm (17). Instead, the literature has demonstrated a relationship between ventral striatum activity and short-term measures of eating behavior [e.g., real-world food temptation (4), short-term weight gain (3), and snack consumption (29)]. Although these motivated behaviors (i.e., eating) may lead to obesity over time, this may not be reflected in our previous (17) and current studies because children have limited autonomy and their diets can be highly influenced by the foods that their adult caregivers provide and rules around food that their caregivers enforce (30). Put simply, neural responsivity to food cues may have a greater influence on BMI later in life when individuals are more independent in deciding what and how much they eat.

Finally, the collinearity between body mass and *FTO* rs9939609 creates additional challenges when attempting to link the *FTO* genotype to brain responses. Prior work has shown that variants in *FTO* correlate with BMI (1) and that BMI (and other adiposity measures such as percent body fat) is correlated with brain activity (17, 31, 32). Although prior reports have used adiposity-matched

participants to explore the effect of *FTO* on neural responses (16), we aimed to circumvent this issue by controlling for BMI (or adiposity) to isolate independent contributions of the *FTO* genotype. Furthermore, we observed neural differences between at-risk heterozygous (AT) and low-risk homozygous (TT) individuals, although no statistical differences existed in BMI or adiposity between these two groups. Collectively, these results suggest that increases in body mass were insufficient to account for or mediate the neural associations with *FTO* rs9939609. However, recent studies have pointed to regulatory mechanisms of *FTO* on adipocyte thermogenesis (33), suggesting the possibility that *FTO* influences adiposity levels before exerting an effect on the brain. The mechanisms underlying the relationship between *FTO* and obesity are likely to be complex and involve multiple layers and potential interactions among physiological and neurological signals. Future studies may be in a stronger position to address this potential confound by directly matching participants based on anthropometric measurements, such as BMI, as in, for example, ref. 16.

Taking these data together, the present study extends prior literature targeting associations between reward-related brain structures and body mass/adiposity by demonstrating a role of genetic risk for obesity. Here we report that children at a greater genetic risk for obesity exhibit heightened reward responses to naturalistic food cues in the NAcc, as well as larger overall NAcc volumes. In addition, we observed a phenotypic distinction between anthropometric and neural measures, suggesting that normal weight children may be genetically predisposed to overeating through an overactive reward system. Overall, these findings may inform future investigations of genetic influences on the neural mechanisms underlying overeating and obesity by providing preliminary evidence for the association between *FTO* rs9939609 and reward-related regions of the brain.

Methods

Participants. Seventy-eight children (42 male) between the ages of 9 and 12 [mean (SD) = 10.3 (0.8) y] were recruited by phone based on participation in a previous study conducted in our laboratory. In this initial study, 200 children were recruited through community fliers and a contact list from the Children's Hospital at Dartmouth. Participants in the present study were all right-handed, native English speakers, reported normal neurological history, and had normal or corrected-to-normal visual acuity. Each subject provided informed consent in accordance with the guidelines set by the Committee for the Protection of Human Subjects at Dartmouth College and received monetary compensation for participating.

Of the 78 scanned participants, 19 were homozygous high-risk for the *FTO* genotype (AA), 37 were heterozygous (AT), and 22 were homozygous low-risk (TT) (Table S1). The distribution of participants was consistent with the Hardy–Weinberg equilibrium (χ^2 test P value = 0.66). Mean BMI and body fat percentages (SD) were 19.3 (4.3) and 20.1 (8.9), respectively. Two participants (one AA, one AT) were excluded from the fMRI analysis because of excessive movement throughout the scan. Eight participants were excluded from the sMRI analysis because of low signal-to-noise ratios (lower than one SD from the mean) in addition to two that did not pass visual inspection. Of the 76 and 68 participants included in the functional and structural analyses, respectively, mean age, BMI, and body fat percentages did not significantly differ from the full (n = 78) sample. Based on parental report, participants were 85.9% white and non-Hispanic, 1.3% white and Hispanic, and 5.1% unknown race and Hispanic, with the remainder (7.7%) being non-white and non-Hispanic. Because previously reported associations between the *FTO* genotype and obesity-related phenotypes are commonly observed across populations with divergent ancestral origins (34, 35), we conducted a sensitivity analysis restricted to non-Hispanic white participants to account for potential confounding by population stratification (36).

***FTO* Genotype.** Buccal cell swabs were collected and stored at room temperature with desiccant capsules (Isohelix). DNA was isolated using DDK-50 isolation kits (Isohelix). Genotyping for *FTO* rs9939609 was conducted with real-time PCR and Taqman chemistry using the 7500 Fast real-time instrument (primers and instrument from Thermo Fisher Scientific). All samples were successfully genotyped and there was 100% genotyping consistency among the 10% blinded replicates.

BMI and Percent Body Fat. Participants were measured under the guise that our MRI scanner required precise height and weight information, thereby keeping subjects naive to the study purpose. Participants' heights were measured using a professional-grade stadiometer, and weights measured on a Tanita scale (model TBF-300A). This scale additionally computed percentage body fat via bioelectrical impedance analysis. BMI was calculated based on participants' height and weight.

Stimuli. Six minutes of food (n = 15) and 6 min of nonfood (n = 13) commercials were matched for total duration (mean food commercial = 22.5 s; mean nonfood commercial = 22.4 s) and embedded as four "commercial breaks" into an episode of an age-appropriate and gender-neutral television show, Nickelodeon's *Figure it Out*. Nonfood commercials were included as a comparison stimulus to account for low-level visual properties inherent to processing dynamic scenes. Commercials were selected based on quality, recency, and relevance to the age group. To control for differential effects of likeability or salience between food and nonfood conditions, a separate cohort of 24 children [mean (SD) age = 11.3 (0.83) y] rated pseudorandomized subsets of commercials for interest (i.e., "How interesting was this commercial?") and excitement (i.e., "How exciting was this commercial?"). Overall, food and nonfood commercials did not differ in interest [$t_{(26)}$ = 0.55; P = 0.59] or excitement [$t_{(26)}$ = 0.07; P = 0.94] ratings.

Scanning Paradigm. All participants were scanned between the 1530 and 1730 hours to control for differential responses to food related to time of day. Participants were asked not to eat for 2 h before the study session to collect a buccal swab for DNA isolation. Because of this, participants were provided with a standardized snack (*Nature's Valley* granola bar) before the scan to ensure that neural responses were not specific to hunger. All participants either consumed the snack or reported not feeling hungry before the scan. During scanning, commercials were presented using PsychoPy v1.80 (37) in pseudorandomized order so that no more than three commercials of the same condition and no two commercials of the same brand were presented in a row. A fixation cross (2.5–15 s) was presented in-between individual commercials. Although functional scans were not acquired during television viewing, a fixation cross was also randomly presented during the show for consistency. Consistent with our cover story, a set of questions about the television show (including commercials) were asked after the scan, allowing us to verify that participants were attentive throughout the entire duration of the scan. The average correct response rate was 84.7% (SD = 0.11), suggesting that participants were attentive throughout the scanning session.

Image Acquisition. Scanning was performed on a 3T Philips Achieve MRI fit with a 32-channel SENSE (Sensitivity Encoding) headcoil. Structural images were obtained using a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) protocol [repetition time (TR) = 9.9 ms; echo time (TE) = 4.6 ms; flip angle = 8°; 1 × 1 × 1-mm^3 voxels]. Functional images were acquired using a T2*-weighted echo planar imaging (EPI) sequence (TR = 2,500 ms; TE = 35 ms; flip angle = 90°; 3 × 3 × 3-mm^3 voxels; sense factor of 2). Four functional runs were collected (105 TRs each) for each participant.

Functional Image Preprocessing. All functional image preprocessing and subsequent analyses were conducted in SPM8 (Wellcome Department of Cognitive Neurology) in conjunction with a suite of tools available for preprocessing and fMRI analyses (https://github.com/ddwagner/SPM8w). Functional images were slice time-corrected and realigned to account for variability because of head motion. Quality assurance analysis was performed to identify scanning runs with substantial head movement. Any run that included a minimum of seven TRs of 1-mm displacement (one SD above the mean across all participants) was excluded from further analysis. As a result, partial data were included for 16 participants (75% for 9 subjects, 50% for 7 subjects). Resulting images were normalized to the MNI-152 template (Montreal Neurological Institute) and spatially smoothed using a 6 mm full-width half-maximum Gaussian kernel.

Structural Image Preprocessing. Structural images were reconstructed using FreeSurfer, an automated segmentation tool that has been demonstrated to label structures comparably to manual tracing techniques (20). Although visual inspection is commonly used to qualitatively examine the quality of structural MRI data, more recent techniques have additionally allowed for quantitative measurements of anatomical data quality (38, 39). To assess data quality in an unbiased manner, Freesurfer's QA tools (https://surfer.nmr.mgh.harvard.edu/fswiki/QATools) were used to calculate signal-to-noise ratios for each subject as well as to generate a series of screenshots taken from various steps throughout the reconstruction pipeline. Structural images that were one SD below the sample mean [17.1 (SD = 2.6)] or that did not pass standard visual inspection were excluded from the analysis shown in Fig. 2. Here, 10 participants were removed from this analysis, leaving 68 high-quality anatomical images; however, the observed effects were similar within the full sample (n = 78) (Fig. S1).

ROI Analyses. For each subject, a general linear model was used to estimate the contributions of food and nonfood commercials on neural activity across the whole brain. Nuisance regressors included six motion parameters, the session mean, and a linear trend to account for scanner drift. Responses to food commercials were compared against nonfood commercials, and resulting parameter estimates were extracted from probabilistic masks of the left and right NAcc. These masks were anatomically defined in an independent sample of adolescents used in a previous study (17), thus removing the possibility of circularity in our analysis (40). Specifically, these masks were probabilistically defined based off of 75% of subjects contributing overlapping voxels to the group-level masks. For structural analyses, estimates of NAcc volumes were extracted for each individual subject using FreeSurfer (20). Left hippocampal volumes were additionally extracted and used as a control region for comparison, similar to previous studies (41).

Functional and structural estimates of NAcc responses and volumes, respectively, were assessed for differences by *FTO* genotype using a one-way ANOVA. Planned contrasts were used to examine recessive (AA > AT and TT), additive (AA > AT > TT), and dominant (AA and AT > TT) models of the *FTO* rs9939609 polymorphism. Structural analyses included estimated intracranial volume as a covariate of no interest to account for overall differences in brain volume. All statistical analyses were performed with and without the inclusion of BMI or percentage body fat (in addition to age and gender) to account for potential effects related to body weight or adiposity (Tables S3 and S4).

Multiple Comparisons Correction. To account for the known collinearity among additive, dominant, and recessive genetic models in addition to potentially collinear measurements (e.g., left and right NAcc structure and function), a stringent approach was used to correct for the detection of false-positive associations (i.e., type I errors). The pairwise correlations (Pearson's r) between all measurements reported throughout the report were computed, producing an 18 × 18 [three genetic models × (two anthropometric variables + four neural variables)] correlation matrix. This matrix represents the linkage disequilibrium among the genetic phenotypes and was used to determine the number of independent tests (M_{eff}) via spectral decomposition software (gump.qimr.edu.au/general/daleN/matSpD). The resulting M_{eff} value was then used to determine the significance threshold (α) based on Šidák correction (42) as well as Bonferroni correction (43). The difference between the Šidák- and Bonferroni-corrected α was negligible (0.0002) and produced equivalent interpretations of significant results. Thus, Šidák correction was used here because of its relevance for genetic models and prevalence in the literature; however, alternative correction procedures [e.g., false-discovery rate (FDR) correction, Bonferroni using M_{eff}] are reported in *SI Text*.

Exploratory Whole-Brain Analysis. In addition to ROI analyses targeting the NAcc, an exploratory whole-brain analysis was performed to facilitate comparison with prior neuroimaging studies on the influence of the *FTO* gene on the brain. Whole-brain contrast maps comparing food commercials to nonfood commercials were used as input into a between-subjects group-level analysis comparing at-risk individuals to low-risk individuals. At-risk individuals included both AT and AA individuals (n = 54), consistent with previous analyses (e.g., ref. 15). Low-risk individuals included TT genotyped individuals only (n = 22). The resulting voxelwise group-level map was thresholded at $P < 0.05$ and cluster-corrected at $P < 0.05$ based on 5,000 Monte Carlo simulations.

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