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Research report

Relation of the multilocus genetic composite reflecting high dopamine signaling capacity to future increases in BMI ☆

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ABSTRACT

Because food intake exerts its rewarding effect by increasing dopamine (DA) signaling in reward circuitry, it theoretically follows that individuals with a greater number of genotypes putatively associated with high DA signaling capacity are at increased risk for overeating and subsequent weight gain. We tested the association between the multilocus genetic composite risk score, defined by the total number of genotypes putatively associated with greater DA signaling capacity (i.e. *TaqIA* A2 allele, *DRD2*-141C Ins/Del and Del/Del genotypes, *DRD4*-S allele, *DAT1*-S allele, and *COMT* Val/Val genotype), and future increases in Body Mass Index (BMI) in three prospective studies. Participants in Study 1 (N = 30; *M* age = 15.2; *M* baseline BMI = 26.9), Study 2 (N = 34; *M* age = 20.9; *M* baseline BMI = 28.2), and Study 3 (N = 162; *M* age = 15.3, *M* baseline BMI = 20.8) provided saliva samples from which epithelial cells were collected, permitting DNA extraction. The multilocus genetic composite risk score was associated with future increases in BMI in all three studies (Study 1, $r = 0.37$; Study 2, $r = 0.22$; Study 3, $r = 0.14$) and the overall sample ($r = 0.19$). *DRD4*-S was associated with increases in BMI in Study 1 ($r = 0.42$), Study 2 ($r = 0.27$), and in the overall sample ($r = 0.17$). *DAT1*-S was associated with increases in BMI in Study 3 ($r = 0.17$) and in the overall sample ($r = 0.12$). There were no associations between the other genotypes (*TaqIA*, *COMT*, and *DRD2-141C)* and change in BMI over 2-year follow-up. Data suggest that individuals with a genetic propensity for greater DA signaling capacity are at risk for future weight gain and that combining alleles that theoretically have a similar function may provide a more reliable method of modeling genetic risk associated with future weight gain than individual genotypes.

Introduction

During the past three decades the prevalence of obesity in the US adult population has risen from below 20% to 35.7% (Centers for Disease Control, 2012). During the same period, childhood obesity has tripled to 17% (Ogden, Carroll, Kit, & Flegal, 2012). Unfortunately, treatments almost never result in lasting weight loss and virtually all obesity prevention programs have not reduced future obesity onset (Stice, Shaw, & Marti, 2006; Turk et al., 2009). An improved understanding of the risk processes that give rise to weight gain should guide the design of more efficacious prevention and treatment interventions, as well as inform the populations to be targeted in prevention programs. The predisposition to obesity is partially genetically determined (Elks et al., 2010; Mei et al., 2012; Warrington et al., 2013). The *FTO* gene has shown the strongest and most consistent associations with adiposity and weight gain (Speliotes et al., 2010); associations that have been confirmed across age groups and ethnically diverse samples (Loos & Yeo, 2014). Research has also explored the association between specific candidate genes that influence dopamine (DA) signaling capacity and risk for obesity.

DA signaling in the reward circuitry and weight gain

DA is the predominant catecholamine neurotransmitter in reward circuitry and is thought to play a role in obesity. Consumption of high-sugar or high-fat food results in DA release in the reward circuitry (ventral striatum) in animal experiments (Avena, Rada, & Hoebel, 2009). In humans, consumption of palatable food causes increased activation in the reward circuitry, including the dorsal- and ventral striatum and orbitofrontal cortex (Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001; Stice, Burger, & Yokum, 2013) and increased DA release in the dorsal striatum, with the amount released correlating with meal pleasantness ratings (Small, Jones-Gotman, & Dagher, 2003) and energy density (Ferreira, Tellez, Ren, Yeckel, & de Araujo, 2012).

Several findings suggest that greater DA signaling capacity may increase risk for future weight gain. A PET study with humans

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(Kessler, Zald, Ansari, Li, & Cowan, 2014) found a positive correlation between BMI and DA release in the dorsal striatum and substantia nigra in response to amphetamine. Lean youth at risk for future obesity by virtue of parental obesity show hyper-responsivity of reward regions to palatable food receipt (Stice, Yokum, Burger, Epstein, & Small, 2011). Critically, hyper-responsivity of reward regions to food intake (Geha, Aschenbrenner, Felsted, O'Malley, & Small, 2013), food images (Demos, Heatherton, & Kelley, 2012), and food commercials (Yokum, Gearhardt, Harris, Brownell, & Stice, 2014) is associated with future weight gain. These findings are consistent with the reward surfeit theory of obesity (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008), which posits that individuals who show greater innate reward responsivity to food intake are at elevated risk for overeating and consequent weight gain. The findings are also consistent with the incentive sensitization model (Berridge, Ho, Richard, & DiFeliceantonio, 2010), which posits that repeated intake of palatable foods results in an elevated responsivity of reward valuation regions to cues that are repeatedly associated with palatable food intake via conditioning, which prompts elevated food intake when these cues are encountered.

Genes associated with DA signaling in the reward circuitry and weight gain

Several genes appear to correlate with DA signaling capacity, among which are the *TaqIA* SNP (rs1800497) in the *DRD2*, the –141C Insertion/Deletion (Ins/Del) polymorphism (rs1799732) in DA receptor D2 (*DRD2-141C*), the *Catechol-O-methyltransferase* (*COMT* Val^{158}Met), the *DRD4* third exon 48 bp VNTR (*DRD4*) gene, and the *SLC6A3* DAT1 VNTR (*DAT1*). Data suggest that individuals with the *TaqIA* A2/A2 allele, *DRD2-141C* Ins/Del and Del/Del allele, *COMT* Val/Val allele, *DRD4* shorter than 7 repeat allele (*DRD4*-S), and *DAT1* 9-repeat allele (*DAT1*-S) have greater DA signaling in the reward circuitry than those with the *TaqIA* A1/A1 allele, *DRD2*-141CIns/Ins allele, *COMT* Met/Met allele, *DRD4* 7-repeat or longer allele (*DRD4*-L), and *DAT1* 10-repeat/10-repeat allele (*DAT1*-L) (Asghari et al., 1995; Heinz et al., 2000; Jonsson et al., 1999; Seeger, Schloss, & Schmidt, 2001). Yet, findings have been somewhat inconsistent regarding the relations of these genotypes to risk for future weight gain. For instance, *TaqIA* A1 allele was found to be associated with greater future weight gain (Muller et al., 2012; Winkler et al., 2012). However, other studies reported null findings (Fuemmeler et al., 2008; Hardman, Rogers, Timpson, & Munafo, 2014; Stice, Spoor, Bohon, & Small, 2008). Fuemmeler and colleagues (Fuemmeler et al., 2008) found a trend relation between the *DRD4*-S genotype and future increases in BMI in adolescents, though Stice and colleagues (Stice, Yokum, Bohon, Marti, & Smolen, 2010) found no main effect of *DRD4* on future weight gain.

A possible explanation for the mixed findings is that the above mentioned studies focused on the effects of individual genotypes, which theoretically explain only a small proportion of variance. Further, multiple genotypes most likely differ in their effects on weight gain in different samples due to allele heterogeneity. Recently, two studies (Nikolova, Ferrell, Manuck, & Hariri, 2011; Stice, Yokum, Burger, Epstein, & Smolen, 2012) found that the total number of alleles putatively associated with high DA signaling, as indexed by a multilocus genetic composite score reflecting high DA signaling capacity, correlated more strongly with elevated fMRI-assessed reward region responsivity than the individual genotypes considered independently. It is possible that a multilocus profiling approach will also account for greater variance in future weight gain as it may capture the cumulative impact of polymorphisms whose individual effects may otherwise go undetected. However, no prospective research has examined the association between the multilocus genetic composite score that reflects DA signaling capacity and future weight gain.

Accordingly, we examined the associations between the multilocus genetic composite reflecting high DA signaling capacity and future increases in BMI. Testing these associations will provide a direct test of the reward surfeit theory of obesity (Stice, Spoor, Bohon, Veldhuizen et al., 2008). Because studies have found that such a multilocus genetic composite score correlates more strongly with elevated reward region responsivity than the individual genotypes that contribute to this score (Nikolova et al., 2011; Stice et al., 2012), and because hyper-responsivity of reward regions in response to food intake (Geha et al., 2013) and food cues (Demos et al., 2012; Yokum et al., 2014) has predicted future weight gain, we hypothesized that individuals with more alleles associated with greater DA signaling capacity would show elevated future weight gain. We tested the association between the multilocus genetic composite risk score and weight gain in three different prospective studies to determine if this relation consistently replicates across various samples varying in baseline BMI and demographics. This is important as (a) no prospective research has examined the association between the multilocus genetic composite risk score that reflects DA signaling capacity and future weight gain and (b) previous studies have found mixed effects of individual genotypes on future weight gain. Replication of the relation of the multilocus genetic composite risk score on future increases in BMI across different samples will improve our knowledge on genetic risk profiles for future weight gain.

Because individuals in one of the three studies were randomized to either a behavioral weight loss treatment or a control condition, it provided an opportunity for exploratory analyses to test if the multilocus genetic composite risk score moderates the effects of the intervention on future change in BMI in this study. We hypothesized that individuals carrying the highest number of alleles associated with greater DA signaling capacity would show less weight loss in response to the treatment than those with fewer of these alleles.

Methods and procedures

Participants

In Study 1, participants were 30 adolescents varying in weight from lean to obese (17 females; *M* baseline age = 15.2 ± 1.1; *M* baseline BMI = 26.9 ± 5.4; *M* BMI 2-year follow-up = 27.2 ± 6.7; 20% Hispanic, 3.3% Native Americans, 63.3% European Americans, and 33.3% mixed race/ethnicity) who were recruited for a pilot study assessing biological and psychological risk factors for adverse effects of food advertisement.

In Study 2, participants were 34 overweight and obese young women (*M* baseline age = 20.9 ± 1.2; *M* baseline BMI = 28.2 ± 3.0; *M* BMI 2-year follow-up = 27.9 ± 3.1; 2.9% Hispanic, 2.9% Native Americans, 11.8% Asian, 73.5% European Americans, 11.8% mixed race/ethnicity), that were drawn from a pilot study evaluating the efficacy of a behavioral weight loss treatment.

In Study 3, participants were 162 lean adolescents (82 females; *M* age = 15.3 ± 1.07, *M* baseline BMI = 20.8 ± 1.9; *M* BMI 2-year follow-up = 21.9 ± 2.3; 11.2% Hispanic, 0.6% Native Americans, 0.6% Asian, 78.4% European American, 20.4% mixed race/ethnicity) that were recruited for an obesity risk factor study.

Those who reported any current use of psychotropic medications or illicit drugs, or current Axis I psychiatric disorder per *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria (American Psychiatric Association, 1994) were excluded. Participants and parents (in case of a minor) provided written informed consent. The Oregon Research Institute Institutional Review Board approved these studies.

Measures

Body mass index

The body mass index (BMI = kg/m^2) was used as a proxy measure for adiposity. Height was measured to the nearest millimeter and

weight was assessed to the nearest 0.1 kg (after removal of shoes and coats). In Study 1 and Study 3, BMI was assessed at baseline and 1- and 2-year follow-up. In Study 2, BMI was assessed at baseline, and at 3-month, 6-month, 1-year, and 2-year follow-ups. Although BMI does not distinguish between increased mass in the form of fat, lean tissue or bone and hence can lead to significant misclassification (McCarthy, Cole, Fry, Jebb, & Prentice, 2006; Prentice & Jebb, 2001), BMI correlates with direct measures of total body fat such as dual energy X-ray absorptiometry ($r = 0.80$ to 0.90) and with health measures including blood pressure, adverse lipoprotein profiles, atherosclerotic lesions, serum insulin levels, and diabetes mellitus in adolescent samples (Dietz & Robinson, 1998; Mei et al., 2002; Steinberger et al., 2005). Further, raw BMI scores are superior to age- and sex-adjusted percentiles or BMIz scores for modeling change over time in longitudinal data analyses (Berkey & Colditz, 2007).

Genotyping

Participants were asked to provide saliva, from which epithelial cells were collected, using a commercial product (Oragene, DNAgenotek). One participant was unable to provide a saliva sample and was excluded from all analyses. DNA was extracted from the samples using standard salting-out and solvent precipitation methods, yielding an average of 45 g of DNA. Stice et al. (2012) provide greater details about the genotyping. The following genotype groups were defined: (a) *TaqIA*: A1 homozygotes, A1/A2 heterozygotes, and A2 homozygotes; (b) *COMT* val^{158}met assay: Met homozygotes, Val/Met heterozygotes, and Val homozygotes, (c) *DRD2*-141C Ins/Del assay: Ins homozygotes, Ins/Del heterozygotes, and Del homozygotes, (d) *DRD4*: *DRD4* 7-repeat or longer allele (*DRD4*-L) versus shorter alleles (*DRD4*-S) (20), and (e) *DAT1* assay: 10-repeat/10-repeat homozygotes (10R/10R), 10-repeat/9-repeat heterozygotes (9R/10R), and 9-repeat/9-repeat homozygotes (9R/9R).

Statistical analysis

Multilocus genetic composite risk score

We calculated a multilocus genetic composite reflecting the total number of the five genotypes, paralleling the general approach used by previous studies (Nikolova et al., 2011; Stice et al., 2012). Genotypes putatively associated with high DA signaling received a score of 1 and those putatively associated with low DA signaling received a score of 0. Further, genotypes associated with intermediate signaling strength received a score of 0.5. Specifically, *TaqIA* A2/A2, *COMT* Val/Val genotypes, *DRD2*-141C Ins/Del and Del/Del, *DRD4*-S, and *DAT1*-S were assigned a score of 1 ('high'); *TaqIA* A1/A1, *COMT* Met/Met genotypes, *DRD2*-141C Ins/Ins, *DRD4*-L, and *DAT1*-L were assigned a score of 0 ('low'), and *TaqIA* A1/A2 (Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991) and *COMT* Met/Val genotypes (Egan et al., 2001) received a score of 0.5. The scores were then summed to create the multilocus composite risk score (Study 1: $M = 2.65 \pm 0.87$; Study 2: $M = 2.49 \pm 0.97$; Study 3: 2.53 ± 0.91).

Model building

All models were fit with linear mixed effects models using the lme function in the nlme package from the R project (Pinheiro, Bates, DebRoy, Sarkar, & R Core Team, 2013). Linear mixed models accommodate multilevel data structures (i.e., time points nested within individuals) and are ideal for growth curve modeling when assessments occur at uneven intervals and not all participants complete each assessment, both characteristics of the present data. Time was represented with a linear natural-log representation of time in months from the baseline assessment that included BMI at 3- (Study 2), 6- (Study 2), 12- (Study 1–3), and 24-month (Studies 1–3) follow-ups as the outcomes. All models controlled for baseline BMI and sex (only in Study 1 and Study 3). We also controlled for intervention (0 = no, 1 = yes) in Study 2 as participants in this study were randomized to either a behavioral weight loss treatment (n = 16) or a control condition (n = 18). Independent variables included baseline BMI, sex, intervention, multilocus genetic composite risk score and time as well as all two-way interactions between the independent variables and time. For each model reported herein, we followed recommendations from Singer and Willet (2003) in which unconditional linear and nonlinear growth models are fit to determine the best model of change prior to adding other independent variables to the model. The best unconditional model was selected using Akaike Information Criterion (AIC) values following criterion from Burnham and Anderson (2002). After establishing an unconditional growth model, we fit models with the multilocus genetic composite risk score and the multilocus genetic composite risk score × time interaction to examine the association between the multilocus genetic composite risk score and future weight gain in each study. In Study 2, we also fit a second model with the multilocus genetic composite risk score × condition (weight loss intervention vs control) interaction and the multilocus genetic composite risk score × condition × time interaction to examine the moderating effects of the multilocus genetic composite risk score on the relation between intervention condition and change in BMI. Intercept coefficients were random on participant to account for non-independence across repeated measurements within participants. We examined model assumptions by inspecting residual by predicted values and normal probability plots of the person-level random effects. Visual examination indicated a random distribution around zero in the residuals and a straight line for the residual probability plot. We evaluated outliers with the criteria of a Cook's distance *F* probability value greater than 0.50 (Kutner, Nachtsheim, Neter, & Li, 2005). In only one case was this criterion met and because it did not alter the pattern of results, we retained this case in the data set. These results suggest that no univariate or multivariate outliers contributed unduly to the observed main and interactive effects reported herein.

Results

Descriptive statistics

Table 1 presents the descriptive statistics of the genotype groups over the total sample. The average rate for successful genotyping was as follows: *TaqIA*: 100%, *COMT*: 100%, *DRD2-141C*: 97%, *DRD4*: 100%, and *DAT1*: 100%. χ^2 analyses indicated that there were no significant relations between genotype status and self-reported ethnicity, race, or sex, suggesting that ancestry and sex are not potential confounds. Except for *DAT*1 ($\chi^2 = 7.61$), all of our genes are in Hardy–Weinberg equilibrium. χ^2 analyses also indicated that there were no significant differences between the 3 studies on the multilocus genetic composite risk score and *TaqIA*, *COMT*, *DRD2-141C*, *DRD4*, and *DAT1* genotype status. The multilocus genetic composite risk score and individual genotypes were not significantly correlated with baseline BMI in the studies.

As a first step, unconditional linear growth models for BMI (i.e., BMI was regressed on a linear time variable) were fit following recommendations from Singer and Willet (2003). The average BMI slope in Study 1 was 0.52 (range: –0.14–0.90), indicating that the average participant showed an increase in his/her BMI score by about 0.52 units per year (which corresponds to approximately 1.52 kg per year at the average height in the sample). The average BMI slope was –0.11 (a .30 kg per year decrease; range: –0.25–0.17) in Study 2 and 0.56 (a 1.63 kg per year increase; range: –0.01–0.91) in Study 3.

The multilocus genetic composite risk score × time interaction was associated with increases in BMI over 2-year follow-up in all three studies (Study 1: $r = 0.37$, $p = 0.01$; Study 2: $r = 0.22$, $p = 0.02$; Study 3: $r = 0.14$, $p = 0.02$) (Fig. 1A–C), suggesting that participants

Table 1
Descriptive statistics for the genotype groups (N = 225).

Genotype	N	Dopamine profile score	Ethnicity
TaqIA			
A2/A2	143 (62.2% female)	High	9.1% Hispanic; 84.6% Caucasian; 0.7% American Indian/Alaska Native; 1.4% Asian; 13.3 mixed races
A1/A2	75 (49.3% female)	Intermediate	16% Hispanic; 72% Caucasian; 8% American Indian/Alaska Native; 4% Asian; 16% mixed races
A1/A1	7 (85.7% female)	Low	14.3% Hispanic; 100% Caucasian
*COMT*Val158Met			
Val/Val	47 (59.6% female)	High	17% Hispanic; 72.3% Caucasian; 2.1% American Indian/Alaska Native; 2.1% Asian; 23.4% mixed races
Met/Val	117 (59% female)	Intermediate	10.3% Hispanic; 82.1% Caucasian; 2.6% American Indian/Alaska Native; 3.4% Asian; 12.0% mixed races
Met/Met	61 (57.4% female)	Low	9.8% Hispanic; 85.2% Caucasian; 4.9% American Indian/Alaska Native; 9.8% mixed races
DRD2 – 141CIns/Del			
Del/Del	2 (0% female)	High	50% Caucasian; 50% mixed races
Ins/Del	52 (55.8% female)	Intermediate	15.4% Hispanic; 69.2% Caucasian; 7.7% American Indian/Alaska Native; 23.1% mixed races
Ins/Ins	165 (60% female)	Low	10.3% Hispanic; 85.5% Caucasian; 1.2% American Indian/Alaska Native; 2.4% Asian; 10.9% mixed races
DRD4			
DRD4-S	126 (55.6% female)	High	8.7% Hispanic; 79.4% Caucasian; 2.4% American Indian/Alaska Native; 3.2% Asian; 15.1% mixed races
DRD4-L	99 (62.6% female)	Low	15.2% Hispanic; 82.8% Caucasian; 4% American Indian/Alaska Native; 1% Asian; 12.1% mixed races
DAT1			
9R/9R	6 (100% female)	High	100% Caucasian
9R/10R	99 (54.5% female)	Intermediate	9.1% Hispanic; 81.8% Caucasian; 4% American Indian/Alaska Native; 1% Asian; 13.1% mixed races
10R/10R	120 (60% female)	Low	14.2% Hispanic; 79.2% Caucasian; 2.5% American Indian/Alaska Native; 3.3% Asian; 15.0% mixed races

Main effects of the multilocus genetic composite risk score on increases in BMI over 2-year follow-up.

with a higher number of alleles associated with elevated DA signaling capacity showed greater weight gain than those with fewer of these variants. The effect sizes suggest that the multilocus genetic composite risk score effects were stronger in the two samples with overweight and obese individuals (Studies 1 and 2) compared to the sample with healthy-weight individuals (Study 3).

Comparison of main effects of the multilocus genetic composite risk score and individual genotypes on increases in BMI over 2-year follow-up

We examined whether the multilocus genetic composite risk score explained greater variance in weight gain than the individual genotypes. For these analyses, we combined the three samples into one (N = 225) to increase our sensitivity to detect potentially small effects of the individual genotypes and to decrease Type 1 errors due to multiple testing. Models were run separately for each individual genotype and for the multilocus genetic composite risk score. All models controlled for baseline BMI, sex, and intervention. The multilocus genetic composite risk score × time interaction again showed a significant positive association with future increases in BMI over 2-year follow-up ($r = 0.19$, $p < 0.001$) in the combined sample (Table 2). With regard to the predictive effects for the individual genotypes, the *DRD4* × time interaction ($r = 0.14$, $p = 0.003$) and DAT1 × time interaction ($r = 0.12$, $p = 0.01$) were significantly related to increases in BMI over 2-year follow-up; *DRD4*-S homozygotes showed greater weight gain than *DRD4*-L carriers and the *DAT1*-S carriers showed greater weight gain than the *DAT1*-L carriers (Table 2). Because the *DRD4*-S and *DAT1*-S were significantly associated with future increases in BMI in the overall sample, we next tested the effects of *DRD4* × time interaction and *DAT1* × time interaction on increases in BMI in the individual samples. The *DRD4* × time interaction was positively related to increases in BMI in Study 1 ($r = 0.42$, $p = 0.002$) and Study 2 ($r = 0.27$, $p = 0.004$), but not Study 3 ($r = 0.05$, $p = 0.36$). The *DAT1* × time interaction was positively related to increases in BMI in Study 3 ($r = 0.17$, $p = 0.004$), but not in Study 1 ($r = 0.04$, p = 0.80) and Study 2 ($r = 0.04$, $p = 0.69$).

Given that Study 2 differed in study design (randomized weight loss intervention) and sample (only females) from Study 1 and Study 3, we also tested these models in the combined data from Study 1 and Study 3 (N = 191), excluding data from Study 2. The multilocus genetic composite risk score × time interaction was positively associated with increases in BMI over 2-year follow-up in this smaller sample ($r = 0.17$, $p < 0.001$). The effect size did not significantly differ from the effect size found in the larger combined sample. The *DRD4* × time interaction ($r = 0.12$, $p = 0.02$) and *DAT1* × time interaction ($r = 0.13$, $p = 0.01$) were also significantly related to increases in BMI over 2-year follow-up in this smaller combined sample. We also tested directly whether the correlation between the multilocus genetic composite risk score and increases in BMI differed for Study 2 data versus the data from Studies 1 and 3. We created a dummy coded vector with Study 2 subjects receiving score 1 and all other subjects score 0. The interaction between Study and multilocus genetic composite risk score was not significantly associated with increases in BMI ($r = 0.01$, $p = 0.85$).

Interactions between the multilocus genetic composite risk score and weight loss intervention in the prediction of increases in BMI over 2-year follow-up

The multilocus genetic composite risk score × condition × time interaction was positively associated with increases in BMI over 2-year follow-up ($r = 0.21$, $p = 0.03$). We divided the sample by means of a median split of the multilocus genetic composite risk score and calculated the mean BMI change over 2-year follow-up for both groups. Figure 2 shows that in the weight loss intervention group, those with a high multilocus genetic composite risk score, show less weight loss over 2-year follow-up than those with a low multilocus genetic composite risk score. In the control condition, those with a high multilocus genetic composite risk score showed greater increases in BMI compared to those with a low multilocus genetic composite risk score.

Discussion

The primary aim of the present study was to evaluate the relation between a genetic propensity for high DA signaling capacity in reward regions, as defined by the multilocus genetic composite risk score, and future weight gain. As hypothesized, there was a significant positive association between the multilocus genetic composite risk score and increases in BMI over 2-year follow-up in all three studies as well as the combined sample. These effects were found while controlling for other factors (baseline BMI, sex, and intervention). The fact that this result occurred in all three separate samples suggests that this effect is robust. The results are in line with the reward surfeit theory of obesity (Stice, Spoor, Bohon,

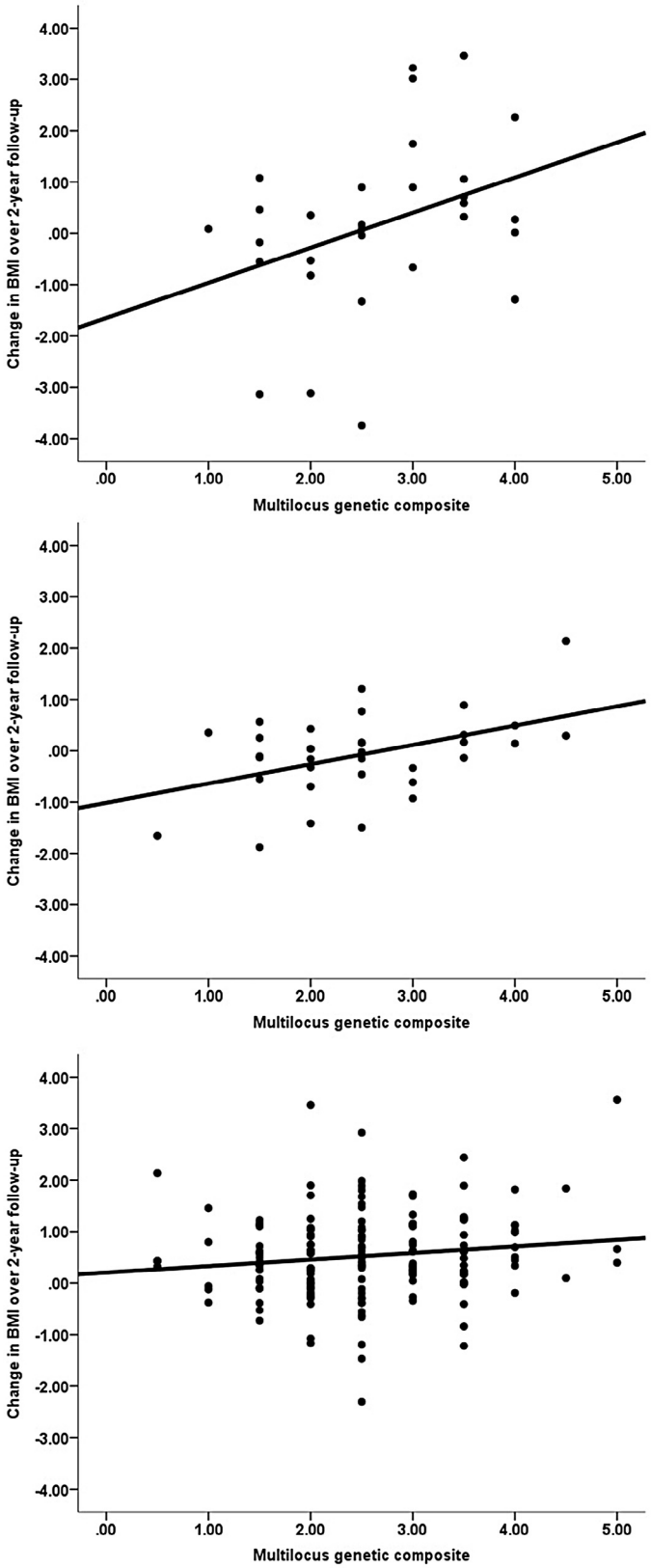

Fig. 1. Partial regression plots showing the effects of the multilocus genetic composite risk score on change in BMI units over 2-year follow-up in (A) Study 1, (B) Study 2, and (C) Study 3, while controlling for baseline BMI (Studies 1–3), sex (Studies 1–3), and intervention (Study 2).

Table 2
Main effects of the multilocus genetic composite risk score, *TaqIA*, *COMT*, *DRD2-141C*, *DRD4*, and *DAT1* on increases in Body Mass Index (BMI) over 2-year follow-up (N = 225), while controlling for baseline BMI, sex (female = 1; male = 0), and intervention (weight loss intervention = 1; control group = 0).

Variable	*B*	SE	*df*	*t* value	*p*
Multilocus genetic composite					
Intercept	0.15	0.55	462	0.27	0.78
Time	0.11	0.21	462	0.54	0.59
Baseline BMI × Time	–0.00	0.01	462	–0.3	.76
Sex × Time	–0.18	0.07	462	–2.76	.01
Intervention × Time	–0.61	0.15	462	–4.18	<.001
Multilocus genetic composite × Time	0.14	0.03	462	4.14	<.001
TaqIA					
Intercept	0.09	0.56	462	0.16	.87
Time	0.50	0.21	462	2.38	.02
Baseline BMI × Time	–0.00	0.01	462	–0.13	.90
Sex × Time	–0.20	0.07	462	–3.05	.002
Intervention × Time	–0.60	0.15	462	–4.08	<.001
TaqIA × Time	–0.06	0.12	462	–0.55	.58
COMT					
Intercept	0.17	0.53	462	0.33	.74
Time	0.38	0.20	462	1.91	.06
Baseline BMI × Time	–0.00	0.01	462	–0.12	.91
Sex × Time	–0.21	0.07	462	–3.07	.002
Intervention × Time	–0.64	0.15	462	–4.27	<.001
COMT × Time	0.15	0.09	462	1.64	.10
DRD2-141C					
Intercept	0.16	0.51	451	0.31	.76
Time (months)	0.50	0.19	451	2.57	.01
Baseline BMI × Time	–0.00	0.01	451	–0.5	.62
Sex × Time	–0.20	0.07	451	–3.00	.003
Intervention × Time	–0.58	0.15	451	–3.96	<.001
DRD2-141C × Time	0.09	0.07	451	1.23	.22
DRD4					
Intercept	0.23	0.51	462	0.44	.66
Time	0.36	0.19	462	1.87	.06
Baseline BMI × Time	–0.00	0.01	462	–0.27	.79
Sex × Time	–0.19	0.07	462	–2.89	.004
Intervention × Time	–0.54	0.15	462	–3.67	<.001
DRD4 × Time	0.19	0.06	462	2.94	.003
DAT1					
Intercept	0.16	0.51	462	0.31	.76
Time	0.40	0.19	462	2.09	.04
Baseline BMI × Time	–0.00	0.01	462	–0.31	.76
Sex × Time	–0.20	0.07	462	–2.97	.003
Intervention × Time	–0.62	0.15	462	–4.25	<.001
DAT1 × Time	0.17	0.06	462	2.69	.01

Note: *ß* = standardized regression coefficient; SE = Standard Error; df = degrees of freedom.

Veldhuizen et al., 2008), and suggest that individuals with a genetic propensity for greater DA signaling have a biologically based elevated reward region responsivity (Nikolova et al., 2011; Stice et al., 2012) which may render them more vulnerable to food cues and unhealthy eating behaviors, resulting in future weight gain. Yet, it should be noted that other findings are difficult to reconcile with the reward surfeit model of obesity. That is, previous studies have found that DA agonists (e.g., amphetamine) that increase DA signaling lead to weight loss and DA antagonists (e.g., neuroleptics) that reduce DA signaling lead to weight gain (Heal, Smith, Gosden, & Nutt, 2013; Wirshing et al., 1999). This may imply that the mechanism of weight gain in response to an antagonist drug is qualitatively different from the mechanism of weight gain in response to innate hypersensitivity of reward regions. Also of note, human studies have found an inverse relation between BMI and illicit drug use, and a lower risk for substance use disorders in obese versus lean individuals (Blendy et al., 2005; Blüml et al., 2012; Simon et al., 2006; Warren, Frost-Pineda, & Gold, 2005). Future research will be needed to identify the differential effects of innate hypersensitivity of reward regions versus DA antagonists on weight gain.

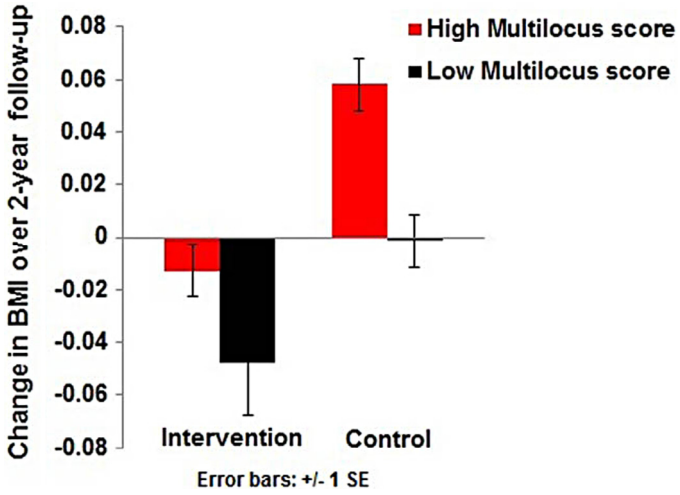

Fig. 2. Change in BMI over 2-year follow-up in Study 2 predicted by the interaction of the multilocus genetic composite score and condition (i.e. weight loss intervention vs control group) and increases in BMI over 2-year follow-up.

A recent study (Davis et al., 2013) found that the multilocus genetic composite profile was positively correlated with self-reported food addiction, binge eating, food cravings, and emotional eating. Yet, post-hoc analyses in our combined dataset indicated that there were no significant associations of the multilocus genetic composite risk score with self-reported food cravings (Food Craving Inventory (White, Whisenhunt, Williamson, Greenway, & Netemeyer, 2002)) at baseline ($r = -0.04$) and increases in self-reported food craving over 2-year follow-up ($r = 0.07$). Further, food cravings were not significantly associated with increases in BMI ($r = 0.03$). Future studies should explore how objectively measured eating behaviors determine the effects of the multilocus genetic composite risk score in the prediction of increases in BMI.

We also tested whether the multilocus genetic composite risk score moderated the effects of weight loss treatment on change in BMI over 2-year follow-up in Study 2. In the weight loss intervention group, those with a high multilocus genetic composite risk score show less weight loss over 2-year follow-up than those with a low multilocus genetic composite risk score. In the control condition, those with a high multilocus genetic composite risk score showed greater increases in BMI compared to those with a low multilocus genetic composite risk score. These findings converge with several studies that found that individual genotypes associated with DA signaling interact with treatment in the prediction of weight loss success (Cameron et al., 2013; Roth, Hinney, Schur, Elfers, & Reinehr, 2013). Overall, these findings imply that qualitatively different weight loss interventions may be needed depending on genetic risk.

We also tested whether the multilocus genetic composite risk score was associated with greater variance in future weight gain than the individual genotypes. Only *DRD4* and *DAT*1 were associated with future weight gain; *DRD4*-S homozygotes and *DAT1*-S carriers showed greater increases in BMI than *DRD4*-L carriers and *DAT1*-L. The *DRD4* finding is comparable with the findings of Fuemmeler and colleagues (Fuemmeler et al., 2008) who found a trend between *DRD4*-S and increases in BMI from adolescents to adulthood. Interestingly, the *DRD4-S* genotype was associated with future weight gain in the two smaller samples varying in weight from lean to obese (Studies 1 and 2), but not in the larger sample consisting of healthy-weight adolescents (Study 3). In contrast, the *DAT1-S* genotype was associated with future weight gain in the larger sample consisting of healthy-weight adolescents, but not in the two smaller samples varying in weight from lean to obese. These findings may suggest the *DRD4*-S and *DAT*1-S genotypes interact with weight status in their prediction of future weight gain. Although the effects of the *DRD4*-S in Studies 1 ($r = 0.42$) and 2 ($r = 0.27$) and the effects of *DAT1-S* in Study 3 ($r = 0.17$) were slightly stronger than the effects of the multilocus genetic composite risk score in these individual studies (Study 1: $r = 0.37$; Study 2: $r = 0.22$; Study 3: $r = 0.14$), the multilocus genetic composite risk score was associated with increases in BMI in all three separate samples. This pattern of findings may suggest that the multilocus genetic composite risk score is a more reproducible predictor in that it emerged in multiple samples. Further, the effect of the multilocus genetic composite risk score on increases in BMI in the combined sample ($r = 0.19$) was slightly stronger than the effects of the *DRD4*-S ($r = 0.14$) and *DAT1*-S ($r = 0.12$) genotypes.

It was noteworthy that the predictive effects for both the multilocus genetic composite risk score and the *DRD4* genotype were stronger in the two samples with overweight and obese individuals (Studies 1 and 2) than in the sample with only adolescents in the healthy weight range (Study 3). This finding converges with the results of a study (Beyerlein, von Kries, Ness, & Ong, 2011) that found that a genetic risk score for obesity significantly correlated with BMI and fat mass in children, particularly in those with a higher weight status. It is possible that epigenetic gene regulation, including DNA methylation and histone modifications, plays an important role in driving these differences. Environmental factors, like stress and nutrition, modulate gene expression via epigenetic mechanisms (Schwenk, Vogel, & Schurmann, 2013). These mechanisms can be active during intrauterine and early postnatal development as well as throughout adult life (Schwenk et al., 2013). Future research will be needed to examine how epigenetic mechanisms contribute to the differential effects of genotypes associated with high DA signaling and future weight gain in samples varying in weight status. Another explanation for this finding is that the weaker predictive effects from the sample that contained only healthy-weight adolescents may have occurred because by excluding individuals who were already overweight or obese in Study 3 sample, but not the Study 1 and 2 samples, the latter two samples may have contained a greater proportion of individuals at risk for future weight gain, which increased sensitivity.

The multilocus genetic composite risk score and the individual genotypes were not associated with baseline BMI. This pattern of findings may have emerged because the participants were right-censored in that most of the participants had not shown all of the unhealthy weight gain that they will eventually show because the average age was 16.1 in the total sample at baseline. Alternatively, it is possible that other risk factors are more potent predictors of future weight gain during childhood and early adolescence, such as variation in exercise, which tends to begin to decline in adolescents for most individuals in the US (McMurray, Harrell, Creighton, Wang, & Bangdiwala, 2008), an effect that is more pronounced in females (Sallis, 1993).

It is important to consider the limitations of the present study when interpreting the findings. First, the multilocus genetic composite risk score was estimated as a cumulatively additive effect of 5 genotypes. However, this method assumes that all genotypes are independently associated with increased risk for weight gain. Future studies with greater power are needed to test this assumption and to check for potential interactions between these genotypes. Second, although BMI is widely used to assess adiposity, is inexpensive, and shows high test–retest reliability, it does not distinguish between increased mass in the form of fat, lean tissue or bone and hence can lead to misclassification (McCarthy et al., 2006; Prentice & Jebb, 2001). It is possible that by using a direct measure of fat mass (for example, dual energy X-ray absorptiometry) additional or stronger effects of the multilocus genetic composite risk score would have been found. Future studies testing the associations of the multilocus genetic composite risk score and changes in fat mass are needed

to examine these relations more closely. Third, the sample sizes of all three studies as well as the combined sample were small, which limits the confidence that can be placed in the findings, even if the results did replicate across all three samples examined herein. Finally, it is possible that confounding effects due to unknown environment factors and false-positive associations due to biased selection may have influenced the effects of the genotypes in this study. Independent replication is needed before definitive conclusions can be made about the role of these genotypes on risk of future weight gain.

In conclusion, results provided support for the hypothesis that a multilocus profiling approach can be used to create a genetic risk profile for future weight gain based on genotypes associated with DA signaling. This is in line with several longitudinal studies (Elks et al., 2010; Mei et al., 2012; Warrington et al., 2013) that found that a genetic score based on the combination of GWAS risk SNPs (e.g., variants in or near *FTO*, *MC4R*, *NEGRI*, *TMEM18*, and *BDNF*) is a better predictor of BMI and future weight gain than the individual variants. Further, recent research suggest that the multilocus genetic composite risk score is associated with food addiction and eating pathology (Davis et al., 2013) and addictive behaviors (Davis & Loxton, 2013). Collectively, these results imply that it may be useful to investigate the additive effects of genotypes that affect DA signaling captured by multilocus composite risk scores on traits and behaviors that exert their rewarding effects by increasing DA in the reward circuitry. It might be also worthwhile to investigate additional genes that may impact DA signaling capacity, such as tyrosine hydroxylase genes involved in DA synthesis, genotypes that influence all five of the DA-receptors, and monoamine oxidase genotypes involved in DA metabolism. Adding additional genes associated with DA signaling may increase the explained variance in weight gain, which is modest in the current samples.

To our knowledge, the current study is the first to examine the effect of the multilocus genetic composite reflecting high DA signaling on increases in BMI. The results lend support for the involvement of genotypes associated with high DA signaling on future weight gain. Our findings therefore contribute to a further understanding of genetic risk processes for risk for unhealthy future weight gain and might highlight pathways that can be targeted for prevention and treatment interventions for obesity.

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