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FTO affects food cravings and interacts with age to influence age-related decline in food cravings

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ABSTRACT

The fat mass and obesity associated gene (FTO) was the first gene identified by genome-wide association to correlate with higher body mass index (BMI) and increased odds of obesity. FTO remains the locus w largest and most replicated effect on body weight, but the mechanism whereby FTO affects body weight development of obesity is not fully understood. Here we tested whether FTO is associated with differe food cravings and a key aspect of dopamine function that has been hypothesized to influence food mechanisms. Moreover, as food cravings and dopamine function are known to decline with age, we ex effects of age on relations between FTO and food cravings and dopamine function. Seven-eight healthy s between 22 and 83 years old completed the Food Cravings Questionnaire and underwent genotyping f rs9939609, the first FTO single nucleotide polymorphism associated with obesity. Compared to TT homoz individuals carrying the obesity-susceptible A allele had higher total food cravings, which correlated with BMI. Additionally, food cravings declined with age, but this age effect differed across variants of FTO rs99 while TT homozygotes showed the typical age-related decline in food cravings, there was no such decline A carriers. All subjects were scanned with [18F]fallypride PET to assess a recent proposal that at the chemical level FTO alters dopamine D2-like receptor (DRD2) function to influence food reward relat chanisms. However, we observed no evidence of FTO effects on DRD2 availability.

1. Introduction

Studies of heritability have found that genetic differences explain 40% to 70% of the variance in individual susceptibility to obesity [12,26], which affects > 10% of the world's population [6]. In 2007, the fat mass and obesity associated gene (FTO) became the first gene identified by genome-wide association studies to correlate with higher body mass index (BMI) and increased odds of obesity [15,33]. Subsequent genome-wide studies have linked other loci with obesity susceptibility, but FTO remains the locus with the largest effect [36] and is the most widely replicated across ethnic groups [25]. The risk allele is also common, with the minor allele frequency ranging from 12% in East

It has also been proposed that FTO influences food reward chanisms. Individuals with at least one A allele of FTO rs993960 first FTO single nucleotide polymorphism associated with obesity) been reported to show greater externally driven eating [40], lo satiety [10,41], enhanced fMRI response to food [20], and report frequent loss of control over eating than those having two T a [39]. The control of eating is particularly hard in the conte heightened food cravings [17], but little data have addressed wh FTO rs9939609 is associated with alterations in food cravings study [18] observed no relation between FTO and participant sponses on one question about how often they experienced cravi the previous week, but there was an indication of a possible intera

Asians to 42% in Europeans [23]. The mechanism whereby FTO affects body weight and the development of obesity is not well understood, but evidence to date suggests a role for FTO in adipogenesis, energy metabolism, and nutrient intake [42].

between FTO and diet on the change in craving from baseli 6 months after participating in a weight loss program, with evide an FTO effect only arising in those with high protein intake. In e ating such a result, it is worth noting that food craving

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multidimensional construct [4]. It is not clear which aspects of craving this single-question test captured and how different aspects of cravings relate to FTO. It is also unclear whether the restriction of the sample to overweight and obese subjects impacted the ability to observe effects.

Given the importance of dopamine to reward and addictive behavior [11], it is striking that at the neurochemical level, mice with deficient FTO expression exhibit characteristics similar to mice lacking midbrain dopamine D2 receptors (DRD2) [2,16]. Moreover inactivation of the FTO gene impaired DRD2-dependent neuronal and reward responses in mice, though the study did not observe a significant difference in body weight or DRD2 expression between FTO-deficient and control mice [16]. Still, other evidence of FTO effects on dopamine-dependent reward learning [34] and resting state functional connectivity in dopaminergic circuitries [30] has led to the recent proposal that FTO alters DRD2 function in the presence of an obesogenic diet to confer risk for obesity [38]. Evidence of an association between FTO and DRD2 function in humans would further support this hypothesis.

Potential relations between FTO, cravings, and DRD2 availability must unfold in the context of life-span development. Fat mass is well-known to increase across adulthood [37] and at least one FTO risk gene (rs1421085) has been reported to impact the trajectory of weight gain as well as personality traits and ventral and medial prefrontal brain functions [5]. At the neurochemical level, the most replicated finding in the dopamine imaging literature is the robust decline in DRD2 availability across adulthood [19,21]. We recently reported that associations between DRD2 and BMI change with age [9]. Finally, both the intensity of craving and the number of foods craved decline with age [1,19,31]. It is not yet known whether FTO influences the age-related decline in either food cravings or DRD2. However, given the developmental trajectories of these phenotypic variables, it is important to determine whether any potential relations with FTO vary or interact with age.

The present study had three objectives. First, we examined the role of FTO rs9939609 in food cravings in individuals spanning the BMI continuum from normal weight to obese. Nine dimensions of food cravings were assessed using the psychometrically validated Food Cravings Questionnaire [4] to understand the specificity of the relation between FTO rs9939609 and food cravings. Second, we tested the hypothesis that FTO influences DRD2 availability, assessed using PET and the high-affinity DRD2 radioligand [18F]fallypride. Lastly, we explored effects of age on the relation between FTO, food cravings, and DRD2 to determine whether expected age-related declines in food cravings and DRD2 availability vary across FTO rs9939609 allele groups. The results of these inquiries may shed light on possible mechanisms whereby FTO influences body weight that can be utilized to facilitate greater specificity for therapies combatting obesity.

psychostimulants (excluding caffeine) more than twice at any ti their life or at all in the past 6 months, or any psychotropic medic in the last 6 months other than occasional use of benzodiazepin sleep. Any illicit drug use in the last 2 months was grounds for sion, even in subjects who did not otherwise meet criteria for subs abuse. Urine drug tests were administered, and subjects testing po for the presence of amphetamines, cocaine, marijuana, PCP, op benzodiazepines, or barbiturates were excluded. Written info consent was obtained from all subjects. This study was approved b Institutional Review Boards at Yale University and Vanderbilt versity and performed in accordance with the ethical standards 1964 Declaration of Helsinki and its later amendments. Dat available at the Open Science Framework.

2.2. Genotyping of FTO

Blood samples from each subject were genotyped for rs9939609 via Sequenom analysis performed at Vanderbilt Unive VANTAGE Genomics Core (see [32] for detailed Sequenom genot methods).

2.3. Food cravings questionnaire – Trait version

The Food Cravings Questionnaire assesses motivational state promote food cravings and ingestive behaviors and has been de strated to possess good internal consistency and test-retest relia [4]. The self-report questionnaire consists of 39 questions assess dimensions of food cravings: 1) having intentions or plans to con food, 2) anticipation of positive reinforcement that may result eating, 3) anticipation of relief from negative states and feeling result of eating, 4) lack of control over eating, 5) thoughts o occupation with food, 6) cravings as a physiological state, 7) emo that may be experienced before or during food cravings or eati cues that may trigger food cravings, and 9) guilt from cravings a for giving into them.

2.4. PET data acquisition

PET imaging was performed on a GE Discovery STE scanner lo at Vanderbilt University Medical Center. The scanner had an axi solution of 4 mm and in-plane resolution of 4.5–5.5 mm FWHM center of the field of view. [18F]fallypride ((S)-N-[(1-allyl-2-py dinyl)methyl]-5-(3[18F]fluoropropyl)-2,3- dimethoxybenzamide)

2. Methods

2.1. Subjects

Seventy-eight healthy subjects between 22 and 83 years old (mean age 49.9 ± 18.0 years, 46 females, mean BMI 27.0 ± 5.1) from the Nashville, TN metro area were recruited to participate in this study. Exclusion criteria included any history of psychiatric illness on a screening interview (a Structural Interview for Clinical DSM-IV Diagnosis was also available for all subjects and confirmed no history of major Axis I disorders) [13], any history of head trauma, any significant medical condition, or any condition that would interfere with MRI (e.g. inability to fit in the scanner, claustrophobia, cochlear implant, metal fragments in eyes, cardiac pacemaker, neural stimulator, pregnancy, and metallic body inclusions or other contraindicated metal implanted in the body). Subjects with major medical disorders including diabetes and/or abnormalities on screening comprehensive metabolic panel or

2.6. [18F]fallypride binding potential (BP_{ND}) image calculation

Voxelwise D2/D3 binding potential images were calculated using the simplified reference tissue model, which has been shown to provide stable estimates of [18F]fallypride BP_{ND} [35]. The cerebellum served as the reference region because of its relative lack of D2/D3 receptors [3]. The cerebellar reference region was obtained from an atlas provided by the ANSIR laboratory at Wake Forest University. Limited PET spatial resolution introduces blurring and causes signal to spill onto neighboring regions. Because the anterior cerebellum is located proximal to the substantia nigra and colliculus, which both have DRD2, only the posterior 3/4 of the cerebellum was included in the region of interest (ROI) to avoid contamination of [18F]fallypride signal from the midbrain nuclei. The cerebellum ROI also excluded voxels within 5 mm of the overlying cerebral cortex to prevent contamination from cortical signals. The bilateral putamen ROI, drawn according to established guidelines [27] on the MNI brain, served as the receptor rich region in the analysis. The cerebellum and putamen ROIs were registered to each subject's T1 image using FSL non-linear registration of the MNI template to each individual subject's T1. T1 images and their associated cerebellum and putamen ROIs were then coregistered to the mean image of all realigned frames in the PET scan using FSL-FLIRT (http://www.fmrib.ox.ac.uk/fsl/, version 6.00). Emission images from the 3 PET scans were merged temporally into a 4D file. To correct for motion during scanning and misalignment between the 3 PET scans, all PET frames were realigned using SPM8 (www.fil.ion.ucl.ac.uk/spm/) to the frame acquired 10 min post injection. Model fitting and BP_{ND} calculation were performed using the PMOD Biomedical Imaging Quantification software (PMOD Technologies, Switzerland). Binding potential images represent the ratio of specifically bound ligand ([18F]fallypride in this study) to its free concentration (Fig. 1).

Mean BP_{ND} in the striatum, which has the highest concentration of postsynaptic DRD2 in the brain, and the midbrain, the site of dopamine neurons on which presynaptic DRD2 are located, were extracted to test for association with FTO rs9939609. The bilateral midbrain and 3 striatal ROIs (caudate, putamen, and ventral striatum/nucleus accumbens) were drawn in MNI standard space using previously described guidelines (Fig. 1) [8,27], registered to PET images using the same transformations for cerebellum registration to PET images, and thresholded at 0.5 after coregistration to exclude voxels on the border that had < 50% probability of being part of the ROI, thus ensuring high

produced in the radiochemistry laboratory attached to the PET following synthesis and quality control procedures described Food and Drug Administration IND 47,245. [18F]fallypride is a stituted benzamide with very high affinity to D2/D3 receptors [28 emission acquisition scans were performed following a 5.0 mCi bolus injection of [18F]fallypride (specific activity > 3000 Ci/m CT scans were collected for attenuation correction prior to each three emission scans, which together lasted approximately 3.5 h, two 15-min breaks for subject comfort. PET images were reconstr with decay correction, attenuation correction, scatter correction calibration.

2.5. MRI data acquisition

Structural MRI scans were performed on a 3 Tesla Phillips Ac scanner located at the Vanderbilt University Institute for Im Science (VUIIS). T1-weighted high-resolution 3D anatomical

tissue probability for each ROI masks. Relations between rs9939609 and BP_{ND} outside the striatum and midbrain were exa with an exploratory voxelwise analysis.

3. Results

3.1. FTO rs9939609 and food cravings

There were 10 AA homozygotes, 40 AT heterozygotes, and 2 homozygotes. The allele frequencies were in Hardy-Weinberg e brium ($^2 = 0.542$, $p > 0.4$). There was no difference in age or g composition between TT homozygotes and individuals carrying at one A allele. Compared to TT homozygotes, A carriers had higher food cravings score (Fig. 2A). We explored the specificity of FTO e on food cravings by examining the role of FTO in each of the ni mensions of food cravings. At the significance level corrected for tiple comparisons of nine dimensions ($p < 0.006$), A carriers s higher than TT homozygotes on 3 dimensions: anticipation of from negative states and feelings as a result of eating, having inter or plans to consume food, and emotions that may be experienced b or during food cravings or eating. A carriers also scored higher other dimensions at the uncorrected significance level ($p <$ anticipation of positive reinforcement that may result from eatin thoughts or preoccupation with food. There were trends ($p < 0.$ A carriers having higher guilt from cravings and/or for giving into and lack of control over eating. There was no difference betwe homozygotes and A carriers in responses to cues that may trigger cravings and cravings as a physiological state (Table 1). These r did not change when we controlled for age, gender, and BMI.

3.2. Total food cravings and BMI

Total food craving scores positively associated with BMI (= $t_{74} = 2.236$, $p < 0.05$), controlling for age and gender. Howev seen in Fig. 2B, this association was driven by 3 participants with in the Obese class III category (40), and was weaker without the participants (= 0.20, t = 1.71, $p < 0.1$). Unexpectedly, BMI di significantly associate with FTO rs9939609 (= 0.04, t_{71} = $p > 0.7$).

3.3. E ects of age on FTO rs9939609 and total food cravings

As expected, food cravings declined with increasing

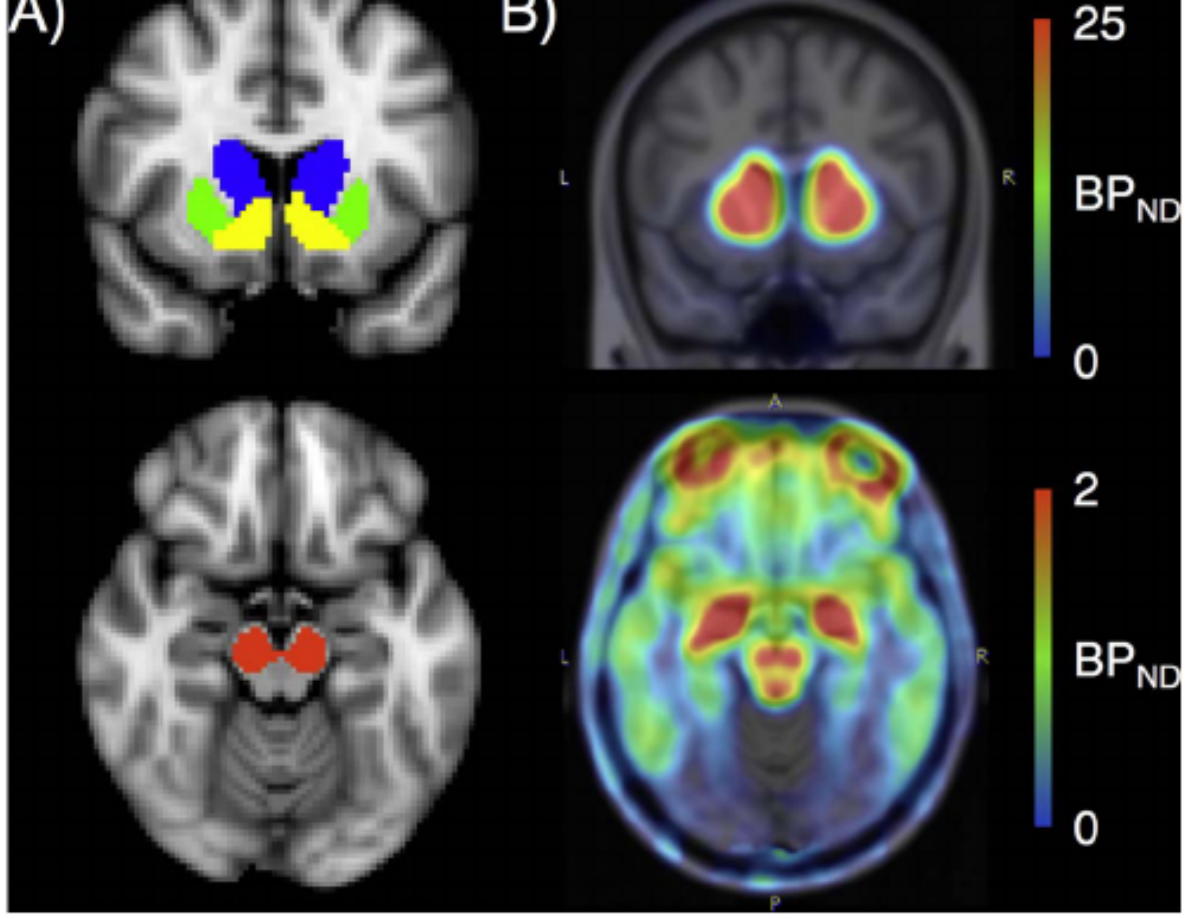

Fig. 1. [18F]fallypride BP_{ND} images reflecting DRD2 availability. A) Shown are regions of

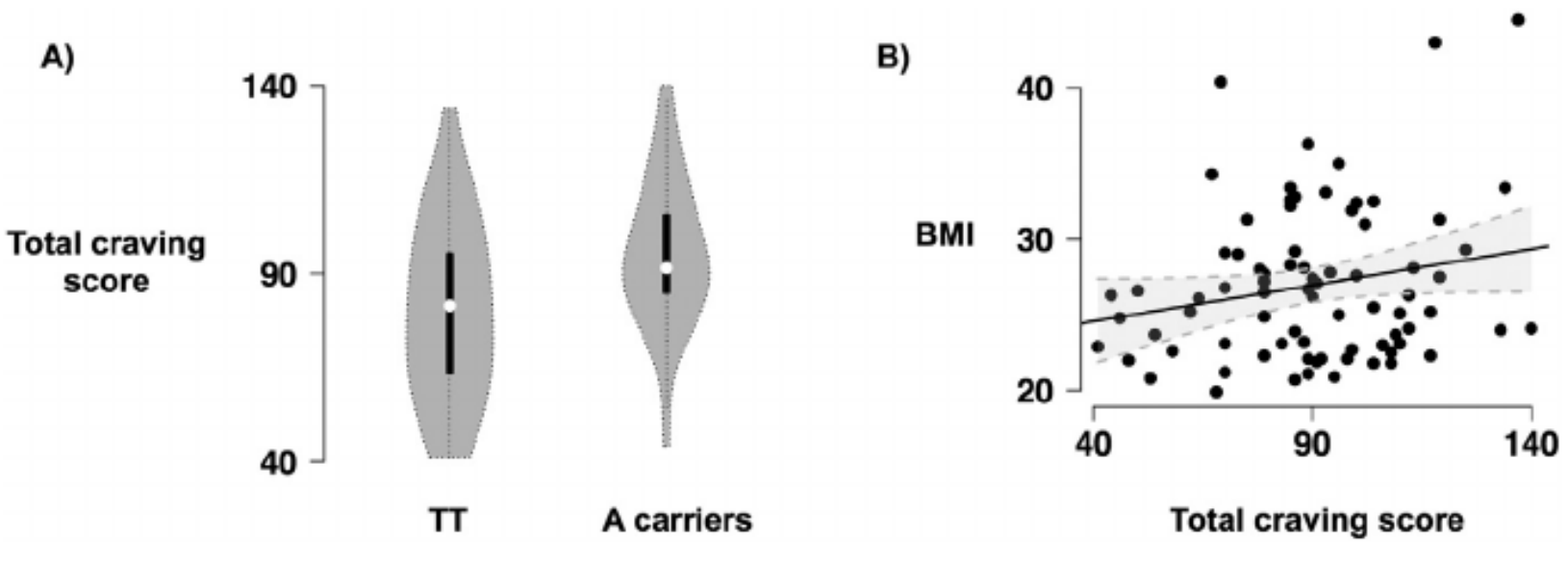

Fig. 2. FTO, food cravings, and BMI. A) Compared homozygotes, A carriers had higher total food c (t_{76} = 3.02, $p < 0.01$). B) Food cravings were po associated with BMI (t_{74} = 2.236, $p < 0.05$).

$p > 0.5$, all $|r| < 0.12$). [18F]fallypride BP_{ND} declined with age as expected (all $r < 0.48$, all $p < 0.00001$), but there was no significant interaction of age and FTO rs9939609 on BP_{ND} (all $p > 0.1$, all $|r| < 0.17$).

Food cravings did not correlate with [18F]fallypride BP_{ND} in the striatum or midbrain (all $p > 0.1$, all $|r| < 0.16$). Additionally FTO rs9939609 did not significantly interact with [18F]fallypride BP_{ND} in the striatum or midbrain to predict food cravings (all $p > 0.1$, all $|r| < 0.18$). Results controlled for gender and age.

4. Discussion

Among individuals spanning the BMI continuum from normal weight to obese, those with at least one FTO rs9939609 obesity-susceptible A allele, relative to TT homozygotes, reported higher food cravings. This relation remained after controlling for BMI, suggesting that FTO rs9939609 influences food cravings independent of individual differences in BMI. These results are congruent with a previous finding that individuals with the A allele reported higher lack of control over eating, which positively correlates with food cravings [17,39]. Of the nine dimensions of food cravings, FTO rs9939609 was most strongly associated with emotions (predominantly negative) that may be experienced before or during food cravings or eating, the anticipation of relief from negative states and feelings as a result of eating, and having intentions or plans to consume food. These three dimensions suggest that FTO rs9939609 particularly influences processes that promote food

(r_{76} = 0.28, $p < 0.05$) (Fig. 3A). Furthermore, age interacted FTO to predict food cravings (= 0.70, t = 2.06, $p < 0.05$). cravings declined with age among TT homozygotes (r_{26} = $p < 0.01$), but among A carriers, there was no significant correl between food cravings and age (r_{48} = 0.13, $p > 0.3$) (Fig. Results did not change after controlling for gender and BMI.

3.4. FTO rs9939609 and DRD2 availability

There was no significant difference between TT homozygotes a carriers in [18F]fallypride BP_{ND} in the midbrain or striatum: cau putamen, and ventral striatum (Fig. 4) (Table 1). Voxelwise analys not identify any significant difference between TT homozygotes a carriers in BP_{ND} outside the striatum and midbrain, in additi confirming the lack of such association in the striatum and midb even at the liberal voxel-level threshold of $p < 0.001$ uncorrecte multiple comparisons. Sun et al. [38] proposed that FTO interacts an obesogenic diet to alter DRD2 function and consequently weight, suggesting that the relation between FTO and DRD2 mig more discernable among obese individuals. There were 18 subjects

Interestingly, the two dimensions not associated with FTO rs993 (cravings as a physiological state and cues that may trigger food ings) are the two dimensions that involve sensory cues, such as ex food cues and physiological sensations. This specificity of rs9939609 effects on food cravings suggests that FTO rs993960 fluences the cognitive and motivational, rather than sensory, proc involved in food cravings. The specificity of observed FTO rs993 effects may explain a previous study's observation of no relatio tween FTO rs9939609 and response on one question about r craving frequency [18] as this unvalidated generic question may been too general to capture features of craving related to rs9939609. We note that our suggestion that FTO has less impa responses to sensory cues in our adult sample stands in contras past finding that the FTO risk allele was associated with parental r of enhanced food responsiveness (eating when food is availab children [40]. This may reflect differences in constructs across sures or a developmental difference. Responses to reward mature development from lower-order sensory processing in subcortica limbic regions to higher-order processing in frontal cortical brain that allow integration of valuation and top-down goal driven beh [22], and so the impact of FTO may be developmentally specific

Consistent with the extant literature, food cravings declined a adulthood. Our results further demonstrated that FTO rs993960 teracted with age to predict food cravings. Among TT homozy food cravings declined with age as previously reported. How among individuals carrying the obesity-susceptible A allele, ther no significant decline in food cravings with age. This preservati

and food seeking behavior as a countermeasure to negative states.

Table 1
Demographics, food cravings scores, and [18F]fallypride BP_{ND}.

	A carriers	TT homozygotes	t_{76}	p-value	95% CI
N	50	28			
Age (yrs)	49.0 ± 18.5	51.6 ± 17.2	0.60	0.551	5.94, 1
Gender	29F	17F	0.23	0.818	
Total craving score	95.3 ± 19.5	80.2 ± 23.8	3.02	0.003 **	5.11, 24
Planning	8.4 ± 2.3	6.7 ± 2.3	3.10	0.003 **	0.60, 2.7
Pos Reinforcement	13.4 ± 3.6	11.2 ± 3.4	2.63	0.010 *	0.53, 3.8
Neg Relief	7.2 ± 2.1	5.6 ± 2.1	3.13	0.003 **	0.57, 2.5
Lack Control	12.9 ± 4.4	11.1 ± 4.2	1.73	0.088	0.27, 3.
Thoughts	13.2 ± 4.4	10.9 ± 4.0	2.31	0.024 *	0.32, 4.3
Hunger	11.4 ± 2.8	10.7 ± 2.7	0.98	0.331	0.67, 1.
Emotion	9.6 ± 3.4	7.3 ± 3.2	2.88	0.005 **	0.70, 3.8
Environment	11.5 ± 3.7	10.1 ± 4.0	1.54	0.127	0.41, 3.
Guilt	7.7 ± 2.6	6.6 ± 2.6	1.94	0.056	0.03, 2
Caudate BP_{ND}	13.8 ± 3.6	13.5 ± 3.6	0.33	0.743	1.42, 1.
Putamen BP_{ND}	23.2 ± 3.5	22.7 ± 3.8	0.51	0.613	1.27, 2.
Ventral striatal BP_{ND}	14.0 ± 2.5	14.0 ± 2.8	0.07	0.941	1.25, 1.1
Midbrain BP_{ND}	1.2 ± 0.2	1.2 ± 0.2	0.62	0.540	0.07, 0.

Note: Planning = having intentions or plans to consume food; Pos Reinforcement = anticipation of positive reinforcement that may result from eating; Neg Relief = anticipation of
from negative states and feelings as a result of eating; Lack Control = lack of control over eating; Thoughts = thoughts or preoccupation with food; Hunger = craving as a physiol

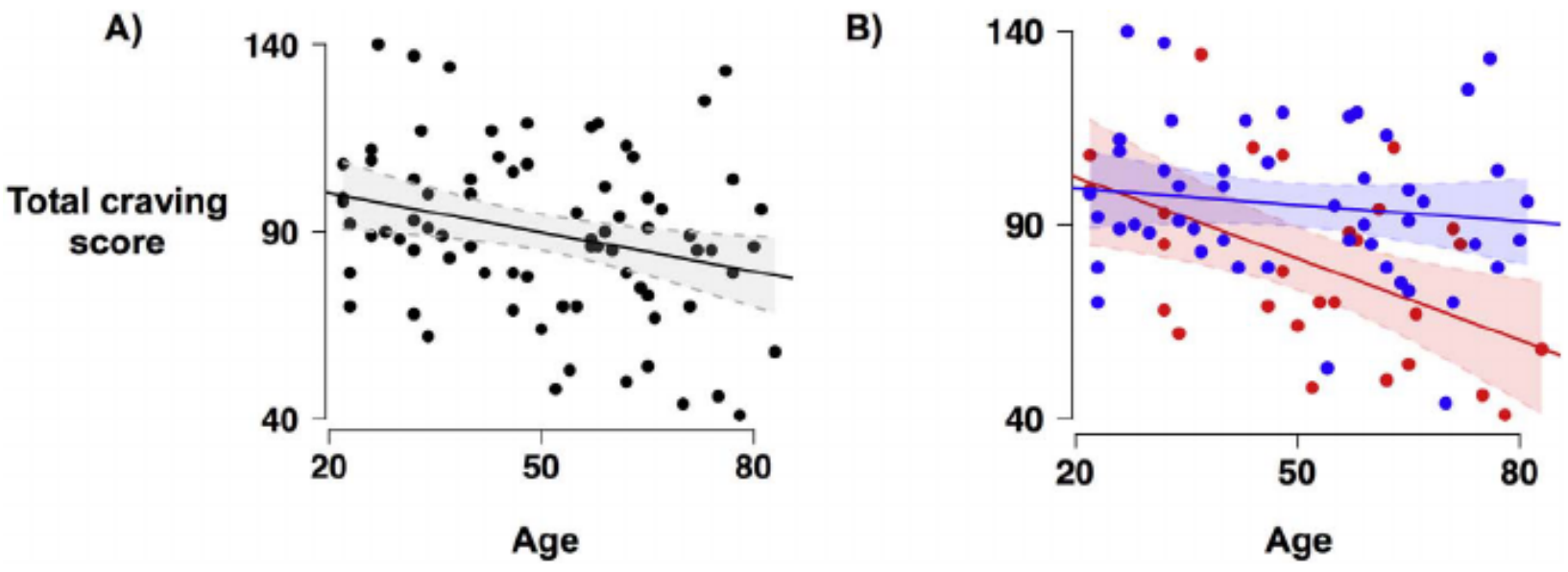

Fig. 3. FTO-age interaction on food cravings. A
cravings declined with age across all s
(r_{76} = 0.28, p < 0.05). B) Among TT homozy
food cravings declined with age (r_{26} = 0.51, p <
(red), but among A carriers, there was no significa
relation between food cravings and age (r_{48} =
p > 0.3) (blue). (For interpretation of the referen
colour in this figure legend, the reader is referred
web version of this article.)

food cravings across adulthood may be specific to craving for fat, rather than protein or carbohydrate, as age-related decline in fat intake has been found significantly reduced among A carriers [5]. Given the positive association between food cravings and BMI, in our data and as previously shown [14], these results suggest that individuals carrying the A allele are at risk for larger weight gain over the course of aging as fat mass in the body often increases with age [29]. We note that FTO rs9939609 did not associate with BMI in this sample. Genome-wide studies found the relation between FTO and BMI by scanning the genome of tens of thousands of subjects, and the effects have been replicated [24]. It is possible that the lack of effect here just reflects low statistical power, but we cannot rule out that selection biases, such as the requirement that all subjects be medically and psychiatrically healthy, with no contraindications for scanning and willing to participate, may have limited our ability to observe an effect. The lack of an FTO effect on BMI in this sample strongly suggests that FTO effects on craving are not a consequence of differential BMI across groups.

We explored the proposal that FTO modulates DRD2 function to influence body weight. Using PET-[18F]fallypride to assess DRD2 availability, we did not observe any significant association between FTO rs9939609 and DRD2 availability, nor any relation between DRD2 availability and food cravings. Sun et al. [38] hypothesized that FTO interacts with an obesogenic diet to alter DRD2 function and body

specific aspects of DRD2 function. Additionally, although rs99396
the first single nucleotide polymorphism in the FTO gene assoc
with obesity, other FTO single nucleotide polymorphisms have
linked to obesity since then and it is not known whether other
single nucleotide polymorphisms affect DRD2 function. Noneth
until there is evidence showing FTO effects on DRD2 function i
mans, the present results suggest caution in translating such effe
mice to FTO function in humans.

It is worth noting that our finding of a positive correlation bet
food cravings and BMI was weaker without 3 Obese class III pa
pants, and that a previous study did not observe a relation betwee
rs9939609 and food craving in obese individuals [18]. These r
suggest that obese subjects may represent a distinct category wit
ferent relationships between FTO, food cravings, and BMI. Futur
dies with sufficient number of obese and non-obese participants w
provide clarity. Moreover the present study excluded individuals
major medical conditions including those associated with obesity,
as diabetes. Individuals with obesity-related medical conditions
also represent another category from individuals without these me
conditions in the context of FTO. We additionally note that FTO e
on BMI vary across ethnicities [24], and this may impact relation
tween FTO and food cravings in different ethnic groups. While
effect size is similar among individuals of Asian and European des

weight, suggesting that the relation between FTO and DRD2 might be more discernable among obese individuals. We also did not observe any relation between FTO rs9939609 and DRD2 availability among participants with BMI > 30. Besides DRD2 availability, there are other characteristics of DRD2 function such as receptor affinity, susceptibility to desensitization, and responsiveness to up/down regulation [7]. Our data did not speak to the relation between FTO rs9939609 and these

the frequency of the FTO obesity-susceptible A allele is much among Asians than Europeans. Also, relative to Europeans, Af Americans exhibit lower correlations between different FTO nucleotide polymorphisms linked to obesity, and this may impac associations with obesity traits [24]. The present study did not sufficient representation of different ethnic groups to address the r ethnicity in FTO effects.

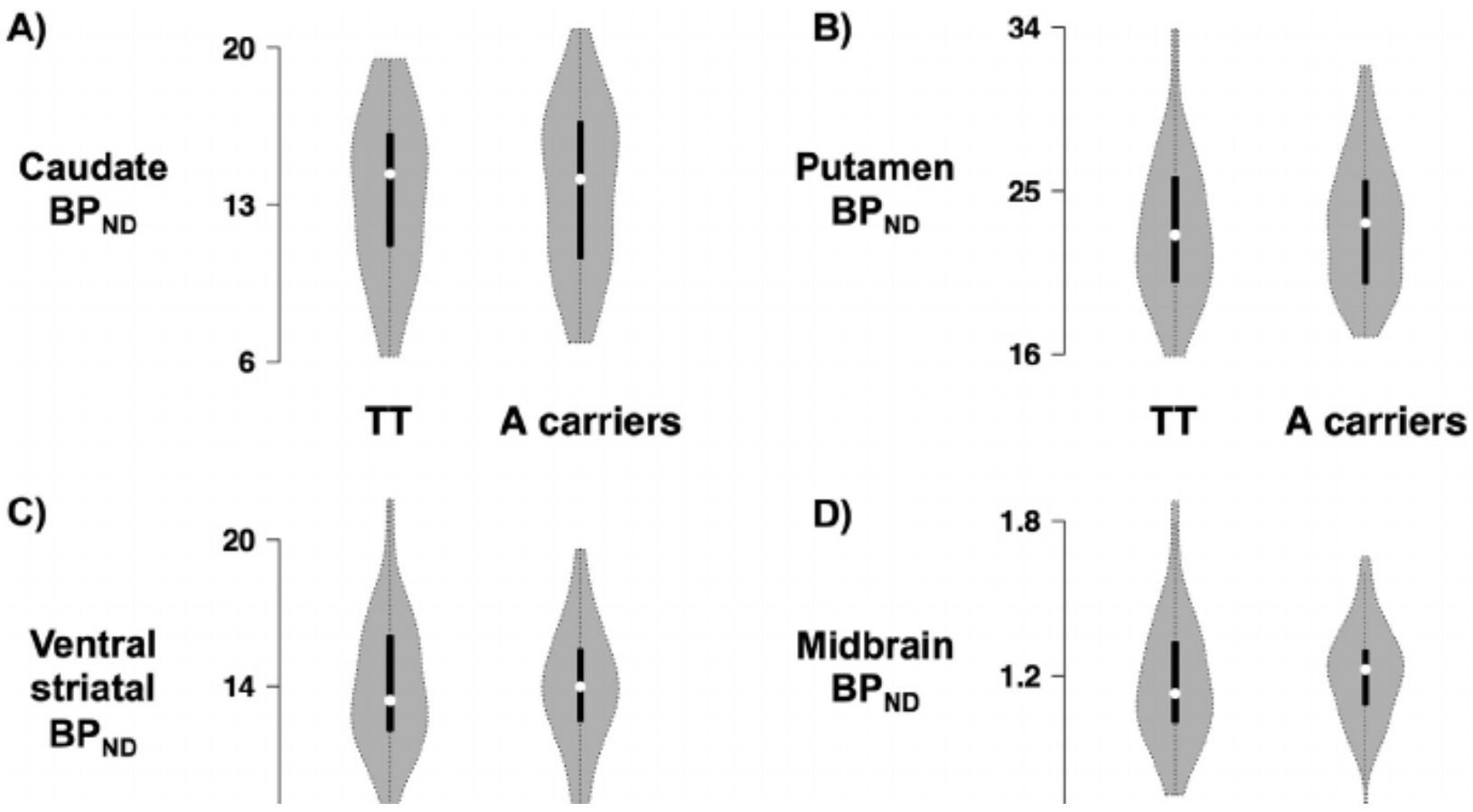

Fig. 4. FTO and DRD2 availability. No significant ence between TT homozygotes and A carriers in [1 ypride BP_{ND} in the A) caudate (t_{76} = 0.33, p > putamen (t_{76} = 0.51, p > 0.5), C) ventral s (t_{76} = 0.07, p > 0.5), or D) midbrain (t_{76} p > 0.5).

A clear limitation of this study is the small sample size, which was necessitated by the expense, time, and safety demands of PET imaging. Although this study had the advantage of testing specific hypotheses of FTO function, genomic studies often involve tens, if not hundreds, of thousands of subjects, because single gene effects are typically modest. This naturally suggests caution in interpreting underpowered analyses. Additionally, although the wide age range in this study allowed an examination of age effects on FTO function, it also introduced a variable that might have obscured the ability to detect some FTO effects, which could explain the lack of a relation between FTO rs9939609 and BMI in this study even though this association has been reported by multiple researchers.

In conclusion, the present results showed that relative to FTO rs9939609 TT homozygotes, individuals with at least one A allele reported greater food cravings, which positively correlated with BMI. A carriers also did not show the typical age-related decline in food cravings, suggesting that they are at risk for larger weight gain over the course of aging as fat mass often increases with age. While these conclusions are limited by the small sample size, and do not indicate the precise mechanism through which FTO influences food craving, we hope that the present findings encourage future studies to examine FTO's impact on food craving in a broader sample.

Con ict of interest

All authors report no conflict of interest.

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