Psychiatry Research 220 (2014) 513–518

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

COMT met allele differentially predicts risk versus severity of aberrant eating in a large community sample

Shannon D. Donofry [a,*], Kathryn A. Roecklein [a,b], Jennifer E. Wildes [c], Megan A. Miller [a], Janine D. Flory [d], Stephen B. Manuck [a]

[a] Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA
[b] Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA, USA
[c] Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[d] Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

ARTICLE INFO

Article history:
Received 13 June 2014
Received in revised form
25 July 2014
Accepted 20 August 2014
Available online 27 August 2014

Keywords:
Catechol-O-methyltransferase gene
Prefrontal cortex
Dopamine
Aberrant eating
Eating disorders
Bulimia

ABSTRACT

Prefrontal dopamine (DA) transmission participates in the reinforcement of reward-driven behaviors like eating. Because catechol-O-methyltransferase (COMT) degrades DA and is expressed in the prefrontal cortex, variation in the *COMT* gene may modulate eating behavior. Previous studies have shown that the met allele of the *COMT* val158met single nucleotide polymorphism (SNP) is associated with Bulimia Nervosa (BN). The specific aim of this study was to test whether the met allele increased risk for, and severity of, eating disorder symptomatology in community volunteers. Caucasian adults ($N=1003$; 51.2% female) from the University of Pittsburgh Adult Health and Behavior Project (AHAB) were genotyped and completed the Eating Disorders Inventory (EDI). Logistic and Poisson regression analyses assessed genotype-dependent presence and severity of eating disorder symptomatology. The met allele was significantly associated with the presence of symptoms on the Bulimia subscale and the severity of Body Dissatisfaction scores. All EDI subscales significantly predicted BMI. To our knowledge, these are the first data indicating that the *COMT* met allele increases risk for some symptoms of disordered eating, while increasing severity of others, in a community sample. These novel findings may have important implications for understanding the etiology of heterogeneous disordered eating phenotypes.

1. Introduction

Binge eating is a feature of several eating disorders, including Binge Eating Disorder (BED), Bulimia Nervosa (BN), and Anorexia Nervosa (AN) Binge-Eating/Purging Type, and affects as much as 5% of the general population (Arcelus et al., 2014; Hilbert et al., 2012; Micali et al., 2013; Mitchison et al., 2012). Defined as periods of excessive eating coupled with a subjective feeling of loss of control, binge eating is associated with clinically significant distress and disability (Striegel-Moore et al., 2001; Tanofsky-Kraff and Yanovski, 2004; Vannucci et al., 2013). Individuals who report loss of control over eating demonstrate greater psychological comorbidity and weight gain compared to those who overeat without experiencing loss of control (Tanofsky-Kraff and Yanovski, 2004), even among individuals without an eating disorder (Vannucci et al., 2013). Moreover, individuals who binge eat are more likely to be overweight or obese than those who do not binge eat (Striegel-Moore et al., 2001; Wilfley et al., 2000). Prospective longitudinal research has demonstrated that aberrant eating is associated with more frequent weight-related cognitive distortions, weight gain, and weight-related disease (Tanofsky-Kraff and Yanovski, 2004). Collectively, these findings suggest that many of the mental and physical health consequences associated with eating disorders also are present in subclinical aberrant eating, highlighting the importance of exploring etiological mechanisms influencing aberrant eating among individuals without a diagnosable eating disorder.

Growing evidence suggests that dopaminergic signaling may promote and maintain aberrant eating behavior (Blumenthal and Gold, 2010; Stice and Burger, 2012). In rat models of binge eating, surges in extracellular dopamine (DA) and altered DA receptor binding within the mesolimbic dopaminergic system (MDS) following a meal are evident in rats that have developed binge-like food intake patterns (Rada et al., 2005). Further, binge eating induced changes in DA signaling have been associated with enhanced responsivity to cues of impending food reward, particularly following a period of dietary restriction (Avena, 2007). This suggests that motivation to consume palatable foods is greater

* Corresponding author. Tel.: +1 412 624 4315; fax: +1 412 624 4428.
E-mail address: sdd14@pitt.edu (S.D. Donofry).

http://dx.doi.org/10.1016/j.psychres.2014.08.037
0165-1781/

under conditions of restricted access to food (Avena et al., 2005). Dietary restraint is considered an important predictor of aberrant eating (Fairburn et al., 2003), and mediates the effect of drive for thinness and body dissatisfaction on subsequent episodes of aberrant eating (Stice et al., 1998; Wilfley et al., 2000). Therefore, changes in DA signaling enhance motivation to eat following dietary restraint, and may account for the relationship between affect and weight-related cognitive distortions in aberrant eating.

The catechol-O-methyltransferase (COMT) enzyme plays an important role in terminating the action of DA following release from presynaptic terminals (Chen et al., 2004). COMT expression is most abundant in the prefrontal cortex (PFC; Dreher et al., 2009), a region strongly innervated by MDS structures that participates in response inhibition and reward-related contingency learning (Ridderinkhof et al., 2004). Individuals who associate food more strongly with the experience of pleasure may be at greater risk for aberrant eating, and the strength of this association appears to be strongly dependent on DA processing (Mathes et al., 2009; Ridderinkhof et al., 2004). DA levels are significantly higher in *COMT* knockout mice relative to wild-type controls (Gogos et al., 1998), suggesting that COMT may contribute to eating behavior through its effects on DA levels. Therefore, sequence variations in the *COMT* gene may predict individual differences in aberrant eating.

In humans, a functional single nucleotide polymorphism (SNP) that codes for an amino acid substitution at codon 158 of the *COMT* gene is associated with increased risk for eating disorders (val158-met; Frieling et al., 2006; Mikołajczyk et al., 2006). Enzymatic activity in individuals homozygous for the methionine (met) allele is reduced by 25–75% compared to valine (val) carriers (Chen et al., 2004; Lachman et al., 1996). Lower enzymatic activity may produce elevated DA levels, enhancing DA mediated sensitivity to reward cues (Dreher et al., 2009). It is expected that carriers of the low activity met allele would be more responsive to food cues (Dreher et al., 2009), thus increasing their risk for aberrant eating. Consistent with this hypothesis, the met allele has been associated with greater activation in the ventral striatum during anticipation of food reward, and in the orbitofrontal region of the PFC following delivery of a reward (Dreher et al., 2009). Importantly, the orbitofrontal region is thought to be involved both in the encoding of stimulus value and the regulation of food intake (Kringelbach, 2005). Met allele carriers with a diagnosed eating disorder have also been shown to score higher on self-report bulimia scales relative to val homozygotes (Frieling et al., 2006). In addition, there is evidence to suggest that the met allele is preferentially transmitted to female probands with BN (Yilmaz et al., 2011). These findings indicate that variation in *COMT* could influence aberrant eating.

As of yet, it is unknown whether the *COMT* val/met polymorphism is related to aberrant eating among individuals who exhibit normative or sub-clinical aberrant eating. Although the candidate gene approach to the study of genotype–phenotype relationships has some disadvantages (e.g. difficulty with replication), the power to detect such relationships is far greater for the candidate gene approach relative to the genome wide association approach (Amos et al., 2011). Further, many of the disadvantages of the candidate gene approach can be overcome by the use of large samples ($N > 200$) and choosing polymorphisms with known biological significance (Amos et al., 2011; Tabor et al., 2002). The *COMT* val/met SNP has well documented functional effects (Amos et al. 2011; Chen et al., 2004; Dreher et al., 2009), and has been linked to variation in several processes known to depend on prefrontal signaling (Mier et al., 2009), making it an excellent candidate for study in the context of aberrant eating. Therefore, the specific aim of the present study was to determine whether the *COMT* met allele increases risk for and severity of aberrant eating among a large sample of midlife community volunteers. It was hypothesized that met allele carriers will be more likely to exhibit aberrant eating, and have a higher body mass index (BMI).

2. Methods

2.1. Participants

Participants included 1295 medically healthy adults from the Adult Health and Behavior Project (AHAB), an extensive registry of behavioral and biological measures collected from a mid-life community sample recruited in Western Pennsylvania between 2001 and 2005 (Erickson et al., 2013; Manuck et al., 2010). Exclusion criteria included a clinical history of neurologic illness, cardiovascular disease, cancer treatment within the previous year, schizophrenia, or other psychoses. Volunteers were also excluded if they reported current use of insulin, glucocorticoid, antiarrhythmic, psychotropic, or prescription weight-loss medications. Data collection occurred over the course of several laboratory visits, and informed consent was obtained in accordance with the guidelines of the University of Pittsburgh Institutional Review Board. To avoid confounding by population heterogeneity, unknown extent and variability of European genetic admixture among African Americans, and race/ethnicity differences in *COMT* val158met allele frequencies (Palmatier et al., 1999), study analyses were limited to the 1081 AHAB participants of European American ancestry. Of these individuals, those who were not successfully genotyped ($n=64$; 5.9%), who met criteria for an eating disorder at the time of participation ($n=1$, BN), or who were missing data for any of the EDI scales ($n=13$) were excluded, yielding a final sample size of 1003.

2.2. Measures

2.2.1. Eating disorders inventory (EDI)

Participants completed the Drive for Thinness, Bulimia, and Body Dissatisfaction subscales of the EDI (Garner et al., 1983). The EDI and its subscales have been shown to possess adequate internal consistency (Cronbach's α ranging from 0.82 to 0.90), construct validity, and discriminant validity (Espelage et al., 2003; Garner et al., 1983). Further, the EDI has been shown to be useful for identifying at-risk individuals in healthy samples who display subthreshold symptoms of either AN or BN (Engelsen and Laberg, 2001; Klemchuk et al., 1990; Shoemaker et al., 1994). Respondents indicate on a 6-point scale the extent to which a statement applies to their eating-related thoughts or behavior, ranging from "never" to "always." The present study utilized the full 0–6 scale with untransformed scores for all analyses.

2.2.2. Structured clinical interview for DSM-IV-TR disorders (SCID) (First et al., 1996)

Participants were interviewed using the SCID for lifetime and current history of DSM-IV Axis I disorders by masters or doctoral level clinicians, and consensus diagnoses were determined by a licensed clinical psychologist (JDF).

2.2.3. BMI

Height and weight were measured, and used to calculate BMI ((weight[lbs]/height[in^2]) × 703).

2.3. Genotyping

DNA was isolated from white blood cells using the PureGene kit (Gentra Systems, Minneapolis, MN, USA). The genomic region of interest was amplified using polymerase chain reaction. The *COMT* val/met SNP was genotyped using florescence polarization (Chen et al., 1999). Consistent with previous studies (Frieling et al., 2006), the met/met genotype was coded as 1, the val/met genotype was coded 0.5, and the val/val genotype was coded 0.

2.4. Analytic plan

Preliminary analyses indicated that scores on the EDI subscales were positively skewed and zero-inflated, and were thus in violation of the assumptions of Ordinary Least Squares (OLS) regression. Violation of these assumptions can lead to biased estimates of regression coefficients, limiting interpretability of results (Cohen et al., 2003). An alternative to OLS, the two-process hurdle model, accounts for positive skew by assuming a logistic regression model for zero vs. non-zero responses and a Poisson distribution for the non-zero responses (Atkins and Gallop, 2007; McDowell, 2003). Regression coefficients were separately estimated for comparisons of zero responses to any responses and for comparisons among all non-zero responses (i.e. severity of symptoms among those who endorse them; McDowell, 2003). As such, the hurdle model provides a method for determining whether the factors that contribute to the occurrence of symptoms differ from those that contribute to the severity of symptoms, which may help elucidate the processes underlying heterogeneity in symptom presentation among individuals with aberrant eating.