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Consideration of the *BDNF* Gene in relation to two phenotypes: Hoarding and Obesity

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Abstract

The gene coding for the brain derived neurotrophic factor (*BDNF*) has emerged as an interesting candidate for multiple brain and brain disorder-related phenomena. The primary aim of the present investigation was to consider the relationship between the *BDNF* Val66Met variant and two phenotypes: compulsive hoarding as a symptom dimension of obsessive compulsive disorder (OCD), and body mass index (BMI). We examined the *BDNF* gene in a large (N=301) clinical sample of probands with OCD. Participants were classified as hoarding or non-hoarding using a strict, multi-measure grouping approach. Results revealed that the Val/Val genotype was linked with hoarding classification and more severe hoarding behaviors, as well as greater BMI levels. Hoarding status was also associated with greater BMI scores, with individuals in the hoarding group being far more likely to be classified as obese compared to the non-hoarding group. Our findings may provide a distinct avenue through which hoarding and BMI could be linked. These findings are suggestive of a complex gene, body weight, and psychopathology relationship wherein a primitive, survival “thrifty gene” strategy may be conserved and represented in a subgroup of humans manifesting severe hoarding symptoms.

Keywords

brain derived neurotrophic factor gene; Val66Met SNP; hoarding; OCD; body mass index

INTRODUCTION

Across recent animal and human genetic investigations, the brain derived neurotrophic factor (BDNF) has emerged as an interesting candidate for multiple pathologies (Bath & Lee, 2006; Duman & Monteggia, 2006). BDNF is a member of the neurotrophin family that influences neuronal transmission and plasticity, and plays an important role in the synaptic development and survival of several neuronal systems, including glutamatergic (Falkenberg, Lindefors, Camilli, Metsis, & Ungerstedt, 1996), dopaminergic (Guillin et al., 2001) and serotonergic systems (Djalali et al., 2005). Given the influence of BDNF on neuronal

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functioning, variants in the *BDNF* gene have been evaluated in relation to a number of disease-associated phenotypes. In particular, a non-synonymous single nucleotide polymorphism (SNP; rs6265), which results in a valine (Val) to methionine (Met) substitution at codon 66 in the 5' pro-region of the human *BDNF* protein (Val66Met), has been investigated as the only known functional variant.

The Val66Met variant leads to changes in BDNF protein distribution in the central nervous system, along with alterations in hippocampal size and function (Govindarajan et al., 2006; Monteggia et al., 2004). Studies with gene-targeted murine models have demonstrated that *Bdnf* variation is linked with memory impairment, greater avoidance, greater anxiety, aggression, and obesity (Chen et al., 2006; Kernie, Liebl, & Parada, 2000; Lyons et al., 1999; Monteggia, et al., 2004; Ren-Patterson et al., 2006; Rios et al., 2001). Parallel findings have emerged from human investigations. For example, the Val66Met SNP has been associated with hippocampal volume variations, altered memory performance (Egan et al., 2003), and weight regulation (Gray et al., 2006; Gunstad et al., 2006; Shugart et al., 2009). Additional investigations have found that the Val allele is associated with the *Neuroticism* personality variable, and thus may be relevant to the broad construct of anxiety (Lang et al., 2005; Sen et al., 2003). Considering specific psychiatric conditions, the Val66Met *BDNF* SNP has been associated with multiple neuropsychiatric disorders, including eating disorders (Ribases et al., 2003; Ribases et al., 2004) and obsessive compulsive disorder (OCD) (Hall, Dhillia, Charalambous, Gogos, & Karayiorgou, 2003).

The primary aim of the present investigation was to examine the *BDNF* Val66Met variant in relationship to two phenotypes: compulsive hoarding within the context of a larger OCD sample, and body mass index (BMI). OCD has been identified as a global, public health concern (Lopez & Murray, 1998), with a lifetime prevalence of approximately 2–3% (Angst et al., 2004). The symptoms of OCD are broadly conceptualized as distressing and recurrent intrusive thoughts and compulsive behaviors, though recent reports have highlighted the high degree of heterogeneity in the presentation (Mataix-Cols, Rosario-Campos, & Leckman, 2005). One symptom type that has emerged as a related, yet potentially separate phenomenon from OCD, is hoarding. Hoarding is defined as the acquisition of and failure to discard possessions, which results in debilitating clutter and impairment (Frost & Hartl, 1996). Research on this syndrome has identified hoarding as the most familial symptom type among OCD sibling pairs (Hasler et al., 2007), and has also highlighted certain phenomenological elements that set it apart from other OCD symptoms (Pertusa et al., 2008). Efforts are under-way to clarify the diagnostic status of hoarding, including its relationship to OCD (Mataix-Cols et al., 2010; Pertusa et al., 2010). Until this question is resolved, there is a growing consensus that etiological and phenomenological investigations should take hoarding and other possible OCD sub-phenotypes into account to reduce sample heterogeneity and clarify research findings.

There are several lines of support for jointly considering hoarding, BMI, and *BDNF*. The regulation of energy expenditures and eating behaviors has been linked with *BDNF* in animal research (Lebrun, Bariohay, Moyse, & Jean, 2006b; Xu et al., 2003), as well as human investigations that found associations with obesity and eating disorders (Monteleone et al., 2005; Ribases et al., 2005). Energy expenditures/eating behaviors might also be dysregulated in relation to hoarding, as suggested by a recent investigation that found individuals with hoarding had significantly greater BMI levels (obese range) than non-hoarding family-members (Tolin, Frost, Steketee, Gray, & Fitch, 2008). From an evolutionary perspective, animals have developed two main strategies for managing energy demands prior to and during times of diminished food availability and other stresses: (1) gaining weight by increasing internal fat storage and (2) hoarding actual food stores (de Kort & Clayton, 2006; Francis, 2005; Healy, de Kort, & Clayton, 2005; Prentice, 2005). In

addition, research in mice and other rodents has found a correlation between hoarding and body weight in the context of stressful environments (Brodin, 2007). If we consider clinical hoarding as an exaggerated or dysregulated form of an adaptive evolutionary behavior (Leckman & Mayes, 1998), then it may be hypothesized that individuals with hoarding could be at risk for enhanced internal fat production and storage mechanisms that contribute to elevations in BMI. In addition, it may also be hypothesized that a common genetic basis links these two phenotypes.

In addition to this evolutionary-based hypothesis, a second line of evidence focused on the role of emotion regulation supports our aim of considering hoarding, BMI, and *BDNF* together. Both hoarding and dysregulated eating have been linked with difficulties in emotion regulation. Research in children has found that loss of control eating is associated with dysfunctional emotion regulation strategies (Czaja, Rief, & Hilbert, 2009), and emotion regulation difficulties in toddlers is a significant predictor of pediatric obesity (Graziano, Calkins, & Keane, 2010). In addition to the large literature on emotional eating in adults and the relationship between self-regulation and obesity/binge eating disorder (Davis, Patte, Curtis, & Reid, 2010; Newman, O'Connor, & Conner, 2007; Polivy & Herman, 2002), a series of three experimental studies by Evers and colleagues (Evers, Marijn Stok, & de Ridder, 2010) found that emotional self-regulatory difficulties were linked with greater food consumption, particularly of comfort-foods. Although less extensively researched, there is also support for emotion regulation difficulties and greater emotional reactivity associated with hoarding behaviors, as evidenced by lower levels of distress tolerance and greater avoidance behaviors (Steketee & Frost, 2003; Timpano, Buckner, Richey, Murphy, & Schmidt, 2009). Turning to the *BDNF* literature, the Val/Val genotype has been associated with greater HPA-axis reactivity (Alexander et al., 2010) and interacts with the serotonin transporter polymorphism (5-HTTLPR) to influence cognitive reactivity and dysfunctional thinking (Wells, Beevers, & McGeary, 2010).

Although there have been investigations to examine the association between BMI and the Val66Met *BDNF* polymorphism (Gunstad, et al., 2006; Shugart, et al., 2009), as well one study on the BMI-hoarding relationship (Tolin, et al., 2008), the link between hoarding and *BDNF* has not been adequately considered. Following an initial report of a strong association between *BDNF* and OCD (Hall, et al., 2003), a handful of studies have considered the symptom dimensions of OCD (Katerberg et al., 2009; Wendland, Kruse, Cromer, & Murphy, 2007). Unfortunately, none of these investigations adequately assessed hoarding, relying instead on measures (e.g., YBOCS) that have been found to be insufficient in fully capturing the hoarding phenomenon (Cromer, Schmidt, & Murphy, 2007).

The primary aim of this investigation was to examine the relationships between the *BDNF* Val66Met variant, compulsive hoarding, and BMI. In contrast to past investigations (Alonso et al., 2008; Wendland, et al., 2007), we sought to carefully capture the hoarding construct by relying on two complementary, multi-method assessments: a dichotomous classification and a continuous measure of severity. Based on the extant literature, we hypothesized that the homozygote Val/Val genotype would be associated with both hoarding and greater BMI levels, and that hoarding would be associated with greater BMI. In addition to examining the primary relationships between *BDNF* and the two phenotypes, we also set out to consider the relationship between genotype and a combination phenotype of hoarding and obesity, within a more exploratory vein. We hypothesized that those individuals with the combination phenotype would have the greatest proportion of the Val/Val genotype.

METHODS

Participants

This study recruited 301 OCD probands from an ongoing outpatient OCD program at the National Institute of Mental Health. Participants were recruited in the general context of an OCD study through referrals, websites, conferences and newspaper advertisements, and the NIMH website. Advertisements specifically mentioned interest in hoarding behaviors. Study data were collected from consecutive intakes across a 10 year time-span. Inclusion criteria for participation consisted of being at least 18 years of age and having a primary OCD diagnosis based on the Structured Clinical Interview for DSM-IV (SCID; First, 2001). Exclusion criteria included active schizophrenia or psychosis, or severe mental retardation that did not permit an evaluation. All procedures were in accordance with American Psychological Association standard ethical guidelines, and this study was approved by the Institutional Review Board prior to data collection.

The sample consisted of 122 (40.5%) men and 179 (59.5%) women. Participants were generally well educated, with 64.0% reporting a college degree and 20.7% achieving a graduate degree. The sample was primarily Caucasian (88.4%), but included small groups of Hispanic (2.4%), Asian (2.2%), African American (2.4%), and other (4.6%) participants. The mean age of the sample was 39.1 (SD=13.4); please see Table 1 for further sample characteristics.

Measures

Structured Clinical Interview for DSM-IV-TR Axis I Disorders Patient Edition (SCID-P)—The SCID-P (First, 2001) was used to diagnose major DSM-IV Axis I disorders, including OCD. Interviews were conducted by trained and clinically experienced interviewers (RN and masters-level psychologist). To ensure reliability, a blind diagnostic procedure was used in which two independent reviewers evaluated each SCID. Any diagnostic discrepancies were discussed with the PI (D. Murphy). SCID diagnoses demonstrated excellent reliability with kappas ranging from .86–.93 for the various comorbid disorders (e.g., major depression, eating disorders); primary OCD diagnoses were highly reliable with a kappa value of .96 and 98% agreement.

Hoarding Classification—This study used a strict definition of hoarding that combined both the Yale-Brown Obsessive Compulsive Scale (YBOCS) symptom checklist and an interview-based clinical assessment of hoarding. The YBOCS (Goodman et al., 1989a; Goodman et al., 1989b) is a reliable assessment of OCD symptom severity, and includes a symptom checklist for a range of OCD symptoms, including two items on saving and difficulty discarding. In the current investigation the YBOCS-SC was administered as a self-report measure (Steketee, Frost, & Bogart). Patients who endorsed both of the YBOCS-SC hoarding questions and confirmed hoarding symptoms during the clinical interview were classified as hoarders. Patients who did not report hoarding on the YBOCS-SC or who did not describe hoarding symptoms during the interview were placed in the non-hoarding group. This method is described in detail in a previous report by our group (Wheaton, Timpano, Lasalle-Ricci, & Murphy, 2008), and represents a conservative approach to identifying those individuals with definite hoarding symptoms.

Saving Inventory-Revised (SIR)—The SIR is a well-validated 23-item questionnaire designed to measure hoarding-related behaviors and symptom severity. Participants are required to answer items using a 5-point scale ranging from 0 (not at all) to 4 (almost all/complete). The measure includes three factor analytically derived subscales, including acquisition (e.g., “How distressed or uncomfortable would you feel if you could not acquire

something you wanted?”), clutter (e.g., “How much of your home does clutter prevent you from using?”), and difficulty discarding (e.g., “To what extent do you have difficulty throwing things away?”). The SIR has been found to have strong internal consistency (Coles, Frost, Heimberg, & Steketee, 2003), good test-retest reliability, and satisfactory convergent validity (Frost, Steketee, & Grisham, 2004).

Body Mass Index—The BMI, defined as body weight (kg)/height (m²), is the established standard for measuring body composition, and is highly correlated with body fat composition (Khosla & Lowe, 1967). Standard guidelines were used to define underweight (BMI<19), normal (BMI 19–24), overweight (BMI 25–29.9) and obese (BMI >30) groups (NIH, 1998). BMI was calculated from self-reported weight and height, in-line with other recent investigations (e.g., Keel & Heatherton). Although small biases have been reported in self-reported height and weight, studies have uniformly concluded that self-reports are reliable and valid (Bowman & Delucia, 1992; Imrhan, Imrhan, & Hart, 1996; Spencer, Appleby, Davey, & Key, 2002; Stunkard & Albaum, 1981).

Genotyping

The *BDNF* Val66Met polymorphism (dbSNP rs6265) was genotyped by a 5'-exonuclease assay (TaqMan SNP genotyping assay-on-demand; Applied Biosystems, Foster City, CA, USA) using oligonucleotide primers GCC CAA GGC AGG TTC AAG AG and AAC TTT CTG GTC CTC ATC CAA CAG as well as fluorescent probes VIC-ACT TTC GAA CAC gTG ATA G-MGB and FAM-CTT TCG AAC ACa TGA TAG-MGB for Val66 and Met66, respectively, as reported previously (Wendland, et al., 2007). In a total reaction volume of 8 μ L, 5–20 ng of genomic DNA were mixed with TaqMan Universal PCR master mix (Applied Biosystems) and genotyping assay to 1 $\times$ final concentrations. Thermocycling and fluorescence acquisition conditions were as recommended using an MJ Chromo4 continuous fluorescence detector (Bio-Rad, Hercules, CA, USA) connected to a PC running Opticon Monitor software version 3.1. Genotypes were scored by endpoint fluorescence analysis using global minimum baseline subtraction. The overall genotype completion exceeded 98%; no-template-controls and a randomly chosen subgroup of 15% samples run in duplicate consistently yielded expected results.

Using the Genetic Power Calculator (Purcell, Cherny, & Sham, 2003), we determined that our sample had 17% power at $p=.05$ (risk allele frequency=0.8; disease prevalence=0.25; genotypic relative risk Aa=2 and AA=2; marker allele frequency=0.2 at $D'=1$ with risk variant).

Statistical analyses

Genotype data were analyzed for Hardy-Weinberg equilibrium (HWE) using the Pearson and log likelihood ratio χ^2 as well as exact test with the de Finetti program (Cannings & Edwards, 1968). All other statistical analyses were carried out using the Software Package for Social Sciences (SPSS) version 14.0 for Windows. To examine possible population stratification, we conducted an ANOVA with phenotype/genotype as the dependent variable and strata (self-reported ethnicity) as the independent variable. Both logistic regression for dichotomous dependent variables and linear regression for continuous dependent variables were used for the remaining analyses, as appropriate. Primary analyses examined hoarding/obesity status, whereas secondary analyses considered the continuous variables. All tests were performed with a two-sided $p < 0.05$. Given missing data, the N varies somewhat for the secondary analyses with the two continuous variables (SIR $n=198$; BMI $n=254$).

RESULTS

The *BDNF* genotype frequency was 4% for Met/Met ($n=12$), 31.9% for Val/Met ($n=96$), and 64.1% for Val/Val ($n=193$). The frequency of alleles was 0.80 for Val and 0.20 for Met, in line with previous reports (Hall, et al., 2003; Lang, et al., 2005). The observed genotype distribution did not significantly deviate from Hardy-Weinberg equilibrium with any of the statistical tests utilized. We compared the Val/Val group to Met allele carriers in our analyses, in line with other reports (Lang, et al., 2005; Oroszi et al., 2006), and given the evidence that the Met allele may be functionally dominant (Chen, et al., 2006; Sen, et al., 2003). There was no effect of population strata on either phenotype or the genotype/allele distribution, and all ethnicity sub-samples were therefore considered jointly.

Sample descriptions are provided in Table 1. The hoarding group scored markedly higher on the SIR than the non-hoarding group ($t = -13.78, p < .001$). Of the sample, 4.3% ($n=11$) were in the *underweight* category, 43.3% ($n=110$) were in the *normal* category, 25.2% ($n=64$) were in the *overweight* category, and 27.2% ($n=69$) fell into the *obesity* category. Given that age is often correlated with weight/BMI levels, we examined age at BMI assessment and found no differences based on hoarding ($t = .44, p < .67$) or genotype ($t = .42, p < .68$) status. Age was therefore not included as a covariate in the following analyses.

BDNF and compulsive hoarding¹

Results demonstrated that those individuals with the Val/Val genotype were at a significantly greater risk than Met carriers (risk ratio: 1.8) of being classified in the hoarding group (Wald = 6.84, $p < .01$, OR = 2.2, 95% CI = 1.22 – 3.97). Allele-wise comparison revealed a significant difference (Wald = 4.07, $p < .04$ OR = 1.68, 95% CI = 1.02–2.78) in that the frequency for the Val allele was significantly higher among the hoarding group than in the non-hoarding group. Considering hoarding symptom severity, we found that the Val/Val genotype (mean SIR = 31.1, SD = 22.3) was significantly associated with greater hoarding symptom severity ($\beta = .15, t(198) = 2.12, p < .03$), compared to Met carriers (mean SIR = 24.3, SD = 19.5).

BDNF and BMI¹

With regard to a possible association between *BDNF* and BMI we found individuals with the Val/Val genotype were more likely to be classified as obese relative to Met carriers with a risk ratio of 1.8 (Wald = 6.91, $p < .01$, OR = 2.18, 95% CI = 1.24 – 4.40). Allele-wise comparison also revealed a significant difference (Wald = 6.53, $p < .01$ OR=2.05, 95% CI = 1.18–3.55), in that the Val allele was associated with obesity to a greater degree than the Met allele. Secondary analyses found that the Val/Val genotype (mean BMI=27.5, SD = 7.10) was associated with greater BMI levels ($\beta = .15, t(254) = 2.34, p < .02$), compared to Met carriers (mean BMI = 25.6, SD = 5.6)

Compulsive hoarding & BMI¹

We found that hoarding group status was significantly associated with higher BMI (Wald = 8.44, $p < .01$, OR = 1.1, 95% CI = 1.02 – 1.11). Similarly, greater SIR hoarding severity scores were linked with greater BMI levels ($\beta = .32, t(190) = 4.45, p < .001$), explaining 9.7% of the variance. We next considered the weight categories, by comparing the SIR hoarding symptom severity scores for each weight group. The overall ANOVA was significant ($F = 11.42, p < .001$), though post-hoc comparisons revealed that the underweight,

¹We conducted a series of supplemental analyses using an alternative grouping strategy. Specifically, we categorized the sample using an established clinical cut-off for the SIR (Frost and colleagues have identified a score of 40 or above as being typical in clinical hoarding samples). We found that this approach also provided the same pattern of findings.

normal and overweight groups did not significantly differ from one another. Those individuals in the obesity category evidenced markedly greater hoarding severity, and we therefore compared the non-hoarding and hoarding groups on dichotomous *obesity* classification (obese versus non-obese groups). Results revealed that individuals in the hoarding group were over two times more likely to be classified as obese compared to non-hoarders (Wald = 14.22, $p < .001$, OR = 3.29, 95% CI = 1.77 – 6.12).

Relationship between BDNF and a combination phenotype

The sample was divided into four groups based on each participant's hoarding and obesity status: hoarding-obese; hoarding-only; obese-only; neither. Frequencies of the *BDNF* variants for each of these groups are presented in Table 2. Chi-square analysis revealed an overall significant difference ($\chi^2 = 7.83$ (df=3), $p < .05$). More fine-grained comparisons demonstrated that the hoarding-obese group was significantly different from the neither group ($\chi^2 = 5.71$ (df=1), $p < .05$) in the proportion of Val/Val variants, but not significantly different from either the hoarding-only or the obese-only groups. The hoarding-only, obese-only, and neither groups did not significantly differ from one another.

DISCUSSION

The present report is the first to examine associations between *BDNF*, hoarding, and BMI in a large sample of individuals with OCD. Results revealed that the Val/Val genotype was associated with the hoarding group and the highest levels of hoarding symptom severity, as well as higher BMI levels and obesity classification. Our results regarding the relationship between *BDNF* and BMI levels fit within a growing literature examining the association between the *BDNF* Val66Met variants, body mass index, and eating disorders (Ribases, et al., 2004; Shugart, et al., 2009). *BDNF* and its receptor, TrkB, have known roles in body weight regulation, via effects on food intake and metabolic rate, with *BDNF* alterations in rodents leading to hyperphagia and obesity (Ren-Patterson et al., 2005; Wang, Bomberg, Billington, Levine, & Kotz, 2007).

We found that within this OCD sample *BDNF* was associated with hoarding symptoms, which sheds additional light on the literature examining the OCD-*BDNF* link. Following the seminal report by Hall and colleagues (2003)—which considered several *BDNF* SNPs with both single locus and multi-SNP haplotype tests and found a strong role of Val66Met in OCD—a series of investigations have examined the role of *BDNF* in OCD. Additional support for the role of *BDNF* has emerged from findings related to the *BDNF* receptor gene and *BDNF* secretion in OCD samples (e.g., Alonso, et al., 2008). Despite growing evidence that the marked heterogeneity associated with OCD might impact etiological investigations (Mataix-Cols, et al., 2005), not all of these investigations considered potentially more homogeneous sub-groups. More recent studies have analyzed factors that may separate OCD into more meaningful and uniform sub-phenotypes, including age of onset and the symptom dimensions (Katerberg, et al., 2009); however, the characterizations of these sub-groups might not always lead to the identification of differences. This is particularly poignant in consideration of hoarding. The largest study to date of sibling pairs with OCD found that individuals with marked hoarding showed linkage to a different chromosomal region than individuals without definite hoarding symptoms (Samuels et al., 2007). This finding, in conjunction with our results, brain imaging evidence, and symptomatic and gender differences in hoarding compared to other forms of OCD, provide further credence to the growing notion of hoarding as a separable and distinct phenomenon (Pertusa, et al., 2008; Saxena, 2008).

The association between hoarding and BMI reported in this sample supports an earlier report of a hoarding-obesity association (Tolin, et al., 2008). Within the animal literature, hoarding

behaviors have been associated with food intake dysregulation (Deacon, 2006). Long-term selection [45 generations] for body weight in chickens led to “compulsive feeding” and a nine-fold difference in weight accompanied by *Bdnf* expression differences identified by array analysis (Ka et al., 2009). The set-point for hoarding food in response to food deprivation is closely regulated by elements of the HPA axis, and multiple studies have demonstrated high correlations between body weight, different stresses, and hoarding (Brodin, 2007; Manosevitz, 1965). Once again, there are only limited studies to date that have examined these relationships in humans, but it should be noted that greater levels of traumatic life stress have been linked with hoarding, compared to non-hoarding OCD (Cromer, et al., 2007).

Our findings should be considered in light of several limitations. While our investigation represents the second largest BDNF-OCD association study, a primary limitation is our sample size. This, arguably, had the greatest impact on our combination phenotype analyses, where cell-sizes among the four groups varied dramatically and most likely contributed to the lack of significant differences between the hoarding-obese group and the hoarding-only/obese-only groups. Conclusions emerging from these analyses should therefore be tempered accordingly. A second limitation is that we only focused on a single polymorphism, rather than multiple variants within the BDNF gene. Our reliance on self-reported weight and height constitutes another limitation of the present study. Previous investigations have demonstrated reporting bias in height and weight; however, such errors are typically small (Spencer, et al., 2002) and no association has been found between misreporting height/weight and psychological variables (Yannakoulia, Panagiotakos, Pitsavos, & Stefanadis, 2006). A similar limitation was our assessment of ethnicity by self-report. Although we did not find any difference in the phenotype and genotype/allele distribution by population strata, we cannot rule-out the possibility that population stratification could influence the results. Future research should consider Ancestral Information Markers as an alternative to self-report on ethnicity. A final limitation is that we considered hoarding solely within a larger OCD sample, which may not capture the full range of the hoarding phenomenon (Pertusa, et al., 2008). We have tried to address this concern with our recruitment methods, which focused on hoarding, and the use of two measures to characterize hoarding symptoms; however, replication in hoarding samples not recruited within the context of OCD will be necessary.

Our findings point to a number of avenues for future research. Considering the three-fold association we identified (i.e., *BDNF*-hoarding, *BDNF*-BMI, and hoarding-BMI) and our exploratory analyses with the combination phenotype, it may be of interest to examine mechanisms through which hoarding, BMI, and *BDNF* are related. Emotion regulation difficulties, which have been associated with both phenotypes and the *BDNF* SNP (Evers, et al., 2010; Timpano, et al., 2009; Wells, et al., 2010), may be one such mechanism, or endophenotype, that accounts for the associations noted. This is particularly interesting in consideration of the animal literature, where *Sert*-deficient mice and those interbred with *Bdnf*-deficient mice display greater stress responses, anxiety, and obesity (Ren-Patterson, et al., 2005). Studies have further revealed that BDNF administration reduces feeding behaviors and blood glucose in obese and diabetic rodents, apparently via a central, probably hypothalamic mechanism (Lebrun, Barriohay, Moyse, & Jean, 2006a). This same mechanism may play a role in humans, perhaps via alterations in activity-dependent secretion of BDNF (Egan, et al., 2003).

Future investigations on complex phenomenon, such as hoarding, BMI, and a potential combination phenotype, may want to consider the intricacies of gene $\times$ gene $\times$ environment interactions (Lander & Schork, 1994; Murphy et al., 2003). Given that *BDNF* has been found to interact with other genes or gene systems, such as the serotonergic system

(Kaufman et al., 2006; Wells, et al., 2010), which in turn have been associated with OCD and obesity (Fuemmeler et al., 2008; Wendland et al., 2008), examining polygenetic relationships may be a fruitful avenue for further clarifying the relationships between *BDNF*, hoarding, and BMI. Future investigations of these epistatic interactions may also warrant consideration of factors such as environmental modifiers and sex.

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Table 1

Association between BDNF, compulsive hoarding, and BMI.

(N)	Total Sample (301)	Hoarding Group (77)	Non-Hoarding Group (224)
<i>BDNF allele and genotype frequencies</i>			
Val/Val	193 (64%)	59 (77%)	134 (60%)
Val/Met	96 (32%)	14 (18%)	82 (37%)
Met/Met	12 (4%)	4 (5%)	8 (4%)
Met allele	120 (20%)	22 (14%)	98 (22%)
Val allele	132 (80%)	132 (86%)	350 (78%)
<i>Clinical correlates</i>			
Sex: female- <i>n</i>	179 (60%)	44 (57%)	135 (60%)
Age-at-assessment (SD)	39.1 (13.4)	38.6 (13.0)	39.2 (13.5)
Age-of-onset (SD)	14.2 (9.4)	12.8 (9.0)	14.7 (9.4)
YBOCS total score (SD)	22.8 (7.8)	24.3 (6.5)	22.2 (8.2)
SIR total score (SD)	28.6 (21.6)	47.1 (16.5)	20.6 (16.8)
BMI (SD)	26.8 (6.7)	28.8 (8.2)	26.1 (5.9)
hoarding group status- <i>n</i>	77 (26%)		
obesity group status- <i>n</i>	69 (27%)	29 (45%)	40 (21%)

Note. Age-at-assessment = mean age at assessment; Age-of-onset = mean age at onset of OCD symptoms; BMI = mean body mass index score; hoarding status = percentage of sample classified in hoarding group; obesity status = percentage of sample classified in obesity group; SIR = mean Saving Inventory Revised total score; YBOCS = mean Yale Brown Obsessive Compulsive Scale total score.

Table 2

Association between BDNF and a combination phenotype of hoarding and obesity.

<i>Groups</i>	<i>BDNF Val66Met Variants</i>			
	<i>Val/Val</i>		<i>Met carriers</i>	
	<i>frequency</i>	<i>%</i>	<i>frequency</i>	<i>%</i>
Hoarding-Obese	24	83%	5	17%
Hoarding-only	26	72%	10	28%
Obese-only	28	70%	12	30%
Neither	141	60%	94	40%

Note. Hoarding-Obese = individuals classified in the hoarding and obese categories; Hoarding-only = individuals classified in the hoarding category but not the obese group; Obese-only = individuals classified in the obese category but not the hoarding group; Neither = individuals not classified as either hoarding or obese.