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An obesity-associated risk allele within the FTO gene affects human brain activity for areas important for emotion, impulse control and reward in response to food images.

Title

An obesity-associated risk allele within the *FTO* gene affects brain activity for areas important for emotion, impulse control, and reward in response to food images.

Running Title

FTO Associated Brain Activity

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ABSTRACT

Understanding how genetics influences obesity, brain activity, and eating behavior will add important insight for developing strategies for weight-loss treatment, as obesity may stem from different causes and as individual feeding behavior may depend on genetic differences. To this end, we examined how an obesity risk-allele for the *FTO* gene affects brain activity in response to food images of different caloric content via fMRI. 30 participants homozygous for the rs9939609 single nucleotide polymorphism were shown images of low- or high-calorie food while brain activity was measured via fMRI. In a whole-brain analysis, we found that people with the *FTO* risk-allele genotype (AA) had increased activity than the non-risk (TT) genotype in the posterior cingulate, cuneus, precuneus, and putamen. Moreover, higher BMI in the AA genotype was associated with reduced activity to food images in areas important for emotion (cingulate cortex), but also in areas important for impulse control (frontal gyri and lentiform nucleus). Lastly, we corroborate our findings with behavioral scales for the behavioral inhibition and activation systems (BIS/BAS). Our results suggest that the two genotypes are associated with differential neural processing of food images, which may influence weight status through diminished impulse control and reward processing.

Keywords:

fMRI, FTO, SNP, BMI, food images, obesity

INTRODUCTION

Genetic differences may influence satiety and metabolism via effects in the brain (Singh, 2014; Yeo, 2014). One such example is the influence of the *fat mass and obesity associated* (*FTO*) gene on brain activity governing feeding behavior. Several different *FTO* single nucleotide polymorphisms (SNPs) are associated with a higher body mass index (BMI) (Sällman Almén et al., 2013; Scuteri et al., 2007a), and higher energy intake (Speakman, 2013). Current theory suspects that risk alleles of these SNPs may increase obesity via effects in the brain to modulate feeding behavior and metabolism (Singh, 2014; Yeo, 2014). Moreover, experiments in rodents show that changes in *FTO* expression levels in the hypothalamus affect feeding behavior (Frederiksen, Skakkebaek, & Andersson, 2007; Olszewski et al., 2009; Tung et al., 2010). However, whether the hyperphagia and subsequent obesity induced in these experiments is due solely to metabolic changes or to manipulations of the reward response to food is still controversial. Indeed, obesity may depend on psychological characteristics, specifically those related to reward or self-control (Gerlach, Herpertz, & Loeber, 2015). Personality scales for the Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS), which measure punishment and reward sensitivity respectively, are two such tools which correlate with inactivity and poor diet (Carver & White, 1994; Dietrich, Federbusch, Grellmann, Villringer, & Horstmann, 2014; Meule, 2013; Voigt et al., 2009). Furthermore, some suggest obesity could be given a differential diagnosis and treatment regimen based on this distinction between obesity caused by physiological factors or by psychological effects (Yu et al., 2015). Thus, *FTO* could promote obesity through metabolic effects, augmented reward signaling, or a combination of both.

Obesity is increasingly considered an addiction-type disorder with disruptions of the reward pathway, and several fMRI studies have explored this topic (Batterink, Yokum, & Stice, 2010; Brooks, Cedernaes, & Schiöth, 2013; Gearhardt AN et al., 2011; Goldstone et al., 2009; Tomasi et al., 2015; Volkow, Wang, Tomasi, & Baler, 2013; Zhang et al., 2015). To date, however, few fMRI studies have examined how genetic profile is associated with brain responses to food in obesity. A recent study found that people with the *FTO* risk allele for rs8050136 had reduced activity in the right prefrontal cortex while viewing food images in a postprandial state, but not while fasting (Heni et al., 2014). Another study found that fasted participants with the risk allele for rs9939609 had lower activations in areas important for both reward and metabolism when shown food images, such as the hypothalamus, ventral tegmental area and substantia nigra, posterior insula, globus pallidus, thalamus, and hippocampus. They also showed that circulating ghrelin may affect brain areas important for both metabolism and reward signaling depending on genotype (Karra et al., 2013). Notably, their cohort of participants had a normal BMI with no obese participants. Thus, possible interactions between genotype and BMI on brain activity remain unstudied.

Against this background, we explore for the first time the association between *FTO* genotype, BMI, and neural responses to food images of either low- or high-calorie content. In whole-brain analysis of BOLD responses to food images, we test whether the genotype homozygous for the at-risk allele for rs9939609 (which is A) (Dina et al., 2007; Frayling et al., 2007; Scuteri et al., 2007b) affects brain activity differently from the homozygous genotype with the non-risk allele (T). We also examine within-group regressions between BMI and BOLD responses to food images within each genotype and behavioral characteristics of each genotype.

METHODS

Participants

Prior to any experimental procedures, all participants gave written informed consent to the study which conformed to the Declaration of Helsinki and approved by the local ethics committee. Participants were 30 right-handed, northern-European males, with a mean age of 26 ± 1 years, recruited locally in Uppsala, Sweden by advertisement. Genotyping of the *FTO* single nucleotide polymorphism (SNP) rs9939609 was performed with a pre-designed Taqman single-nucleotide polymorphism genotyping assay (Applied Biosystems, Foster City, USA) and an ABI7900 genetic analyzer with SDS 2.2 software at the Uppsala Genome Center (http://www.genpat.uu.se/node462). The genotype call rate was 97.8%. Only homozygous participants were included in the study. There was a similar distribution of body mass index (BMI) for each genotype of the rs9939609 SNP: 26.8 ± 1.2, with a range of 13.1 kg/m^2 in the AA genotype (n = 13), and 24.1 ± 0.7, with a range of 9.7 kg/m^2 in the TT genotype (n = 17). Hunger ratings were also assessed on a 1-10 scale with higher numbers indicating greater feelings of hunger.

Behavioral Questionnaires

Clinical measures for punishment sensitivity and reward-seeking behavior were acquired using the Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS) questionnaires (Carver & White, 1994). Both consisted of 24 items. Each item was represented by a statement, where the participant indicated how much s/he agreed or

disagreed on a four-point scale. The BIS included only one scale, evaluating the reactions to the anticipation of punishment and anxiety, while the BAS included three subscales: Drive, which represents the pursuit of desired goals; Fun Seeking, which evaluates the desire for new rewards and impulsivity; and Reward Responsiveness, which focuses on positive reactions anticipating rewards.

fMRI Paradigm and Image Acquistion

Images of food were presented in the scanner using MRI-compatible goggles (NordicNeuroLab, Bergen, Norway) attached to the headcoil. The food images were shown at 3 second intervals and no images were repeated. Participants were instructed to imagine what it felt like to eat the food presented. Blood oxygen-level dependent (BOLD) signals in response to food stimuli were measured as participants were shown images of low-calorie (LC) food, high-calorie (HC) food, or control (C) images in five cycles of the following block design pattern: C, LC, C, HC. Each block contained 6 images. In total, the number of measurements collected for each group was 54 for control, 30 for LC, and 30 for HC. Low and high calorie food images were determined by caloric content and selected for familiarity according to local palate, and were controlled for visual features (color, size, etc.). Caloric content of the HC and LC images was confirmed by their perceived caloric content in focus groups representative of the population to be studied. Example HC images were cakes, pies, ice cream, candy, fried foods, and hamburgers. Example LC images were vegetables, fruits, and salads without high-calorie dressing. Control images were a grey screen with a crosshair in the center.

Participants were scanned at 08:00 following an overnight fast of at least 8 hours, i.e., were in a fasted state during testing. Structural and functional brain images were acquired

with a Philips 3-Tesla (Achieva, Philips Healthcare, Best, Netherlands) using a standard head coil. 125 volumes were registered during the T2*-weighted echo-planar imaging (EPI) sequence with whole brain coverage of 30 slices (slice thickness = 3 mm; 1 mm gap, interleaved scan order, in-plane resolution: (3 mm x 3 mm), repetition time (TR) = 3 s; echo time (TE) = 35 ms, flip angle = 90°).

Preprocessing of fMRI data

All preprocessing steps were performed using software package Statistical Parametric Mapping (SPM, version 8, http://www.fil.ion.ucl.ac.uk/spm/), implemented in MATLAB (version R2014a, 11 FEB 2014, 8.3.0.532, 64-bit). The images were realigned and estimated to remove movement artefacts in the data. EPI images were further matched with the structural image using coregistration. The anatomical image was segmented to strip away unnecessary tissue in the images. Tissue probability maps were introduced in the segmentation step to differentiate between gray matter, white matter and cerebrospinal fluid in each individual. Volume was calculated based on the extracted tissue maps of each subject. The gray matter and white matter volumes were added together to find the total brain volume (TBV), to serve as a nuisance covariate in the analyses. Then, functional images were normalized to fit the segmented anatomical image. Finally, images were smoothed using a Gaussian function (8 mm full-width, half-maximum (FWHM)) to minimize noise and bias.

Statistical Analysis

All fMRI statistical analysis was performed using the same versions of SPM and MATLAB listed in preprocessing steps. For all whole-brain results, a family wise error

(FWE) corrected significance level was set at $p < 0.05$ to correct for multiple testing. For the main analysis of the imaging data, we tested a contrast between the neural responses to images of high calorie (HC) foods to the neural response of images from low calorie (LC) foods. This contrast was then tested using a between-groups t-test followed by directional post-hoc comparisons as well as with a multiple regression analysis testing for interactions between genotype and BMI, BIS, or BAS individually. The t-test used both BMI and total brain volume (TBV, grey matter + white matter) as covariates of no interest, while the multiple regression analysis used only TBV as a covariate of no interest.

Region of interest (ROI) analysis was performed by preparing masks of brain areas based on previous MRI studies on *FTO* (de Groot et al., 2015; Karra et al., 2013). Bilateral masks of such areas were produced using the Wake Forest University Pickatlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003) within SPM. Small volume corrections were performed on clusters trending towards significance using a 6 mm radius sphere over the greatest FWE-corrected suprathreshold voxel.

For the within-group regression analyses, the same contrast of HC versus LC was used and TBV served as a covariate of no interest. For both genotypes, positive or negative correlations between BMI and BOLD signal were tested.

Other statistical tests, as well as the principle component analysis (PCA) were performed with R statistical software (version 3.2.1, 64-bit) using the FactoMineR package (Lê et al., 2008). Results for the PCA were considered significant if the percentage of inertia summing from the two largest eigenvalues exceeded values listed in a significance table based on 10,000 analyses with similar numbers of individuals and independent variables (Lê et al., 2008).

RESULTS

The obesity-associated *FTO* SNP rs9939609, is associated with increased activity in response to food images.

First, we tested for a difference in the processing of food stimuli as measured by fMRI depending on genotype and/or body-mass index (BMI). We tested 30 participants (13 AA and 17 TT) in a fasted state. BMI for the AA genotype was significantly higher than the non-risk TT genotype (Student's t-test, $p < 0.05$), as expected from previous reports (Fredriksson et al., 2008; Sällman Almén et al., 2013). There was no significant difference in age between groups of differing genotype (Student's t-test, $p = 0.7$; Table 1). BOLD signals were measured as participants were shown images of low-calorie (LC) food, high-calorie (HC) food, or control images in a block design format. Patients were instructed to imagine the feeling of eating the food presented. We compared one contrast in our analysis: HC versus LC, which tests the neural response discriminating food images of different caloric contents.

Between-group comparisons found three clusters with greater activity in the AA genotype compared to the TT genotype. (Figure 1A). Areas included the posterior cingulate cortex (PCC), cingulate gyrus, cuneus, and precuneus (Table 2). A multiple regression analysis found an interaction between genotype and BMI, post-hoc comparisons found significant clusters for the AA genotype while BMI was decreasing in the PCC, cingulate gyrus, middle occipital gyrus, and precuneus (Supplementary Table 1).

Based on results from previous studies (de Groot et al., 2015; Karra et al., 2013), we performed a region-of-interest (ROI) analysis on areas putatively associated with *FTO* genotype: such as the insula, putamen, and nucleus accumbens. Within the t-test comparison between genotypes, a significant cluster showing greater activity in the AA genotype was

found in the putamen (Figure 1B) after performing a small-volumes correction using a 6 mm-radius sphere over the lowest FWE-corrected p-value in the cluster (Table 2).

Differential patterns of neural activation in each *FTO* genotype depending on body-mass index.

We then tested regressions of BMI and whole brain activity within each genotype. We tested both positive and negative regressions in the HC versus LC contrast. Two regressions yielded results which survived corrections for multiple testing. In addition, there was almost no overlap between the two patterns of activity, with only a small area on the motor cortex showing overlap of clusters from each genotype, neither of which survived corrections for multiple testing (Figure 3A). In the AA genotype, there was a negative correlation between caloric discrimination (HC versus LC) and BMI (Figure 3B) in the following brain areas: frontal gyrus (medial and superior), lentiform nucleus, cerebellum (declive, uvula, and pyramis), and cingulate gyrus (Table 3); i.e., overweight AA participants had weaker responses to HC images than LC, while normal-weight AA participants had stronger responses to HC images compared to LC. However, in the TT genotype, there was a positive relationship between caloric discrimination and BMI (Figure 3C), but only in a cluster containing the superior temporal gyrus (Table 4). Thus, the two genotypes have a divergence in the neural processing of caloric discrimination to food based on BMI.

Differential patterns of behavior for each *FTO* genotype depending on body-mass index.

We next tested if behavioral questionaires corrobarated the findings from the imaging experiments. We employed two questionaries: the Behavioral Inhibition System (BIS) and

Behavioral Activation System (BAS) questionnaires, which measure punishment and reward sensitivity, respecively (Carver & White, 1994). We choose these questionaires as they represented the main elements of personality that we wished to explore in this study. We then performed a principle component analysis within each genotype using the BIS and the three BAS subscales (Drive, Fun Seeking, and Reward Responsiveness) as variables of interest with BMI as a quantitative supplementary variable. For both analyses, all the variables of interest were well projected and the first two dimensions accounted for ≈80% of the variablity (considered significant based on critera listed in methods under statistical analysis subheading, 81.4 > 80.0 for the AA group and 79.2 > 76.5 in the TT group). Moreover, the variables of interest projected to the same quandrants except for the Drive and Fun Seeking subscales, which were switched between the two different genotypes. Interestingly, the supplementary variable, BMI, was projected in opposite quadrants relative to the BIS depending on genotype. In the AA genotype, BMI correlated positively with the BAS Drive subscale and negatively with BIS, while in the TT genotype, BMI correlated somewhat positively with BIS and negaively with the BAS Fun Seeking subscale. Furthermore, we followed up the association between the BIS and BMI using a multiple regression analysis testing if BIS scores could be predicted by genotype, BMI, or their interaction. This model found significance for the genotype ($p < 0.01$) and interaction terms ($p < 0.01$). Thus, the two genotypes appear to have differing behavioral measures for impulsivivity, punishment, and reward depending on BMI.

DISCUSSION

We examined whether an obesity-associated genotype affects the neural processing of food images with different caloric content and to what extent body-mass index (BMI) is an important factor. We tested 30 male participants homozygous for either the risk (A)- or non-risk (T) allele of the *fat mass and obesity associated* (*FTO*) SNP rs9939609 (13 in the AA group and 17 in the TT group). Participants were shown images of low-calorie (LC) food, high-calorie (HC) food, or control images while blood-oxygen-level dependent (BOLD) signals were obtained via fMRI. We found the AA genotype had increased brain activity compared to the TT genotype when viewing food images with different caloric contents, specifically in areas important for emotion (cingulate gyrus), memory, and self-image (cuneus and precuneus) and reward (putamen). Moreover, while both genotypes had a similar distribution of BMI, ranging between normal-weight to obese in each genotype, we found that BMI was associated with differential activity within each genotype – with comparatively more brain regions associated with BMI in the AA genotype than in the TT genotype. Thus, discrimination between HC and LC foods may be handled differently for each genotype depending on BMI. Next, we corroborate our findings in the imaging study with personality questionnaires examining behavioral characteristics related to impulsivity and reward-processing: namely the Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS) scales. We found that the BIS as well as subscales of the BAS correlated with BMI oppositely in each genotype. Thus, obesity within each genotype may stem from different behavioral characteristics. Our results suggest that this polymorphism of the *FTO* gene affects the processing of visual food stimuli differently, possibly involving emotion, self-image, and reward processing.

In between-groups comparisons, as well as multiple regression analysis, we found significant clusters of brain activity when testing a contrast for caloric discrimination (HC food images opposed to LC food images). Specifically, we found increased neural activation in the AA genotype compared to the TT genotype within the posterior cingulate cortex (PCC), cingulate gyrus, cuneus and precuneus. The PCC is a well-connected and multifunctional brain area associated with emotional processing, and a central node in the default mode network (DMN): involved in arousal/awareness, balancing external and internal thought, and emotion (Leech & Sharp, 2014). Decreased activity in the PCC is associated with low levels of arousal (Fiset et al., 1999). The cuneus and precuneus are also implicated in obesity, as a previous study showed that obese adolescents had less activation in the cuneus and precuneus when viewing food versus non-food commercials (Gearhardt, Yokum, Stice, Harris, & Brownell, 2014). Thus, there may be a difference in the salience of food images depending on *FTO* genotype, and perhaps an increased salience of HC food images for people with the AA genotype leads to an increase in food intake.

Participants with the AA genotype also had increased activity in the putamen compared to TT participants in a region-of-interest analysis. The putamen has an important functional role in reward processing (Delgado, 2007), and several imaging studies have shown increased activity for this structure in obese participants (Boutelle et al., 2015; Jastreboff et al., 2014; Zhang et al., 2015). Thus, in our study, finding increased activity in the putamen for the risk allele (AA) is a supportive finding, as both are associated with obesity. This also further implicates the involvement of the reward system in obesity with the *FTO* risk allele.

Other studies have examined participants of different genetic background for the *FTO* gene using MRI techniques (de Groot et al., 2015; Heni et al., 2014; Karra et al., 2013), but no study has yet included obesity as a factor. However, we only partially replicated previous findings (Karra et al., 2013). For example, for their cohort in a fasted state, they reported

reduced activity in the AA versus TT genotype in the hypothalamus, globus pallidus, thalamus, ventral tegmental area, and substantia nigra (Karra et al., 2013). This difference in results is perhaps because the BMI in our cohort was much more variable, whereas overweight and obese participants in their previous study were excluded. Furthermore, others suggest that BMI should be regarded as a confounding factor (Cole et al., 2013). However, the variability of BMI in our cohort allowed us to perform an analysis with regressions between BMI and BOLD responses. BMI appears to be an important factor in studies of this type, and our results suggest that the neural processing of food images between genotypes may be differentially affected as BMI increases.

Next, we further explored the neural response to caloric discrimination of food images based on BMI. We find that BMI augments the neural response to food images differently within each genotype. As BMI decreased in the AA genotype, neural activity increased in the superior and medial frontal gyrus, lentiform nucleus, cingulate gyrus, middle temporal gyrus, and cerebellar areas: declive, uvula, and pyramis. Thus, the overweight AA participants have less activity in these areas. And, in line with our results, a previous fMRI study also showed reduced activation in the superior and middle frontal gyri as BMI increased (Batterink et al., 2010). Thus, the AA genotype again corresponds with previously-established brain activity in the obese/overweight. Our findings of altered activity among AA participants in cerebellar areas are also pertinent, given the relatively recent association with the cerebellum to emotion (Schienle & Scharmüller, 2013) and appetitive processes (Zhu & Wang, 2007). As for the TT genotype, we found two areas where neural activity positively correlated with BMI: the superior and middle temporal gyri. These affected areas are perhaps due to functional relationships within the default mode network and the temporal lobe network, where functional connectivity is augmented in the obese (Kullmann et al., 2012). From the above, and similar to (Karra et al., 2013), we find a divergence in the processing of food images

between the two genotypes, and our results highlight the importance of BMI as a factor mediating the effect of genotype on neural responses to images of food. Thus, obese as well as normal-weight individuals may be expected to process food images differently depending on their genotype.

Lastly, we corroborate our findings in the imaging study with personality measures from the BIS and BAS scales, as obesity is associated with anomalies in both (Carver & White, 1994; Dietrich et al., 2014; Meule, 2013; Voigt et al., 2009). Higher scores of the BIS are indicative of increased sensitivity to punishment, and correlate positively with such personality measures as harm avoidance, reward dependence, susceptibility to punishment, negative affect, and anxiety, and correlate negatively with optimism and socialization. Whereas higher scores of the BAS and its subscales, are indicative of greater reward sensitivity, and correlate positively with extraversion, novelty seeking, and positive affect, and correlate negatively with harm avoidance, and susceptibility to punishment (Carver & White, 1994). The two genotypes had opposing relationships with BMI and the BIS score. Specifically, BMI in the AA genotype correlated negatively with BIS, while BMI in the TT genotype correlated positively with BIS. This suggests that the overweight/obese people with the AA genotype have less inhibitory personality characteristics than the overweight/obese with the TT genotype. Thus, the AA genotype in our cohort confirms previous reports equating impulsivity with obesity/overeating (Meule, 2013) specifically in one study which also found a negative correlation between BIS and BMI in males (Dietrich et al., 2014). Subscales of the BAS also had different correlations with BMI in each genotype: the Drive subscale correlated positively with BMI in the AA genotype, while the Fun Seeking subscale correlated negatively in the TT genotype. The correlation between the Drive subscale and BMI in the AA genotype corroborates with previous associations with BAS, arousal, and overeating (Voigt et al., 2009) and also a previous fMRI report associating the Drive subscale

with neural activity in response to appetitive food images (Beaver et al., 2006). Thus, people in the TT genotype may possess a reward processing that is optimal for maintaining or decreasing weight, while the AA genotype has a more impulsive attitude and matches traditional descriptions of obesity and unhealthy eating behavior. Indeed, the same *FTO* variant modulated reward processing and avoidance learning (Sevgi et al., 2015). However, we were unable to establish effects of BIS or BAS or interactions with genotype using the brain-imaging data. Thus, while this finding is intriguing, we caution that it requires further validation.

In summary, we show that a genotype homozygous for an *FTO* risk allele for obesity is associated with increased neural response to HC versus LC food images in brain regions associated with emotion, impulsivity, and reward compared to the low-risk for obesity TT genotype, and that BMI is a mediating factor for each genotype. Our results suggest that overweight/obese people with the AA genotype may be prone to unhealthy eating behavior due to food images being less salient at evoking normal appetitive responses compared to overweight/obese people with the TT genotype. Some limitations of this study are the use of only males in the fMRI experiments, as well as the exclusion of the AT genotype. We maintain that BMI is an important factor in fMRI research as well as in the relationship between brain activity and genotype. In conclusion, our findings offer insight into the relationship between *FTO*, obesity, and brain activity; and suggest that overweight/obese populations have different attitudes and functional processing for food images depending on genetic background.

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FIGURE LEGENDS

***Figure 1*. Participants homozygous for the *FTO* risk-allele (rs9939609) have increased brain activity in response to high- and low-calorie food images.** 13 participants homozygous for the *FTO* risk allele (A) and 17 for the non-risk allele (T) were shown images of either low-calorie (LC), high-calorie (HC) food, or control while brain activations were measured via fMRI. A whole-brain, between-groups comparison tested the neural response to foods of different caloric content (HC versus LC contrast) using total brain volume (TBV) and body-mass index (BMI) as covariates of no interest. Greater activity was found in four clusters for participants homozygous for the risk allele (A) compared to the normal allele (T). **A**) Axial brain slices showing significant clusters. Exact MNI z-coordinate given below slices in white numbers, and t-statistics indicated by color-coded scale bar (critical t = 3.5). **B**) A region of interest analysis found a significant cluster within the putamen after a small-volumes correction.

***Figure 2*. Opposite patterns of activity in each *FTO* genotype depending on body-mass index.** For each genotype, the caloric discrimination to food was tested in a contrast between the BOLD response to high-calorie versus low-calorie food images in regressions with body-mass index (BMI). A negative relationship was found between brain activity and BMI in participants with the *FTO* risk genotype (AA), while a positive relationship was found in the non-risk genotype (TT). Patterns of activity were mostly independent of each other, with only a small area in motor cortex overlapping between the two. **A**) Color-coded activity for each genotype (AA in magenta and TT in cyan) imposed on a 3D rendering of the brain. Overlapped activity between genotypes shown as white. **B** & **C**) Threshold images of brain

activity for AA and TT genotype respectively. Axial brain images are shown with respective MNI z-coordinated displayed below and t-statistics indicated by color-coded scale bar (critical t = 4.1 for AA, and 3.8 for TT).

***Figure 3*. The AA genotype displays a different balance of behavioral inhibition and activation systems depending on body-mass index compared to the TT genotype.** Participants completed the Behavioral Inhibition System (BIS) and Behavioral Activation System Questionnaires (BAS) questionnaires. The BIS evaluates inhibitory behavior in the anticipation of punishment and anxiety, while the BAS included three subscales: Drive, which represents the pursuit of desired goals; Fun Seeking, which evaluates the desire for new rewards and impulsivity; and Reward Responsiveness, which focuses on positive reactions anticipating rewards. Principle component analysis was used to compare the relationships of these variables along with BMI in the two different genotypes. The behavioral variables were all well projected in each group. Body-mass index (BMI) was used as a supplementary variable (not included in the analysis, but still plotted to evaluate which variables it correlated with). Interestingly, for each genotype, BMI was projected in opposite quadrants relative to the BIS. The subscales for the BAS were also differently projected relative to BMI for each genotype. **A**) variables factor map for the AA genotype. BMI was negatively correlated with BIS and positively correlated with the BAS Drive subscale. **B**) variables factor map for the TT genotype. BMI was positively correlated with BIS and negatively correlated with the BAS Fun Seeking subscale.