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

It has also been proposed that FTO influences food reward mechanisms. Individuals with at least one A allele of FTO rs9939609 (the first FTO single nucleotide polymorphism associated with obesity) have been reported to show greater externally driven eating [40], lowered satiety [10,41], enhanced fMRI response to food [20], and report more frequent loss of control over eating than those having two T alleles [39]. The control of eating is particularly hard in the context of heightened food cravings [17], but little data have addressed whether FTO rs9939609 is associated with alterations in food cravings. One study [18] observed no relation between FTO and participants' responses on one question about how often they experienced cravings in the previous week, but there was an indication of a possible interaction between FTO and diet on the change in craving from baseline to 6 months after participating in a weight loss program, with evidence of an FTO effect only arising in those with high protein intake. In evaluating such a result, it is worth noting that food craving is a

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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 [<sup>18</sup>F]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.

## 2. Methods

### 2.1. Subjects

Seventy-eight healthy subjects between 22 and 83 years old (mean age  $49.9 \pm 18.0$  years, 46 females, mean BMI  $27.0 \pm 5.1$ ) 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 complete blood count were excluded. Subjects were also excluded if they reported a history of substance abuse, current tobacco use, alcohol consumption > 8 oz of whiskey or equivalent per week, use of

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

### 2.2. Genotyping of FTO

Blood samples from each subject were genotyped for FTO rs9939609 via Sequenom analysis performed at Vanderbilt University's VANTAGE Genomics Core (see [32] for detailed Sequenom genotyping methods).

### 2.3. Food cravings questionnaire – Trait version

The Food Cravings Questionnaire assesses motivational states that promote food cravings and ingestive behaviors and has been demonstrated to possess good internal consistency and test-retest reliability [4]. The self-report questionnaire consists of 39 questions assessing 9 dimensions of food cravings: 1) having intentions or plans to consume food, 2) anticipation of positive reinforcement that may result from eating, 3) anticipation of relief from negative states and feelings as a result of eating, 4) lack of control over eating, 5) thoughts or pre-occupation with food, 6) cravings as a physiological state, 7) emotions that may be experienced before or during food cravings or eating, 8) cues that may trigger food cravings, and 9) guilt from cravings and/or for giving into them.

### 2.4. PET data acquisition

PET imaging was performed on a GE Discovery STE scanner located at Vanderbilt University Medical Center. The scanner had an axial resolution of 4 mm and in-plane resolution of 4.5–5.5 mm FWHM at the center of the field of view. [<sup>18</sup>F]fallypride ((S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[<sup>18</sup>F]fluoropropyl)-2,3-dimethoxybenzamide) was produced in the radiochemistry laboratory attached to the PET unit, following synthesis and quality control procedures described in US Food and Drug Administration IND 47,245. [<sup>18</sup>F]fallypride is a substituted benzamide with very high affinity to D2/D3 receptors [28]. 3D emission acquisition scans were performed following a 5.0 mCi slow bolus injection of [<sup>18</sup>F]fallypride (specific activity > 3000 Ci/mmol). CT scans were collected for attenuation correction prior to each of the three emission scans, which together lasted approximately 3.5 h, with two 15-min breaks for subject comfort. PET images were reconstructed with decay correction, attenuation correction, scatter correction, and calibration.

### 2.5. MRI data acquisition

Structural MRI scans were performed on a 3 Tesla Phillips Achieva scanner located at the Vanderbilt University Institute for Imaging Science (VUIIS). T1-weighted high-resolution 3D anatomical scans (TR = 8.9 ms, TE = 4.6 ms, FOV = 256 × 256, voxel dimensions = 1 × 1 × 1 mm) were obtained for each participant to aid coregistration and spatial normalization of PET images.

## 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/](http://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

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

## 3. Results

### 3.1. FTO rs9939609 and food cravings

There were 10 AA homozygotes, 40 AT heterozygotes, and 28 TT homozygotes. The allele frequencies were in Hardy-Weinberg equilibrium ( $\chi^2 = 0.542$ ,  $p > 0.4$ ). There was no difference in age or gender composition between TT homozygotes and individuals carrying at least one A allele. Compared to TT homozygotes, A carriers had higher total food cravings score (Fig. 2A). We explored the specificity of FTO effects on food cravings by examining the role of FTO in each of the nine dimensions of food cravings. At the significance level corrected for multiple comparisons of nine dimensions ( $p < 0.006$ ), A carriers scored higher than TT homozygotes on 3 dimensions: anticipation of relief from negative states and feelings as a result of eating, having intentions or plans to consume food, and emotions that may be experienced before or during food cravings or eating. A carriers also scored higher on 2 other dimensions at the uncorrected significance level ( $p < 0.05$ ): anticipation of positive reinforcement that may result from eating and thoughts or preoccupation with food. There were trends ( $p < 0.1$ ) for A carriers having higher guilt from cravings and/or for giving into them and lack of control over eating. There was no difference between TT homozygotes and A carriers in responses to cues that may trigger food cravings and cravings as a physiological state (Table 1). These results 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 ( $\beta = 0.26$ ,  $t_{74} = 2.236$ ,  $p < 0.05$ ), controlling for age and gender. However, as seen in Fig. 2B, this association was driven by 3 participants with BMI in the Obese class III category ( $\geq 40$ ), and was weaker without these 3 participants ( $\beta = 0.20$ ,  $t = 1.71$ ,  $p < 0.1$ ). Unexpectedly, BMI did not significantly associate with FTO rs9939609 ( $\beta = 0.04$ ,  $t_{71} = 0.324$ ,  $p > 0.7$ ).

### 3.3. Effects of age on FTO rs9939609 and total food cravings

As expected, food cravings declined with increasing age ( $r_{76} = -0.28$ ,  $p < 0.05$ ) (Fig. 3A). Furthermore, age interacted with FTO to predict food cravings ( $\beta = 0.70$ ,  $t = 2.06$ ,  $p < 0.05$ ). Food cravings declined with age among TT homozygotes ( $r_{26} = -0.51$ ,  $p < 0.01$ ), but among A carriers, there was no significant correlation between food cravings and age ( $r_{48} = -0.13$ ,  $p > 0.3$ ) (Fig. 3B). 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 and A carriers in [18F]fallypride  $BP_{ND}$  in the midbrain or striatum: caudate, putamen, and ventral striatum (Fig. 4) (Table 1). Voxelwise analysis did not identify any significant difference between TT homozygotes and A carriers in  $BP_{ND}$  outside the striatum and midbrain, in addition to confirming the lack of such association in the striatum and midbrain, even at the liberal voxel-level threshold of  $p < 0.001$  uncorrected for multiple comparisons. Sun et al. [38] proposed that FTO interacts with an obesogenic diet to alter DRD2 function and consequently body weight, suggesting that the relation between FTO and DRD2 might be more discernable among obese individuals. There were 18 subjects with BMI > 30 in the present sample. We reanalyzed the data with only these 18 subjects and again observed no relation between FTO rs9939609 and DRD2 availability in the midbrain or striatum (all

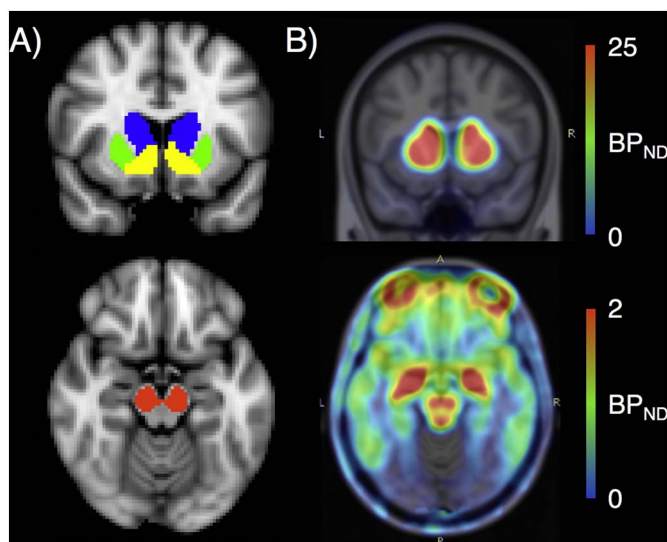


Fig. 1. [18F]fallypride  $BP_{ND}$  images reflecting DRD2 availability. A) Shown are regions of interest from which mean  $BP_{ND}$  were extracted for analyses: caudate (blue), putamen (green), ventral striatum (yellow), and midbrain (red). B) Example of a [18F]fallypride  $BP_{ND}$  image showing high  $BP_{ND}$  in the striatum (top) and midbrain (bottom).

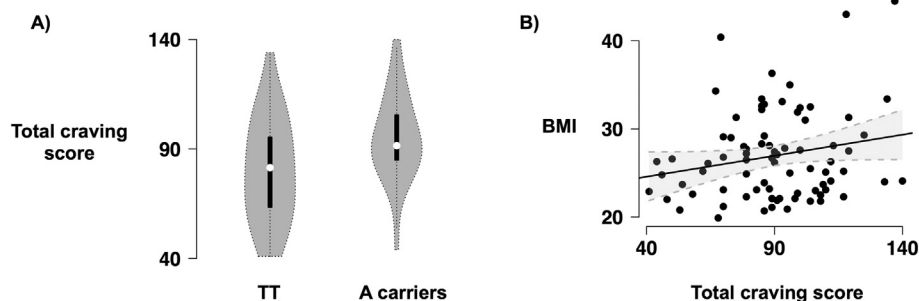


Fig. 2. FTO, food cravings, and BMI. A) Compared to TT homozygotes, A carriers had higher total food cravings ( $t_{76} = 3.02$ ,  $p < 0.01$ ). B) Food cravings were positively associated with BMI ( $t_{74} = 2.236$ ,  $p < 0.05$ ).

$p > 0.5$ , 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 and food seeking behavior as a countermeasure to negative states.

Table 1

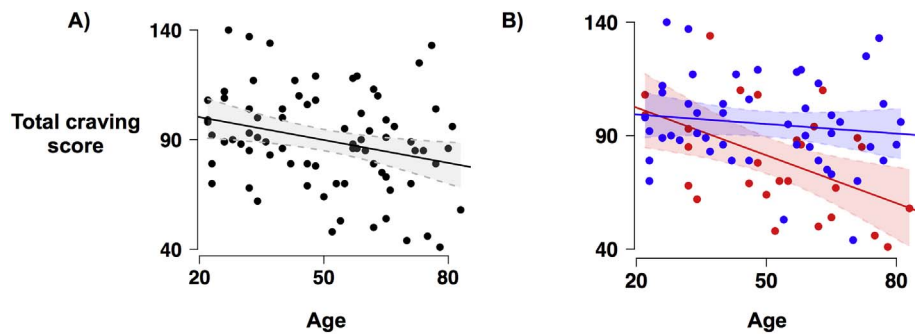
Demographics, food cravings scores, and [18F]fallypride  $BP_{ND}$ .

	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, 11.04
Gender	29F	17F	0.23	0.818	
Total craving score	95.3 ± 19.5	80.2 ± 23.8	3.02	0.003**	5.11, 24.98
Planning	8.4 ± 2.3	6.7 ± 2.3	3.10	0.003**	0.60, 2.77
Pos Reinforcement	13.4 ± 3.6	11.2 ± 3.4	2.63	0.010*	0.53, 3.84
Neg Relief	7.2 ± 2.1	5.6 ± 2.1	3.13	0.003**	0.57, 2.58
Lack Control	12.9 ± 4.4	11.1 ± 4.2	1.73	0.088	- 0.27, 3.81
Thoughts	13.2 ± 4.4	10.9 ± 4.0	2.31	0.024*	0.32, 4.36
Hunger	11.4 ± 2.8	10.7 ± 2.7	0.98	0.331	- 0.67, 1.96
Emotion	9.6 ± 3.4	7.3 ± 3.2	2.88	0.005**	0.70, 3.85
Environment	11.5 ± 3.7	10.1 ± 4.0	1.54	0.127	- 0.41, 3.20
Guilt	7.7 ± 2.6	6.6 ± 2.6	1.94	0.056	- 0.03, 2.37
Caudate $BP_{ND}$	13.8 ± 3.6	13.5 ± 3.6	0.33	0.743	- 1.42, 1.97
Putamen $BP_{ND}$	23.2 ± 3.5	22.7 ± 3.8	0.51	0.613	- 1.27, 2.13
Ventral striatal $BP_{ND}$	14.0 ± 2.5	14.0 ± 2.8	- 0.07	0.941	- 1.25, 1.16
Midbrain $BP_{ND}$	1.2 ± 0.2	1.2 ± 0.2	0.62	0.540	- 0.07, 0.13

Note: Planning = having intentions or plans to consume food; Pos Reinforcement = anticipation of positive reinforcement that may result from eating; Neg Relief = anticipation of relief 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 physiological state; Emotion = emotions that may be experienced before or during food cravings or eating; Environment = cues that may trigger food cravings; Guilt = guilt from cravings and/or for giving into them.

\*\* corrected for multiple comparisons

\* uncorrected.



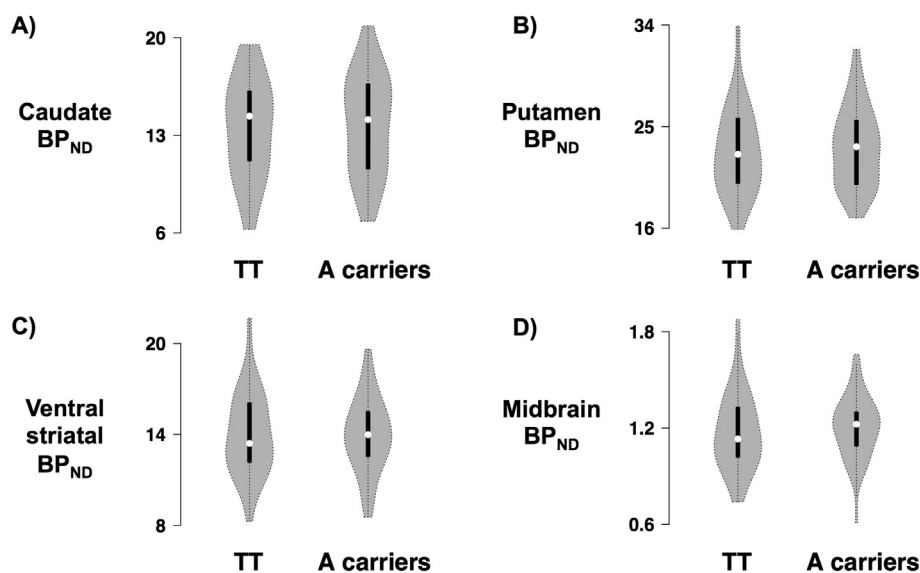
**Fig. 3.** FTO-age interaction on food cravings. A) Food cravings declined with age across all subjects ( $r_{76} = -0.28$ ,  $p < 0.05$ ). B) Among TT homozygotes, food cravings declined with age ( $r_{26} = -0.51$ ,  $p < 0.01$ ) (red), but among A carriers, there was no significant correlation between food cravings and age ( $r_{48} = -0.13$ ,  $p > 0.3$ ) (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the 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 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

specific aspects of DRD2 function. Additionally, although rs9939609 is the first single nucleotide polymorphism in the FTO gene associated with obesity, other FTO single nucleotide polymorphisms have been linked to obesity since then and it is not known whether other FTO single nucleotide polymorphisms affect DRD2 function. Nonetheless, until there is evidence showing FTO effects on DRD2 function in humans, the present results suggest caution in translating such effects in mice to FTO function in humans.

It is worth noting that our finding of a positive correlation between food cravings and BMI was weaker without 3 Obese class III participants, and that a previous study did not observe a relation between FTO rs9939609 and food craving in obese individuals [18]. These results suggest that obese subjects may represent a distinct category with different relationships between FTO, food cravings, and BMI. Future studies with sufficient number of obese and non-obese participants would provide clarity. Moreover the present study excluded individuals with major medical conditions including those associated with obesity, such as diabetes. Individuals with obesity-related medical conditions may also represent another category from individuals without these medical conditions in the context of FTO. We additionally note that FTO effects on BMI vary across ethnicities [24], and this may impact relations between FTO and food cravings in different ethnic groups. While FTO effect size is similar among individuals of Asian and European descents, the frequency of the FTO obesity-susceptible A allele is much lower among Asians than Europeans. Also, relative to Europeans, African-Americans exhibit lower correlations between different FTO single nucleotide polymorphisms linked to obesity, and this may impact FTO associations with obesity traits [24]. The present study did not have sufficient representation of different ethnic groups to address the role of ethnicity in FTO effects.



**Fig. 4.** FTO and DRD2 availability. No significant difference between TT homozygotes and A carriers in [18F]fallypride BP<sub>ND</sub> in the A) caudate ( $t_{76} = 0.33$ ,  $p > 0.5$ ), B) putamen ( $t_{76} = 0.51$ ,  $p > 0.5$ ), C) ventral striatum ( $t_{76} = -0.07$ ,  $p > 0.5$ ), or D) midbrain ( $t_{76} = 0.62$ ,  $p > 0.5$ ).

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.

### Conflict of interest

All authors report no conflict of interest.

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