The relationship between childhood abuse and dissociation. Is it influenced by catechol-O-methyltransferase (COMT) activity?

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Abstract

Dissociation is a failure of perceptual, memorial and emotional integration that is associated with a variety of psychiatric disorders. Dissociative processes are usually attributed to the sequelae of childhood trauma although there are data to suggest that genetic influences are also important. Bipolar disorder (BD), a condition with a strong genetic basis, has also been associated with early psychological trauma. Since childhood trauma is a risk factor for both BD and dissociation, we tested for potential gene–childhood abuse interactions on dissociation in a pilot sample of BD probands and their affected and unaffected relatives (n=178). Dissociation was measured with the Dissociative Experiences Scale (DES II) and childhood maltreatment with the Childhood Trauma Questionnaire (CTQ). The BD and recurrent unipolar depression (MDE-R) groups showed higher levels of self-reported abuse and dissociation than their unaffected relatives. The low-activity Met allele of the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene was associated with lower levels of self-reported dissociation. Further, the functional catechol-O-methyltransferase (COMT) Val158Met polymorphism interacted significantly with total CTQ abuse scores to impact perceived dissociation. The Val/Val genotype was associated with increasing levels of dissociation in participants exposed to higher levels of childhood trauma. The opposite was observed in people with Met/Met genotypes who displayed decreased dissociation with increasing self-reported childhood trauma. The current findings support the involvement of the COMT Val158Met polymorphism in mediating the relationship between trauma and psychopathology.

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Key words: BDNF, bipolar disorder, childhood abuse, COMT, dissociation.

Introduction

Janet (1889) viewed psychopathology through the lens of dissociation; what he termed desaggregation mentale – the forced separation of elements that would normally aggregate together (Spiegel, 2006). In other words, dissociation is a disruption to the normally integrated functioning of perceptual, emotional and memorial systems. This results in the compartmentalization of thoughts, sensations and memories that are too overwhelming for the conscious mind to integrate. The process may be pathological because it leads to a distorted perception of reality, memory deficits, emotional numbing, feelings of disconnectedness with reality, and out-of-body experiences; perhaps explaining why it is associated with depression, anxiety, post-traumatic stress, somatoform and various personality disorders (APA, 1994).

An underlying genetic diathesis for dissociation may exist (Kihlstrom et al., 1994). A twin study of dissociative experiences yielded a heritability score of
48% (Jang et al., 1998). Similarly, post-traumatic stress disorder (PTSD), a condition characterized by salient dissociative features has been shown to have a significant genetic component with a heritability score of ~30% (Stein et al., 2002; True et al., 1993). Further, three personality traits positively correlated with dissociative experiences, openness to experience as defined by the five-factor model, self-transcendence as evinced by the Temperament and Character Inventory, and Absorption as measured by the Tellegen Absorption Scale (TAS) have heritability scores of 61% (Jang et al., 1996), 39% (Ando et al., 2002) and 26–44% (Finkel and McGue, 1997), respectively. Despite these data, however, no genetic association studies have been conducted with this phenotype.

Rather, the overwhelming majority of studies have focused on environmental antecedents of dissociative tendencies, notably childhood trauma. It has been fairly well established that exposure to childhood abuse facilitates the development of dissociative defence mechanisms (Draijer and Langeland, 1999; Simeon et al., 2001; Spiegel and Cardena, 1991; Waldinger et al., 1994; Zlotnick et al., 1994). Whereas dissociative defences may be adaptive at the time of abuse, they can also become automatically and unconsciously elicited by generic stressors, and this reflexive response has been hypothesized to increase the risk of psychiatric illness (Putnam, 1993).

Kiesel and Lyons (2001) carried out an empirical test of this hypothesis in 114 abused children. Using analysis of covariance, the authors found that (self-reported) dissociation mediated the relationship between sexual abuse and psychopathology: the effects of abuse on risk-taking behaviour were no longer statistically significant after controlling for dissociation.

Bipolar disorder (BD), often conceptualized a genetic disorder with high heritability values (Kendler et al., 1995; McGuffin et al., 2003), has also been associated with a history of childhood maltreatment (Hammersley et al., 2003; Read et al., 2005; Spauwen et al., 2006). It is therefore plausible that dissociative processes are equally salient in BD and bipolar spectrum illness; a possibility that to the best of our knowledge has not been adequately explored in the literature.

The first aim of this study was, therefore, to assess the extent of self-reported dissociation in a familial sample of patients with BD. Second, given the evidence that childhood trauma is a risk factor for both BD and dissociation, we used this BD sample to test whether particular genetic variants would be associated with dissociation, and further, to test whether these variants interact with childhood abuse to induce vulnerability to dissociation, and by implication, psychopathology.

Although the molecular genetic basis of dissociation per se is unknown, the COMT Val158Met polymorphism has been implicated in the development of a variety of traits that may be related to dissociation:

1. The gene has been associated with the personality trait, Absorption, which can be argued to predispose individuals to the development of dissociative reactions (Ott et al., 2005).
2. The gene has been associated with hypnotizability, a trait that may be a risk factor for PTSD and other dissociative conditions (Lichtenberg et al., 2000).
3. The gene has been implicated in the regulation of time perception, a trait that is disturbed during the dissociative process (Reuter et al., 2005).
4. Marijuana use appears to elicit dissociative reactions and psychotic behaviour in vulnerable individuals. A genetic variant in the COMT gene has been reported to contribute to this diathesis (Caspi et al., 2005; Henquet et al., 2006).
5. COMT has been shown to regulate the stress-induced activation of opioids which may in turn elicit dissociative symptoms (Zubieta et al., 2003).

Given these data we hypothesized that the COMT gene would interact with childhood trauma to impact dissociative tendencies. In addition to COMT, we carried out exploratory analyses with four other genes that have been previously associated with BD and/or involved in the modulation of the psychological impact of aversive environmental experiences (see Table 1).

Methodology

Sample

A total of 178 Caucasian individuals from 35 BD families participated in the study. Patients were originally recruited from psychiatric hospitals and clinics through their psychiatrists. Family members were recruited through the probands. During the recruitment phase, several subjects approached us directly and asked to participate in the study. A breakdown of the number of individuals per family and diagnosis is provided in Appendix A.

Families usually consisted of a proband and at least one first-degree relative with diagnosis of BD I or BD II. A small number of singletons were recruited because their family members later declined to take part in the study. Family size ranged from 1 to 51. All participants...
(mostly of Afrikaner and British ancestry) were interviewed with the SCID. The sample consisted of 31 individuals with a diagnosis of BD I, 16 with BD II, 38 with recurrent unipolar depression (MDE-R), 26 with a single lifetime episode of depression (MDE-S), and 17 individuals with another diagnosis. The 17 individuals in this group were diagnosed with alcoholism (6), BD not otherwise specified (3), generalized anxiety disorder (3), dysthymia (2), borderline personality disorder (1), delusional disorder (1) and cyclothymia (1). Fifty relatives were unaffected. The average age and educational level of the sample was 48.8 ± 15.4 and 15.2 ± 3.6 yr (including 3 yr of post-high school education), respectively. Males made up 77/178 (43%) of the sample. Approval from the University of Cape Town (UCT) Research Ethics Committee and written consent from the subjects was obtained.

Psychometric testing

The following psychometric tests were administered to the study participants:

The Dissociative Experiences Scale (DES II; Carlson and Putnam, 1993) was designed to measure dissociation in both normal and clinical populations (Bernstein and Putnam, 1986). Items were derived from clinical data, interviews, and discussions with ‘experts’ in dissociation, producing test–retest reliability and internal reliability scores of 0.84 and 0.90, respectively (Bernstein and Putnam, 1986). By 1996, the scale had been used in over 100 studies and formed the basis of a meta-analytical validation (van Ijzendoorn and Schuengel, 1996) which yielded mean reliability and convergent validity scores of 0.93 and 0.67, respectively. Van Ijzendoorn and Schuengel (1996) also found that DES differentiated well between controls, people with various types of non-dissociative psychopathology, and individuals with dissociative conditions such as dissociative identity disorder (DID) and PTSD.

To ensure the validity of our analyses, we transformed the DES scores to approximate normality. For ease of interpretation, we then converted them into a scale ranging from 0 to 10, with higher scores indicating a greater degree of dissociation.

Childhood abuse was measured with the self-report Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). In line with previous assertions that actual observations of child–parent interactions correlate well with self-reported recollections of punitive experiences (Prescott et al., 2000), CTQ scores were reported by Bernstein et al. (2003) to correlate significantly (r = 0.36–0.75) with therapist ratings of abuse. In fact, Dill et al. (1991) have argued that in some circumstances self-report instruments of childhood trauma are more likely to elicit truthful responses than clinical interviews.

The CTQ is composed of the following subscales: physical, sexual, and emotional abuse, and physical and emotional neglect. Each subscale score ranges from 5 to 25, with higher scores indicative of greater maltreatment. A total abuse score (ranging from 25 to 125) was calculated by summing the values obtained on the five subscales.

The Beck Depression Inventory (BDI; Beck and Steer, 1993), a reliable and valid measure of depression was used to detect mild (scores of 10–18), moderate (19–29) and severe depression (≥30). The Altman Self-Rating Mania Scale (ASRM; Altman et al., 1997), a reliable (r = 0.86–0.89) and valid (r = 0.718–0.766)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Putatively functional variant</th>
<th>Association</th>
<th>Reference</th>
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<tbody>
<tr>
<td>COMT</td>
<td>Val158Met</td>
<td>Associated with BD and modulation of response to environmental adversity</td>
<td>Hayden and Nurnberger (2006), Mandelli et al. (2006)</td>
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<tr>
<td>DRD4</td>
<td>48-bp VNTR</td>
<td>Associated with BD and impulsive personality traits</td>
<td>Benjamin et al. (1996), Lopez-Leon et al. (2005)</td>
</tr>
<tr>
<td>BDNF</td>
<td>Val66Met</td>
<td>Associated with BD and modulation of response to environmental adversity</td>
<td>Hayden and Nurnberger (2006), Kaufman et al. (2006), Savitz et al. (2007)</td>
</tr>
<tr>
<td>SERT</td>
<td>5-HTTLPR</td>
<td>Associated with anxiety. Modulates risk of developing depression after exposure to aversive experiences</td>
<td>Caspi et al. (2003), Kaufman et al. (2004), Lesch et al. (1996)</td>
</tr>
<tr>
<td>DAT</td>
<td>3'-VNTR</td>
<td>Associated with BD</td>
<td>Greenwood et al. (2001, 2006)</td>
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BDNF, Brain-derived neurotrophic factor; COMT, Catechol-O-methyltransferase; DAT, dopamine transporter; DRD4, dopamine 4 receptor; SERT, serotonin transporter.
instrument, was used to measure residual symptoms of hypomania in our sample. Scores of ≥6 are considered to be clinically significant (Altman et al., 1997).

The majority of affected individuals were tested in a euthymic state. Excluding the unaffected relatives, the mean BDI score was 9.06 (8.35) and the mean ASRM score was 2.75 (3.04). Most of the participants were tested individually at their homes. A small minority completed the questionnaires in a counselling room in the Division of Human Genetics at UCT.

**Genotyping**

Standard methods were used to perform PCR for the five functional variants (see Table 1 and Appendix B). Variable number tandem repeats (VNTR) and insertion/deletion polymorphisms were scored on the ABI 3100 sequencer (Applied Biosystems, Foster City, CA, USA) while single nucleotide polymorphisms (SNPs) were genotyped using restriction digests and scored on agarose or polyacrylamide gels. Primer sequences were obtained from the literature or designed online. For the 48-bp VNTR of the DRD4 gene we collapsed the multi-allelic polymorphisms into two categories, short (2R, 3R, 4R, 5R) and long (6R, 7R, 8R, 10R) alleles after Benjamin et al. (1996) and Ebstein et al. (1998). In the case of DAT1 we compared the 9R allele to the other variants (two rare variants found in two subjects were included in the same category as the 10R allele).

**Statistical analyses**

We recruited pedigrees with related individuals and therefore only the unrelated individuals in our sample were tested at each marker to produce an estimate of Hardy–Weinberg equilibrium (HWE) using the PEDSTATS program (Wiggington and Abecasis, 2005).

Mixed-effects models were used to determine whether there was a significant relationship between childhood abuse and bipolar-spectrum illness in our sample after controlling for age, gender, and self-reported depression and mania (fixed effects). Similarly, we tested whether DES scores differed across diagnostic group after controlling for the previously mentioned variables.

Mixed-effects models (multilevel regression analysis models) were used to test whether the polymorphisms in question and total abuse scores influenced perceived dissociation after controlling for age, gender, diagnosis, ethnicity (Afrikaner or British ancestry) and self-reported depression and mania (fixed effects). Residual depressive and hypomanic symptoms were controlled for in order to minimize recall bias. Genotype was modelled as a numerical factor indicating the number of copies of the lower frequency allele carried by an individual. This was done after confirming statistically that the heterozygote effect on DES score was midway between those of the two homozygote genotypes (Cordell and Clayton, 2005).

The interaction effect between specific polymorphisms and abuse was the focus of interest in this study. Family of origin was entered into the model as a random factor to control for the fact that participants were related to each other (Thomas, 2004). The scores of the families were assumed to be independent and identically normally distributed. We also assumed independent identically normally distributed within-family errors, independent of the families. This means that we assumed that the correlations between measurements within a particular family would be the same.

When a significant interaction between total abuse and a specific polymorphism on DES was found, we investigated which specific CTQ subscales contributed to the interaction effect. Where the interaction was not significant, we estimated the (main) effect of the relevant polymorphism on DES.

In order to facilitate the interpretation of the interaction between genotype and abuse on dissociative tendencies, a graph showing the observed values as well as the modelled relationship between total abuse and DES score for the genotype is displayed. The average values for each of the numerical factors and the following nominal categories (gender, female; diagnosis, MDE-R; ethnicity, Afrikaner) in the model are used in the graphs. Statistical analysis was done in R (R Development Core Team, 2007), a language and environment for statistical computing and graphics.

**Results**

The mean and standard deviation of CTQ abuse, DES, BDI and ASRM scores stratified by diagnostic group are shown in Table 2.

We investigated the association between diagnosis and CTQ total abuse after controlling for the factors described above. There was a weakly significant association between CTQ total abuse and diagnostic status ($F_{5,129} = 1.93, p = 0.0932$). All five diagnostic groups scored higher on average than the unaffected relatives. Two pairs of diagnostic groups differed significantly: unaffected relatives vs. both the MDE-R
We also investigated the association between diagnosis and DES score after controlling for the factors described above. There was a highly significant association between DES score and diagnostic status ($F_{5,131} = 3.197$, $p = 0.0093$). The following pairs of diagnostic groups differed significantly (after adjusting for the other diagnoses) in mean DES score: ‘Other diagnosis’ with each of MDE-R (adjusted difference = 1.71, $p = 0.0009$), BD I (adjusted difference = 1.51, $p = 0.0037$) and BD II (adjusted difference = 1.26, $p = 0.038$) groups. Mean DES score for unaffected relatives differed from BD I (adjusted difference = 0.7796, $p = 0.0489$) and MDE-R (adjusted difference = 0.982, $p = 0.0096$) individuals. The unaffected relatives and those with non-mood disorders obtained lower mean DES scores than the BD and MDE-R groups.

**Genotyping results**

There were no significant deviations from HWE in our sample. Table 3 gives the $p$ values for the 107 unrelated individuals in our sample.

For each polymorphism we assessed the interaction between total abuse and genotype (numerical) on DES score, after adjusting for the factors described previously. We coded the multi-allelic DRD4 polymorphism as long/short. For DAT we compared allele 9 to all the others combined. The other variants are bi-allelic. The results are summarized in Table 4. For the sake of brevity, $p$ values and $F$ statistics for the tests of gene-abuse interactions only, are shown for each model.

Given the fact that COMT and abuse scores interacted significantly on dissociation, we also tested for a COMT $\times$ Diagnosis $\times$ CTQ interaction which was not significant ($p = 0.681$). The mixed-effects model containing the interaction between total abuse and the COMT Val158Met variant on dissociation is summarized in Table 5.

The estimated standard deviations of the DES score were 1.600 within families and 0.202 between families, indicating that the correlation in DES score between members of the same family was 0.125.

A graph showing the observed data and also the modelled relationship (lines) between CTQ total abuse and DES scores, for the COMT genotype (coded as
The number of Val alleles is shown in Figure 1. The values of all numerical factors in the model were held at their average values. The categorical variables were: gender, female; diagnosis, BP I; ethnicity, Afrikaner.

The functional COMT Val158Met polymorphism interacts ($p = 0.008$, Table 5) with total abuse on perceived dissociation in the following way: when total CTQ abuse scores are low, the estimated mean DES scores are functions of all the predictors in the model, with Val/Val homozygotes exhibiting lower levels of perceived dissociation than their counterparts. The Val/Val homozygotes show a pattern of increasing DES scores with increasing total CTQ abuse. The increase is $0.031 \times (2r0.032) \times 0.033$ units for a unit increase in CTQ abuse. In heterozygous individuals, the estimated DES score shows very little change ($0.032–0.033 = 0.001$) with increasing total CTQ scores. Those individuals with no Val alleles (Met/Met homozygotes) have higher mean DES scores when total CTQ abuse scores are low, but their estimated mean DES score decreases with increasing total CTQ scores at a rate of 0.033 per unit of total CTQ abuse score.

We ran five mixed-effects models, adjusted for the variables mentioned above, in an attempt to determine which CTQ subscales were responsible for the highly significant interaction described above. We found that physical abuse and physical neglect have highly significant interactions with COMT on DES. Emotional abuse and emotional neglect show significant and weakly significant interactions with COMT on DES, respectively. Sexual abuse was the only CTQ subscale that did not interact significantly with COMT on DES (see Table 6). The interactions between COMT genotype and the five CTQ subscales on DES score were all in the same direction as for the total abuse score. There was no interaction between abuse and BDNF on dissociation (see Table 4) but there was an additive genotype effect, as summarized in Table 7. DES score was found to decrease by 0.406 points for each additional BDNF Met allele carried by the individual.
Table 7. Summary of model detailing the effect of BDNF Val66Met on dissociation

<table>
<thead>
<tr>
<th>Effect</th>
<th>s.e.</th>
<th>d.f.</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>5.988</td>
<td>30</td>
<td>0.390</td>
<td>0.390</td>
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<tr>
<td>Age</td>
<td>0.512</td>
<td>30</td>
<td>0.287</td>
<td>0.776</td>
</tr>
<tr>
<td>Gender male</td>
<td>0.103</td>
<td>30</td>
<td>0.203</td>
<td>0.841</td>
</tr>
<tr>
<td>BDI</td>
<td>0.101</td>
<td>30</td>
<td>0.206</td>
<td>0.841</td>
</tr>
<tr>
<td>ASRM</td>
<td>0.075</td>
<td>30</td>
<td>0.206</td>
<td>0.841</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>0.460</td>
<td>30</td>
<td>0.206</td>
<td>0.841</td>
</tr>
</tbody>
</table>

ASRM, Altman Self-Rating Mania Scale; BDNF, brain-derived neurotrophic factor; BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire. Reference categories: Gender, female; Diagnosis, unaffected relatives; CTQ total, sum of abuse scores; Ethnicity (1 = Afrikaner; 2 = British ancestry); s.e., standard error of the estimated effect in the model; d.f., degrees of freedom for t test.

The estimated standard deviations of the DES score were 1.632 within families and 0.002 between families, indicating that in this model, the correlation in DES score between members of the same family was negligibly small.

Discussion

The significantly higher CTQ scale scores in the MDE-R and BD II groups is consistent with previous reports of higher levels of childhood adversity in psychotic and affective illness (reviewed in Read et al., 2005). Congruent with this finding, our BD I and MDE-R groups displayed higher levels of dissociation compared with unaffected relatives. These results may be worthy of follow-up in independent samples with well-characterized abuse histories.

The Met allele of the BDNF Val66Met SNP was associated with lower perceived dissociation, although no significant interaction with self-reported abuse was forthcoming from the data. Since the molecular basis of dissociation has not been explored, this result is difficult to interpret within the context of the extant scientific literature. Nevertheless, there is some indirect evidence for our finding.

Childhood trauma has been associated with dissociation and individuals exposed to childhood abuse display a greater degree of anxiety (McFarlane et al., 2005; Roy, 2002; Stein et al., 2007). Based on the results of our study, it could therefore be hypothesized that carriers of the BDNF Val allele should display more salient anxiety-related personality traits. In line with this argument, Lang et al. (2005) reported greater anxiety-related personality traits as evinced by the State-Trait Anxiety Inventory and the NEO in Val/Val homozygotes. Similarly, Hunnerkopf et al. (2007) reported a DAT1–BDNF interaction such that carriers of the 9R DAT1 allele and the BDNF Met allele displayed lower levels of neuroticism (measured by the NEO personality scale) than non-carriers. On the other hand, Jiang et al. (2005) and Rybakowski et al. (2007) found that the Met66 allele was a potential risk factor for the development of anxiety-related personality traits.

Congruent with these personality data, BDNF knockout mice show an exaggerated response to stressors (Rios et al., 2001) and hippocampal injection of the protein has enduring anxiolytic effects (Cirulli et al., 2004). Further, animal models of early trauma have yielded data suggestive of changes in BDNF expression in response to stress (Faure et al., 2007; Kozlovsky et al., 2007; Rasmussen et al., 2002). Based on these data, however, one would have expected the low-activity BDNF Met allele to be a risk-factor rather than a protective factor for dissociation as found in this study. Clearly our result should be treated with caution until independently replicated.

We found that the COMT Val158Met polymorphism interacted with childhood abuse, as assessed using the total CTQ scores, to influence dissociative tendencies. While the Val/Val genotype was associated with lower DES scores in individuals with low CTQ scores, the same genotype was associated with higher DES scores in individuals who reported higher levels of childhood trauma. Conversely, the Met/Met genotype was associated with lower levels of self-reported dissociative experiences in individuals with elevated scores on the CTQ.

The interaction between COMT and abuse on self-reported dissociation is congruent with a number of other studies. Ott et al. (2005) showed that the Val158Met and T102C variants of the COMT and 5-HT2A receptor genes, respectively, interact to yield higher scores on the TAS. Scores on the TAS, a measure of the disposition to experience altered states of consciousness, were highest in individuals homozygous for the COMT Val allele and the 5-HT2A T allele (Ott et al., 2005).
Lichtenberg et al. (2000) reported an association between a correlated trait, hypnotizability, and the COMT gene although in this case, the heterozygote group was most susceptible to hypnosis. Susceptibility to hypnosis may be a vulnerability factor for the development of dissociative conditions like PTSD (Bliss, 1984; Bryant et al., 2001; Frankel, 1990) although to the best of our knowledge, the role of the COMT Val158Met variant in PTSD has not been assessed.

One correlate of the dissociative experience is a distortion of time perception (Bryant, 2007). Interestingly, Reuter et al. (2005) searched for the genetic correlates of cognitive endophenotypes of schizophrenia and found that the internal clock of COMT Val allele carriers was accelerated compared to Met/Met patients. It could be speculated that a dopamine-driven disturbance in internal clock regulation is a contributing factor to aspects of the dissociative process although this topic is beyond the scope of this paper.

Ott et al. (2005) note that high levels of Absorption bear an attenuated resemblance to the positive symptoms of schizophrenia and drug-induced hallucinations. In line with this notion, marijuana intoxication has been shown to be associated with increased hypnotic susceptibility (Kelly et al., 1978), elevated TAS scores in regular drug-users (Fabian and Fishkin, 1981), and general dissociative feelings (Tart, 1970). Interestingly, the COMT Val allele is a putative risk factor for the development of psychotic symptoms and schizophrenia-spectrum illness after cannabis use (Caspi et al., 2005; Henquet et al., 2006). Caspi et al. (2005) reported that Val/Val homozygotes who used cannabis were ~10 times more likely than Met/Met homozygotes to develop a schizophreniform disorder while Henquet et al. (2006) noted that carriers of the Val allele experienced more cannabis-induced transient psychotic symptoms. Although the mechanism behind this effect is still unclear, we tentatively suggest that dissociative processes may contribute to the psychotogenic effects of cannabis abuse in susceptible individuals.

The other potentially interesting point about Absorption and hypnotic susceptibility is that they are intimately tied to attentional regulation (Crawford, 1994; Fabian and Fishkin, 1981; Ott et al., 2005); a phenotype which has been shown to be impaired in schizophrenia ( Fioravanti et al., 2005; Heinrichs, 2004). This observation may be relevant because the Val allele has been reported to be over-represented in some samples of patients with schizophrenia (Fan et al., 2005; Riley and Kendler, 2006; Williams et al., 2007).

Additional indirect data supporting the validity of our results can be found in the pharmacology literature. Stress-induced activation of the endogenous opioid system has been reported to elicit dissociative symptoms and conversely, treatment with opioid antagonists has been reported to reduce dissociation and improve the treatment of dissociative conditions (reviewed in Simeon, 2004). Opioid release activates the dopaminergic system, especially the mesolimbic DA pathway which in turn regulates the activity of the opioid system (reviewed in Pani et al., 2000; Saxon et al., 2005). Importantly, the COMT Val158Met variant has been shown to regulate the stress-induced activation of the μ-opioid neurotransmitter system, with Met/Met homozygotes displaying less μ-opioid neurotransmission than their heterozygous and Val/Val homozygous counterparts (Zubieta et al., 2003).

Partially consistent with this result, Berthele et al. (2005) showed that the COMT Val allele was associated with a lower number of μ-opioid receptor-binding sites in the caudate nucleus, nucleus accumbens and the mediodorsal nucleus of the thalamus. The regulatory role of COMT on opioid function is further supported by a recent case study of a patient with velocardiofacial syndrome, a condition caused by a microdeletion of the region of chromosome 22 containing the COMT gene. The patient in question repeatedly developed hallucinations after administration of opioid analgesics (Gitlin et al., 2007).

Simeon (2004) notes that besides opioid antagonists, dissociative conditions have been treated with clomipramine, fluoxetine and lamotrigine, all with minimal success. If our result proves to be robust, it may be worthwhile attempting to treat dissociative disorders with modulators of central dopaminergic neurotransmission.

Despite the biological plausibility of a role for COMT in influencing dissociative tendencies, the past history of non-replicated findings in the psychiatric genetics literature suggests that our results should be treated with caution. This caveat applies even more so when additional complexity is introduced into the study by the measurement of gene–environment interactions. Limitations of the study include:

1) The DES provides a subjective measure of dissociative experiences and may therefore be susceptible to response bias or malingering. Scores on the scale have also been associated with general psychological and physical distress (van Ijzendoorn and Schuengel, 1996). Although we attempted to minimize this possibility by controlling for state effects with the BDI and ASRM, it is possible that COMT genotype and abuse as measured using the CTQ interact on a broader
psychopathological phenotype rather than dissociation, per se. In a similar vein, the CTQ is a subjective, retrospective measure of childhood adversity that may be vulnerable to state effects or gene–environment correlations.

(2) Although the distribution of COMT Val158Met alleles did not violate HWE, a relatively low p value of 0.08 was obtained. It is therefore theoretically possible that genotyping errors may have influenced our results. It should be noted, however, that because this was a family-based analysis we could only estimate HWE scores using a subset of unrelated participants.

(3) Our pilot study was conducted in a sample of people with BD and their relatives and it is therefore unclear if our results are generalizable to other populations.

(4) We carried out a variety of statistical tests and did not correct for multiple testing. Nevertheless, given the a-priori evidence of COMT involvement in dissociation, a Bonferroni correction is probably overly conservative in this situation. However, the issue of multiple testing probably does apply to our finding that the BDNF Val66Met allele directly impacts perceived dissociation since there is very little a-priori evidence for the influence of BDNF on this phenotype.

In summary, an enhanced understanding of the underlying neurobiology of the dissociative process is an important long-term goal for psychiatry as it may impact a variety of psychiatric conditions, including BD. Our finding that the Val allele of the COMT Val158Met polymorphism is associated with lower levels of self-reported dissociation in individuals with lower childhood abuse scores but increased dissociation in individuals with higher CTQ scores illustrates the importance of studying gene–environment interactions in attempting to improve our understanding of the behavioural correlates of COMT and other genes.

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Statement of Interest
None.

References


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### Family BP I BP II MDE-R MDE-S Other Unaffected Total

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### Table B1. Genotyping methods

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**TD**: Touch down; **n.a.**: not applicable.