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GABRA2 Genotype, Impulsivity, and Body Mass

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Abstract

Background—The goal of this study was to test a hypothesis associating impulsivity with an elevated body mass index (BMI).

Methods—To this end, we examined associations of BMI with putative genetic, neurophysiological, psychiatric, and psychological indicators of impulsivity in 78 women and 74 men formerly dependent on alcohol or drugs. A second analysis was designed to test the replicability of the genetic findings in an independent sample of 109 women and 111 men with a similar history of substance dependence.

Results—The results of the first analysis showed that BMI was positively correlated with Total and Nonplanning Scale Scores on the Barratt Impulsiveness Scale and the number of childhood symptoms of Attention-Deficit/Hyperactivity Disorder in women. It was also positively correlated, in women, with a *GABRA2* variant previously implicated as a risk factor for substance dependence and an objective electroencephalographic feature previously associated with *GABRA2* and relapse risk. The second analysis confirmed that the correlation between BMI and the substance-dependence-associated *GABRA2* genotype was reliable and sex-specific.

Conclusions—We conclude that an elevated BMI is associated with genetic, neurophysiological, psychiatric, and psychological indicators of impulsivity. The sex difference may be explained by greater opportunities to eat and overeat, a preference for higher calorie foods, a longer duration of alcohol/drug abstinence, or previous pregnancies in women.

INTRODUCTION

This paper presents data supporting the hypothesis of a relationship between an elevated body mass index (BMI) and impulsivity. A critical reader may ask why such data are

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needed, for the former obviously connotes the latter—that is, poor behavior control. Yet, formal observational studies have produced mixed results. The presence versus absence of a relationship between BMI and impulsivity appears to be contingent on the age of the subjects under investigation.

Indeed, in studies of children, there is little[1] or no controversy about the relationship. Overweight children have been found[2] to exhibit less impulse control than normal weight children during a stop-signal reaction time task. Also, children or adolescents with behavior control problems indicative of impulsivity, including Attention-Deficit/Hyperactivity Disorder (ADHD),[3] Conduct Disorder,[4,5] Oppositional Defiant Disorder,[4,5] and alcohol, tobacco, and other drug use,[6] have all been shown to exhibit a greater average BMI than their unaffected peers. Longitudinal studies find that the BMI elevation associated with behavior control disorders is stable throughout the adolescent years.[4]

The controversy about the BMI–impulsivity association is solely limited to studies of adults. It is particularly obvious in studies[7–9] of adult Substance Use Disorders (SUDs), which, like other behavior control disorders, are often characterized by a greater-than-average level of impulsivity.[10] For instance, from an analysis of data from the National Comorbidity Study, Simon and colleagues[11] reported that obesity (a BMI ≥ 30 kg/m²) was not associated with an increased risk of a SUD, but a decreased risk. Yet, Onyike and colleagues[12] evaluated 39,695 respondents to the National Health and Nutrition Examination Survey and found no association between obesity and substance use. Petry and colleagues[13] reported findings from an analysis of 41,654 members of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) dataset. They found that obesity was positively associated with a lifetime diagnosis of an Alcohol Use Disorder (AUD), but not with a history of a Drug Use Disorder (DUD). Their finding is curious because DUDs are typically associated with higher levels of impulsivity and Cluster B personality features, and loss of control over intake, than are the AUDs.[14] DUDs should therefore be more strongly related to BMI and obesity than AUDs if impulsivity mediates the relationship. In addition, Gearhardt and Corbin[15] analyzed the same NESARC dataset and reported a result inconsistent with the conclusion drawn by Petry and colleagues[16]: the frequency of drinking and BMI were inversely related.

An Attempt to Resolve the Confusion

We are therefore confronted with a paradox. In childhood, impulsivity, substance use, and related variables are all positively associated with BMI and obesity. In adulthood, however, the associations are inconsistent or unexpectedly negative. It is therefore likely that an uncontrolled factor emerges between adolescence and adulthood in impulsive individuals to complicate the association. We suspect that excessive and regular use of alcohol and drugs is the factor.

The major goal of this study was to control this factor by examining substance-dependent adults uncomplicated by regular use. More specifically, we studied patients in residential substance abuse treatment programs where abstinence could be verified. We examined women and men separately because female sex has previously[9,16,17] been shown to amplify the relationship of some impulsivity indicators—Antisocial Personality Disorder and Delay Discounting—with BMI.

A second major goal was to test the contributions of a genotype and a biological endophenotype previously implicated in poor behavior control in adults. To this end, we examined a single nucleotide polymorphism (SNP) within the *GABRA2* gene, which encodes a subunit of the GABA_A receptor. Variation in *GABRA2* has been associated with conduct problems,[18] substance use,[19] and SUDs.[18] The endophenotype has power within the

fast beta (19–30 Hz) frequency band of the spontaneous electroencephalogram. Fast beta power has previously been shown to associate with the same *GABRA2* genotype that promotes risk for Conduct Disorder and SUDs.[20]

In addition to *GABRA2* and fast beta power, we examined other likely indicators of impulsivity, including familial density of substance dependence,[21] childhood symptoms of ADHD, and total and subscale scores on the Barratt Impulsiveness Scale (BIS). Scores on depression and anxiety scales were examined to test the discriminant validity of our theory relating externalizing features to BMI and obesity risk.

METHOD

The patients in the principal analysis were recruited from two residential substance abuse treatment facilities in the Hartford, CT region. A different sample of patients was also studied, in an effort to replicate the genetic findings revealed in the principal analysis. The replication sample was drawn from a larger dataset collected and managed by a consortium of NIDA- and NIAAA-funded investigators. It included substance-dependent patients recruited from a wide variety of settings and locations across the eastern United States.[22,23]

Principal Sample

Participants—On average, the principal sample of 152 residential treatment program patients had completed 13 yrs of education. Their age range was 21–55 yr. Seventy percent of the 78 women, and 74% of the 74 men, were European-American (EA).

All of the patients were in good medical health. They were not enrolled if they had a lifetime history of seizures, neurosurgery, head injury with loss of consciousness greater than 30 minutes, schizophrenia, bipolar disorder, major depressive disorder, mental retardation, dementia, or significant medical disorders, including HIV-1 infection or cardiovascular, hepatic, immunologic, or renal disease. Patients with uncorrected deficits in vision or hearing were also excluded.

Recruitment and Clinical Evaluation Procedures—Patients initially deemed eligible for the study were transported to the University of Connecticut Health Center (UCHC) on a weekday morning. An informed consent document, approved by the UCHC Institutional Review Board, was reviewed and signed at that time. Urine and breath samples were then collected and assayed to exclude patients with recent exposure to alcohol, cocaine, amphetamine, marijuana, or heroin. In addition, hair samples (PDT-90™, Psychemedics Inc., Cambridge, MA)were collected to verify self-reports of no drug use during the previous 60 days. Patients admitting substance use, suspected by treatment program staff of substance use, or testing positive for alcohol, cocaine, amphetamine, or heroin use during the previous 2 months were excluded. The maximum duration of abstinence allowed by the protocol was 6 months.

Demographic data and medical and psychiatric histories were obtained from all patients to determine final eligibility. The psychiatric history was obtained with the Computerized Diagnostic Interview Schedule for DSM-IV (CDIS-4[24]). Additional demographic, medical, psychological, and drug use information was garnered from medical records, interviews, and questionnaires, including the BIS-11,[25] Michigan Alcoholism Screening Test (MAST[26]), Drug Abuse Screening Test (DAST-20[27]), Fagerström Test for Nicotine Dependence (FTND[28]), Family History Assessment Module (FHAM[29]), Wender Utah Rating Scale (WURS[30]), the Kaufman Brief Intelligence Test (KBIT[31]), and the Beck Depression (BDI-II[32]) and Anxiety (BAI[33]) Inventories. BMI was calculated from height and weight measured during the visit.

EEG Procedures—The assessment of fast beta electroencephalographic activity occurred in the afternoon after a lunch break. It was recorded over a 5-minute period while patients sat quietly with eyes closed. The reduction and analysis procedures have been described elsewhere.[34]

Replication Sample

The replication sample was formed from a subset of *n*=220 patients who had participated in two large multi-site studies of the genetics of cocaine, opioid, and alcohol dependence.[23,35] They were selected from the multisite studies to resemble, as closely as possible, the drug use and demographic characteristics of patients enrolled in the principal sample. Their characteristics are summarized in Table 2.

The methods used to assess medical and mental health in the replication sample were not identical to the methods used in the principal sample. Accordingly, the entry criteria could not be identical. All of the replication sample patients had a lifetime diagnosis of dependence on cocaine, opioids, or cannabis. Their minimum duration of abstinence (4 months) was slightly longer than the minimum for the principal sample (2 months) because the diagnostic interview, the SSADDA,[36] used 4 months, not 2 months, as a cut point for categorization. The maximum duration of abstinence was 1 year. Unfortunately, in the replication sample, duration of abstinence was not verified with serial toxicology tests of urine or hair as it was in the principal sample. In addition, BMI was based on self-reported height and weight. It was not directly measured as in the principal sample.

Genotyping Procedures for Both Samples

DNA was extracted from peripheral blood samples (primary study) and cell lines, blood, or saliva (replication study). *GABRA2* genotyping procedures have been described previously.[37] Patients were identified as being either homozygous for the low substance-dependence-risk "A" allele (which comprises the low-risk genotype group) or a carrier of the substance-dependence-associated "G" allele (which comprises the high-risk genotype group) at rs279858.

The *GABRA2* genotypes in both samples were distributed in a manner consistent with Hardy-Weinberg equilibrium expectations (principal sample: $p = .9$; replication sample: $p = .9$). In the $N = 123$ European Americans comprising the principal sample, the rates were 22.7% ($n = 28$) GG, 52.8% AG ($n = 65$), and 24.3% ($n = 30$) AA. In the replication sample, the respective rates were 14.1%, 45.4%, and 40.4%.

Analysis Plan

When divided by sex, the sample size was insufficient to support a complex statistical model, such as factor analysis followed by a regression analysis of factor scores. We, therefore, adopted a simple analytic strategy in which regression equations were computed separately for women and men. The equations tested the association of BMI, independently, with Beck Depression and Anxiety Inventory scores, BIS Total Score and three subscale scores (attention, motor, nonplanning), childhood ADHD symptoms retrospectively recalled on the WURS, relative fast beta EEG power at the Fz electrode, *GABRA2* SNP genotype, and the percentage of immediate biological family members greater than age 25 with a lifetime diagnosis of dependence on alcohol or drugs (except nicotine). One covariate employed in every analysis other than the *GABRA2* analysis, which was limited to the 123 European Americans, was a single variable coding for the absence versus presence of European-American ancestry. The covariate was entered because race and ethnicity have previously been associated with BMI and may alter its association with other variables.

FTND total score was also used as a covariate because most patients were active smokers and smoking is likely to influence body mass. The third covariate was age.

The analysis of the replication sample involved a test of the association of the *GABRA2* SNP genotype with BMI by a general linear model. Age and level of nicotine use were specified as covariates. Separate analyses were performed for males and females.

RESULTS

Analysis of the Principal Sample

Table 1 presents the full analysis results for women and men. Table 2 presents a summary of the demographic and psychological characteristics of the two groups.

In brief, the analysis revealed statistically significant associations in women of BMI with ADHD symptoms, BIS-11 impulsivity score, fast beta EEG power, *GABRA2* genotype, and the family density of alcohol and drug dependence. In men, most of the associations—with family density as the only exception—were not statistically significant.

The information presented in Table 2 does not provide clear insight into the source of the sex difference. For example, the women and men did not differ on demographic and substance use variables that might contribute to the associations (eg, FTND, MAST, or DAST-20 scores). Duration of abstinence also did not significantly differentiate the groups, although the women had been abstinent for an average of 35 days longer than men.

To help interpret the results of the primary analyses, we conducted two secondary analyses with the same covariates. The secondary analyses were motivated by a priori hypotheses about pregnancies and recency of substance use as possible moderators of the BMI-by-impulsivity association. Analysis 1 examined the relationship between the number of previous full-term pregnancies reported by women and BMI. The result approached statistical significance ($p = .06$). Analysis 2 tested the association of days of abstinence and BMI. It was statistically significant in women ($p = .03$) but not in men ($p = .20$). The results of these analyses are reported in Table 1.

Analysis of the Replication Sample

The analysis revealed a statistically significant positive association between the high risk *GABRA2* SNP genotype and BMI in women ($p = .02$). The association was not significant in men ($p = .70$). The test for replication in an independent sample was therefore successful.

DISCUSSION

This study tested the hypothesis of a positive relationship between BMI and various indicators of impulsivity in adults with a history of substance dependence. The findings support the hypothesis. Among women, BMI was positively correlated with the Total score and Nonplanning subscale score on the BIS-11, the number of ADHD symptoms, the familial density of substance dependence, and fast beta EEG power. It was not correlated with recent anxiety and depression symptoms measured by the BAI and BDI-II, respectively. In men, BMI was only correlated with the familial density of substance dependence.

This study also revealed a positive correlation, among women, between BMI and a genotype previously associated with both conduct problems[18] and substance dependence.[20,38,39] The correlation was significant among the 123 European-American subjects in the first analysis and the 220 European-American subjects in the replication analysis. The reproducibility of

the *GABRA2* finding across analyses diminishes concerns about the increased risk of Type 1 error associated with the analysis of samples of modest size.

In view of the correlation of BMI with genetic and other likely indicators of impulsivity, and previous evidence associating these indicators with substance dependence, the present findings suggest that an elevated BMI and substance dependence are related through this factor. An overlap between BMI and substance dependence is not a new idea, for Wang and colleagues have previously hypothesized deficits in reward processing as a feature common to both an excess BMI and drug addiction.[40] Our contribution to the literature is demonstrating impulsivity as an additional overlapping feature. Individual differences in impulse control may elevate BMI and obesity risk by impairing the individual's awareness of satiety cues[41] and fostering loss of control over food intake.

A minor but additional contribution to the literature offered by this study is implied by the results shown in Table 1: duration of alcohol and drug abstinence is positively correlated with BMI, albeit in women only. Although this result is not as easily interpreted as the BMI-by-impulsivity correlation, it does suggest an explanation for the morass of findings[11–13,15] in the adult literature regarding the association between substance dependence and BMI: studies that fail to control background variability in recency of use will produce inconsistent results. Of course, one[11] might argue that the large epidemiological studies did control for this background variability by excluding patients with current dependence from the analysis of the lifetime dependence-by-BMI association. But, excluding patients with a current substance use disorder diagnosis does not eliminate patients who continue to use substances excessively but do not exhibit the requisite number of problems from use to be diagnosed as dependent. Their excessive use may still be sufficient to suppress BMI through pharmacological effects on appetite or energy and/or a reduction in resources (time or money) that are available for overeating and weight gain. In this study, we eliminated this confound by requiring alcohol and drug abstinence.

The sex difference found here in the correlation of impulsivity indicators with BMI is consistent with a similar sex difference found previously for two other impulsivity indicators —Antisocial Personality Disorder symptoms[9] and delay discounting task performance.[17] This study, therefore, shows that the correlation generalizes beyond these two indicators. We can offer several speculative explanations for the sex difference.

The first possible explanation relates to the marginally nonsignificant difference between men and women in duration of abstinence shown in Table 2. If this difference is meaningful, then it suggests that the physiological or economic effects of recent substance use may be more persistent in men than women and obscure the association of BMI with other factors. One would accordingly predict that BMI and impulsivity will be correlated in men when the residual effects of their more recent use of alcohol and drugs have dissipated.

A second possible explanation for the sex difference relates to prior pregnancy in women and the hypothesis that impulsivity leads to more pregnancies and a residual increase in BMI. We were able to test this hypothesis by regressing the number of reported pregnancies on BMI (Table 1). The regression findings approached statistical significance ($p = .06$). We, therefore, cannot exclude pregnancy as a possible mediator of the association between impulsivity and BMI in women.

Another category of explanations—more likely than the others—relates to a sex difference in food preference. Previous research has shown that women report greater cravings for sweets than men[42] and a reduced ability to inhibit brain activation in the presence of food.[43] Greater cravings for high-calorie foods that promote rapid weight gain may place women,

especially impulsive women, at greater risk for greater body mass than impulsive men (who may express their impulsivity through, for example, greater substance use).

A final category of explanations relates to a possible sex difference in the opportunity to eat and overeat—that is, in the food environment. Women are traditionally more involved in home life and food preparation than men, particularly in low-income households.[44] As a result, they may have greater access to food throughout the day. Among women who are impulsive, greater access may translate into more weight gain than would be seen in impulsive men.

CONCLUSIONS AND LIMITATIONS

From the findings reported here, we can draw several major conclusions. First, impulsivity and BMI are related in women with a history of substance dependence. In addition, we can conclude that the same *GABRA2* genotype previously implicated in risk for substance dependence is also related to BMI. Finally, we can conclude that recent anxiety and depression symptoms are not related to BMI in this sample.

The present conclusions should be considered cautiously, for they are constrained by several limitations in the study design. The two most obvious limitations are the small size and the homogenous composition of the two samples. Until a follow-up study is performed without these limitations, we do not know if the correlates of BMI shown here will generalize, and be detectable in other racial-ethnic groups or groups less affected by impulsivity and substance dependence.

Another major limitation is the sole use of BMI as the estimate of adiposity and obesity risk. BMI is a convenient index. But, it is not ideal. Future research should include other, more valid measures of adiposity, such as the waist-to-hip ratio or triceps skinfold thickness.

A final limitation relates to questions about the function of the *GABRA2* gene. Despite its robust and well-replicated association with various externalizing disoders, *GABRA2* has not yet been shown to alter amino acid expression. It may instead interact with other genes, such as GABRG1,[45] that are functional to alter when or where they are expressed. Future studies should examine multiple genes and conduct tests of their interactions in modifying risk for an elevated BMI or obesity.

Acknowledgments

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TABLE 1

Regression analysis results for the prediction of current BMI in the principal sample.

Variable	Women (*n* = 78)			Men (*n* =74)		
	=	*t* =	*p* =	=	*t* =	*p* =
WURS ADHD score	0.27	2.4	.01 *	0.05	0.4	.67
BIS-11 total score	0.22	1.9	.05 *	0.10	0.7	.47
Nonplanning	0.24	2.3	.02 *	0.02	0.2	.86
Attention	0.07	0.7	.47	0.14	1.3	.19
Motor	0.11	0.9	.33	0.10	0.8	.38
Fast beta EEG power at Fz	0.32	3.2	.01 *	0.02	0.2	.81
Family density of alcohol and drug dependence	0.32	2.8	.01 *	0.28	2.1	.03 *
GABRA2 genotype @ rs279858 (EA only, *n* = 123)	0.24	2.0	.04 *	−0.04	−0.3	.77
BDI-II	0.13	1.2	.23	0.10	0.8	.39
BAI	−0.03	−0.3	.76	−0.01	−0.0	.96
# Previous pregnancies	0.21	1.8	.06	–	–	–
Days abstinent	0.24	2.1	.03 *	0.15	1.2	.20

Statistically significant beta weights are indicated with an asterisk.

All analyses, except the GABRA2 analysis, used age, FTND total score, and race as covariates

TABLE 2

Demographic and other background characteristics of the principal and replication samples by sex

Principal sample	Women (*n* = 78)	Men (*n* = 74)	$t =$ or $x^2 =$
Age in yrs (SD)	38.2(10.6)	36.1(9.8)	1.3
Yrs education	13.2(2.3)	12.9(2.3)	0.8
% White non-Hispanic	70.5	74.3	0.2
MAST	6.6(6.9)	8.3(6.8)	−1.5
DAST-20	10.7(7.7)	11.7(7.4)	−0.8
Days abstinent	129(53)	94 (82)	1.3
Nicotine dependence score	1.6(2.0)	2.1(2.1)	−1.6
BDI-II	11.2(9.3)	11.3(8.4)	−0.03
BAI	7.9(8.3)	6.9(7.1)	0.7
WURS ADHD score	31.1(22.1)	41.5(23.7)	−2.7
% Alcohol dependent lifetime	43.5	58.1	3.2
% Cocaine dependent lifetime	51.2	60.8	1.4
% Opiate dependent lifetime	41.0	45.9	0.3
% Recurrent major depressive disorder	29.4	20.2	1.7
Replication sample	Women (*n* = 109)	Men (*n* = 111)	$t =$ or $x^2 =$
Age in yrs (SD)	40.5(8.0)	43.2(8.8)	1.9
% Alcohol dependent lifetime	58.7	81.1	12.05[*]
% Cocaine dependent lifetime	82.5	81.9	1.9
% Opiate dependent lifetime	79.8	54.0	15.3[*]
% Nicotine dependent	75.2	72.1	0.1

[*]
$p < 0.05$.