Interaction between serotonin transporter gene, catechol-O-methyltransferase gene and stressful life events in mood disorders

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Abstract

It is well established that stress is a risk factor for onset of mood disorders. Emerging evidence suggests that genetic vulnerability may also moderate individual responsiveness to stress. The most compelling evidence regards the polymorphism within the promoter region of the serotonin transporter gene (SERTPR), which has been reported to moderate the risk for depression, in conjunction with life stressors.

In the present paper we analysed SERTPR in the onset of mood disorders, along with adverse life events, and other candidate genes: the serotonin receptor 1A (5-HT1A), the dopamine receptor D4 (DRD4) and the catechol-O-methyltransferase (COMT). The sample was composed of 686 Italian subjects, affected by major depression and bipolar disorder. Patients were asked to report about life stressors within the year preceding onset of their first mood-disorder episode and genotyped. A ‘case-only’ design was employed to investigate the interaction between genes and stressors. COMT was associated with depression following exposure to stressors ($\chi^2=13.05$, d.f. = 2, $p=0.0015$) and SERTPR also showed a positive association ($\chi^2=6.70$, d.f. = 2, $p=0.035$), mainly among women and among major depressives. The interaction between COMT and SERTPR was also significant ($p=0.0005$). In our retrospective study SERTPR is hypothesized to lead to the onset of major depression via its influence on reaction to adversities, particularly in females. Moreover, COMT was risk factor for onset of both major depression and bipolar disorder, in conjunction with adversities.

Key words: Dopamine, gene–environment, genetics, serotonin, stress.

Introduction

Adverse events, such as parental loss, divorce or financial problems show a substantial causal association with depression (for a review see Paykel, 2003). Emerging evidence suggests that genetic factors play a role in vulnerability to depression, partly by moderating individual responsiveness to stress (Charney and Manji, 2004; Wurtman, 2005). To date, the most compelling evidence for such genetic moderation was reported in a prospective longitudinal study (Caspi et al., 2003) where a polymorphism within the promoter region of the serotonin transporter gene (Heils et al., 1996) was found to moderate the risk for depression among persons exposed to stressful life events.

The genes coding for proteins involved in the synthesis and actions of serotonin (5-HT), particularly the 5-HT transporter protein, are those being explored most extensively as possible mediators of the genetic contribution to depression and anxiety (Deakin, 1998). This is because 5-HT has an inhibitory influence on general positive emotionality, mediated by dopamine (DA) (Spoont, 1992). The polymorphism for the 5-HT transporter protein (SERTPR) produces two main types of genetic variants within the promoter region of the serotonin transporter gene, commonly known as the short ‘s’ allele and the long ‘l’ allele, which differentially modulate the transcriptional activity of the gene’s promoter and thus the amounts of...
messenger RNA and of the protein itself (Lesch et al., 1996). Caspi et al. (2003) found that the ‘s’ allele was associated with the onset of newly diagnosed depression, suicidal ideation and suicide attempts in subjects who experienced recent stressful life events. A similar effect of SERTPR was replicated in a sample of children (Kaufman et al., 2004), a sample of adolescents (Eley et al., 2004), and adults (Kendler et al., 2005).

Thus, the SERTPR polymorphism may be postulated as a genetic liability factor for depressive reaction, after exposure to adverse events. This is compatible with previous observations regarding the association between the ‘s’ allele and anxiety personality traits, such as neuroticism and harm avoidance (Lesch et al., 1996; Schinka et al., 2004; Sen et al., 2004). Based on this evidence, s/s subjects are hypothesized to be more sensitive to stress and, therefore, more likely to develop abnormal responses. Further, the association between the short SERTPR allele and abnormal responses to stressors has been identified by neuroimaging research (Hariri et al., 2002b, 2005). During exposure to fearful stimuli, homozygous subjects for the short SERTPR allele were reported to show more pronounced neuronal activity in the amygdala, compared to 1/1 subjects.

Summing up, research suggests that s/s subjects are more anxious and more prone to depression following exposure to stressful events, and the greater amygdala neuronal activity observed in s/s subjects confirms their higher responsiveness to stressful stimuli. Nevertheless, other genes coding for serotonergic constituents, as well as genes of other neural modulator systems, may exert crucial influences on the response to stress and risk for mood disorders. Thus, in the present paper, we not only tested the effect of SERTPR on the onset of mood disorders connected to adverse life events, but we also investigated the potential involvement of other polymorphisms previously proposed as candidate genes for mood disorders. We hypothesized the involvement of three other polymorphisms: one in the promoter region of the gene coding for serotonin receptor 1A (5-HT_{1A}) (Lemonde et al., 2003), one within the gene coding for dopamine receptor D4 (DRD4) (Lichter et al., 1993) and one within the gene coding for catechol-O-methyltransferase enzyme (COMT) (Kunugi et al., 1997). Other genes could also be candidates, such as the tryptophan hydroxylase 2 (TPH2) (Walther et al., 2003), the dopamine transporter (DAT) (Vandenbergh et al., 1992) and monoamine oxidase A (MAOA) (Sabol et al., 1998), as well as novel candidate genes, for example, the CLOCK gene (Serretti et al., 2005a), the human PER3 (Zylka et al., 1998) or the glycogen synthase kinase 3-beta (GSK3β) (Lau et al., 1999). However, at that time, we did not have sufficient data to include the analysis of these variants as well.

The 5-HT_{1A} (C/G) polymorphism was demonstrated to modulate the rate of transcription of the gene protein and thus the amount of 5-HT_{1A} receptors (Lemonde et al., 2003), which are involved in the modulation of exploratory and fear-related behaviours; reduction in these receptors has been hypothesized to result in heightened anxiety (Ramboz et al., 1998). Recently, 5-HT_{1A} expression was found to be lower in stress-sensitive animals (Bethea et al., 2005), thus, the G variant of 5-HT_{1A}, de-repressing the expression of 5-HT_{1A} auto-receptors and thus reducing serotonergic neurotransmission (Lemonde et al., 2003), may regulate sensitivity to stressors and predispose to develop depressive symptoms.

Among the dopaminergic structures, the DRD4 variable number tandem repeat (VNTR) polymorphism has been involved in personality traits, such as novelty seeking (Benjamin et al., 1996; Ebstein et al., 1996), as well as harm avoidance (Bau et al., 1999; Serretti et al., 2005b). DRD4 has been also found to interact with SERTPR in the same temperamental traits (Auerbach et al., 2001; Ebstein et al., 1998; Lakatos et al., 2003). Receptors encoded by longer alleles have been hypothesized to be less sensitive to DA (Asghari et al., 1995), thus, we may hypothesize a worse response to stressors in long allele carriers of the DRD4 gene.

Finally, the COMT enzyme is involved in the degradative pathway of catecholamines, in particular DA. A variant within the gene coding for this enzyme (COMT) resulting in an amino-acid substitution of valine (Val) with methionine (Met), causes differences in the functional ability of the enzyme to catabolize DA (Weinshilboum and Raymond, 1977). COMT has been hypothesized as a risk factor for attention deficit hyperactivity disorder (McGough, 2005), schizophrenia (Harrison and Weinberger, 2005), alcoholism (Oroszi and Goldman, 2004), bipolar disorder (Tsuchiya et al., 2003) and personality traits, such as harm avoidance and neuroticism (Eley et al., 2003; Enoch et al., 2003; Stein et al., 2005), novelty seeking and extraversion (Reuter and Hennig, 2005; Tsai et al., 2004), and anger-related traits connected with violent suicide (Rujescu et al., 2003). The ‘low activity’ Met variant, leading to an altered dopaminergic regulation, may be hypothesized as being associated with a worse response to stressors.

Given the evidence of potential modulation effects exerted by these genes on behaviour and human
responses to stressful stimuli, we here retrospectively analysed our large sample of mood-disorder patients, in order to investigate their involvement in the onset of the illness together with the exposure to adverse events.

Materials and methods

Design

We employed a ‘case-only’ design (Khoury and Flanders, 1996), based on the use of case subjects only, to assess the magnitude of the association between exposure and the susceptibility genotype. Case subjects are selected as for any case-control study, with the exposure effect assessed only among case subjects. Case subjects without the susceptibility genotype form the control sample. A $2 \times 2$ table [susceptibility genotype (yes/no) and exposure (yes/no)] may be thus analysed. This method has been reported to result in greater precision in estimating interactions than can be obtained by traditional case-control case analyses (Piegorsch et al., 1994).

Sample

The present sample was composed of 686 patients, affected by major depression (unipolar disorder: UP, $n = 323$) and bipolar disorder (BP, $n = 363$), consecutively admitted to the Department of Psychiatry of the San Raffaele Hospital, Milan, Italy. Subjects were previously included in other psychopharmacological and genetic studies (Serretti et al., 1998, 1999, 2002b, 2004). Lifetime diagnoses were assigned according to DSM-IV criteria on the basis of interviews (SCID-I; First et al., 1995) and all available sources of information (previous clinical charts, other clinicians’ reports and information from relatives) (Leckman et al., 1982). Patients were included if they were aged >18 yr, met DSM-IV criteria for BP or UP disorder, with or without psychotic features, whereas the presence of concomitant diagnoses of mental retardation, drug dependence, or other Axis I disorders, together with medical illnesses that impaired psychiatric evaluation, represented exclusion criteria. Demographic and clinical features characterizing the present sample are summarized in Table 1. Informed consent was obtained from all subjects after the aim of the study had been fully explained.

Table 1. Demographic and clinical features of the sample

<table>
<thead>
<tr>
<th>Demographic and clinical features</th>
<th>Yes/No (%)</th>
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<tbody>
<tr>
<td>Females/males</td>
<td>469/217 (68.37/31.63)</td>
</tr>
<tr>
<td>Major depression/bipolar disorders</td>
<td>323/363 (47.08/52.91)</td>
</tr>
<tr>
<td>Adverse events at onset</td>
<td>451/235 (65.74/34.26)</td>
</tr>
<tr>
<td>Peripartum at onset (females only)</td>
<td>91/378 (19.40/80.60)</td>
</tr>
<tr>
<td>Depressive episode at onset (vs. maniac; bipolar only)</td>
<td>291/72 (80.16/19.83)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>229/548 (29.47/70.53)</td>
</tr>
</tbody>
</table>

Mean ± S.D.

| Age (yr)          | 48.02 ± 14.27 |
| Age at onset (yr) | 32.99 ± 15.56 |
| Illness duration  | 15.07 ± 12.81 |
| Recurrence rate (no. episodes/year) | 0.86 ± 1.63 |
| Hospitalizations (mean no.) | 4.62 ± 3.18 |
| Suicide attempts (mean no.; only among attempters) | 1.97 ± 2.12 |

Evaluation of stressful life events

The most common strategy estimating the effects of life events on depression focuses on short-term effects, typically a recall period of no more than 1 yr (Kessler, 1997). Accordingly, all patients included in our sample were asked for life stressors within the year preceding onset of the first mood-disorder episode. Onset was defined as the period in which the first lifetime affective episode, according to DSM-IV criteria (major depressive, manic, mixed or hypo-mania episode) occurred, as evaluated and judged by SCID-I (First et al., 1995).

Collection of stressful life events was made according to the Life-Events and Difficulty Schedule (LEDS; G. W. Brown and T. O. Harris, unpublished data). Unfortunately, the specific type of adverse life event (for example: ‘loss of a loved one’ or ‘working difficulties’) was not recorded for many patients in our
database \((n = 311)\), as this was not our original research purpose. Subjects were thus classified as having experienced \((n = 451)\) or not experienced \((n = 235)\) stressors before onset. In fact, we had all LEDS items for only half of the sample \((n = 375)\). Onset during peripartum (during pregnancy or within 1 yr from childbirth), was always specified. In our sample, onset of mood disorder during the peripartum occurred in 19.40% of patients \((91/595; 45 \text{ UP and 46 BP})\). In the analyses, we globally classified patients as having or not having stressors at onset, then we excluded subjects with peripartum onset, in order to check for biases potentially linked to female sex and to this particular type of event. Among subjects evaluated with the LEDS, we estimated a rate of \(\approx 15\%\) of patients experiencing more than one stressor.

**DNA analysis**

Genomic DNA was extracted from leucocytes by NaCl precipitation \((\text{Lahiri and Nurnberger, 1991})\). Detailed methods of analysis were previously reported \((\text{see Serretti et al., 2001, 2002a, 2003, 2004})\). Subjects were previously included in other psychopharmacological and genetic studies \((\text{Serretti et al., 1998, 1999, 2002b, 2004})\) and here we analysed only those also evaluated with the LEDS for life events. Of these, 670 patients were genotyped for SERTPR, 156 for 5-HT\(_{1A}\), 525 for DRD4 and 337 for COMT. Subjects not genotyped were not different in regard to stressful life events. Subjects with the 5-HT\(_{1A}\) genotype had an average rate of stressful life events of 65.66% vs. 66.03% of the ones not genotyped. COMT figures were 66.17% vs. 65.3% respectively.

**Statistical analysis**

Patients were divided into those characterized by the presence or absence of stressors at their first lifetime mood-disorder episode, and compared on the four genetic polymorphisms with the \(\chi^2\) test; differences where considered significant considering an \(\alpha\)-level of 0.0125 (Bonferroni correction: 0.05/4 polymorphisms). All analyses comparing categorical variables were performed with the \(\chi^2\) test. Logistic regression was used to evaluate the effect of more than one variable on the dependent one (occurrence of life events at onset, coded yes vs. no), and to control the effect of potential confounders.

With an \(\alpha\)-level of 0.0125, in our sample we had a power of 0.80 to detect a small effect size of \(w = 0.13\), that corresponded to a difference of \(\approx 13\%\) between SERTPR genotypes on incidence of adverse events \([\text{odds ratio (OR) } 1.70]\); and a small effect size of \(w = 0.19\), that corresponded to a difference of \(\approx 19\%\) \((\text{OR 2.17})\) between COMT genotypes on incidence of adverse events \((\text{Cohen, 1988})\).

**Results**

**Demographic and clinical features associated with stressors at onset**

The incidence of adverse events within the year preceding onset of a mood disorder was high \((65.74\%, \text{ Table 1})\), confirming stressors as a risk factor for onset of mood disorders. In females the incidence of peripartum at onset was high \((19.40\%\) of all women and 27.74% of women who developed an illness episode after stressors).

Table 3 shows the occurrence of stressful life events preceding the first lifetime episode, stratified by demographic and clinical features. Three findings are noteworthy. First, onset of mood disorders was more often preceded by stressors among women than among men. However, this difference was mainly due to the occurrence of peripartum among women;
excluding peripartum at onset, no difference was observed between women and men ($\chi^2 = 2.08, \text{d.f.} = 1, p = 0.15$). Second, the incidence of adverse events was slightly but significantly higher among UP patients than among BP patients, independently of peripartum. Considering BP patients alone, adverse events were mostly associated with a first depressive episode rather than a manic one. Third, in the overall sample, stressors at onset did not significantly predict lifetime suicide attempts, although a small trend in the direction of a positive association could be observed. Stressors at onset were not significantly associated with age at first lifetime episode, recurrence, nor lifetime number of hospitalizations.

**Genetic polymorphisms associated with stressors at onset**

In our sample, all the genetic polymorphisms, except for SERTPR, were in Hardy–Weinberg equilibrium (Table 2). Among our patients, we observed an excess of the SERTPR s/l genotype. Table 4 shows the incidence rates of stressful events at the first lifetime mood-disorder episode, stratified by each of the four genetic polymorphisms.

We observed significant associations between the Val/Met and Met/Met COMT genotypes and onset connected to stressors. Comparing the l/l SERTPR genotype with those containing the short allele (s/s and l/s genotyped together) (Greenberg et al., 1999), a significant association was observed between the s-containing genotypes and onset of mood disorders after stressors ($\chi^2 = 6.70, \text{d.f.} = 1, p = 0.0097$).

None any of the four polymorphisms was significantly associated with onset of mood disorders during the peripartum in females ($p$ values $> 0.10$). Excluding peripartum, the association between COMT and onset after stressors remained statistically significant ($\chi^2 = 12.53, \text{d.f.} = 1, p = 0.0019$) and SERTPR preserved a positive trend ($\chi^2 = 5.50, \text{d.f.} = 1, p = 0.019$).

Given the higher risk of stressors at onset among women than among men, and among UP patients than among BP patients, we used logistic regression models to test the association between each of the genetic polymorphisms and presence vs. absence of stressors at onset, after controlling for sex and diagnosis (UP/BP depression). 5-HT$_{1A}$ and DRD4 did not show significant associations with stressors at onset, also considering sex and diagnosis. Instead, COMT maintained a strong association with stressors at onset (main effect of COMT: $\chi^2 = 10.62, \text{d.f.} = 1, p = 0.0011$).

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**Table 3. Occurrence of adverse life events at onset of mood disorders, stratified for demographic and clinical features of the sample**

<table>
<thead>
<tr>
<th>Adverse events at onset</th>
<th>(No/Yes)</th>
<th>(No/Yes) (%)</th>
<th>$\chi^2$</th>
<th>d.f.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>141/328</td>
<td>(30.06/69.94)</td>
<td>11.38</td>
<td>1</td>
<td>0.0007</td>
</tr>
<tr>
<td>Males</td>
<td>94/123</td>
<td>(43.32/56.68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression</td>
<td>90/233</td>
<td>(27.86/72.14)</td>
<td>11.16</td>
<td>1</td>
<td>0.0037</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>145/218</td>
<td>(39.94/60.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polarity at onset (bipolar only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive</td>
<td>107/184</td>
<td>(36.77/63.23)</td>
<td>6.06</td>
<td>1</td>
<td>0.014</td>
</tr>
<tr>
<td>Manic</td>
<td>38/34</td>
<td>(52.78/47.22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide attempts</td>
<td>No</td>
<td>177/299</td>
<td>(37.18/62.82)</td>
<td>6.05</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>58/152</td>
<td>(27.62/72.38)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events at onset</th>
<th>No/Yes (mean ± S.D.)</th>
<th>Student’s t</th>
<th>d.f.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46.54 ± 15.25/48.80 ± 13.68</td>
<td>-1.98</td>
<td>683</td>
<td>0.05</td>
</tr>
<tr>
<td>Age at onset (yr)</td>
<td>32.73 ± 13.25/33.13 ± 12.19</td>
<td>-0.40</td>
<td>684</td>
<td>0.69</td>
</tr>
<tr>
<td>Recurrence rate (no. episodes/year)</td>
<td>0.92 ± 1.02/0.83 ± 1.84</td>
<td>0.56</td>
<td>445</td>
<td>0.57</td>
</tr>
<tr>
<td>Hospitalizations (n)</td>
<td>3.25 ± 3.45/5.32 ± 3.57</td>
<td>-0.63</td>
<td>633</td>
<td>0.53</td>
</tr>
</tbody>
</table>
with no significant effect of sex and diagnosis. SERTPR also showed a significant effect (main effect of SERTPR: \( \chi^2 = 8.54, \) d.f. = 1, \( p = 0.0035 \)), although significant effect was also exerted by diagnosis (main effect of diagnosis: \( \chi^2 = 10.08, \) d.f. = 1, \( p = 0.0015 \)) and a positive trend by sex (main effect of sex: \( \chi^2 = 5.37, \) d.f. = 1, \( p = 0.02 \)). SERTPR in fact showed trends for positive associations with stressors among UP patients (\( \chi^2 = 4.50, \) d.f. = 1, \( p = 0.033 \)) and females (\( \chi^2 = 5.45, \) d.f. = 1, \( p = 0.019 \)) but not in BP patients and males.

We considered simultaneously, in a logistic regression analysis, SERTPR, COMT, sex and diagnosis as independent variables, and the occurrence of life events at onset of illness as the dependent variable. Given the associations between SERTPR s-allele containing genotypes and COMT Met-allele containing genotypes with stressors, we dichotomized genotypes accordingly (s-containing vs. 1/1 SERTPR; Met-containing vs. Val/Val COMT). There was a significant effect of the Met COMT variant (main effect of COMT: \( \chi^2 = 11.20, \) d.f. = 1, \( p = 0.00082 \)), a trend for the short SERTPR variant (main effect of SERTPR: \( \chi^2 = 2.87, \) d.f. = 1, \( p = 0.088 \)), but no significant effects of sex (main effect of sex: \( \chi^2 = 2.32, \) d.f. = 1, \( p = 0.13 \)) and diagnosis (main effect of sex: \( \chi^2 = 0.51, \) d.f. = 1, \( p = 0.48 \)). By excluding women characterized by peripartum at onset, the effect of COMT remained significant (main effect of COMT: \( \chi^2 = 11.83, \) d.f. = 1, \( p = 0.0006 \)) as did the trend for SERTPR (main effect of SERTPR: \( \chi^2 = 3.13, \) d.f. = 1, \( p = 0.076 \)).

Using logistic regression, the interaction between SERTPR and COMT on stressors at onset (available on 334 patients genotyped for the two polymorphisms) was statistically significant (overall effect: \( \chi^2 = 15.08, \) d.f. = 2, \( p = 0.00053 \)). As illustrated in Figure 1, subjects carrying the Met*COMT allele and the short*SERTPR allele showed the highest incidence of stressors at onset (76.7% of patients carrying this genotype), followed by those carrying the Met*COMT allele and homozygous for the long SERTPR allele (64.63%...
of patients carrying this genotype) and by those homozygous for the Val*COMT allele and carrying the short*SERTPR allele (54.4% of patients carrying this genotype). Those with the lowest incidence of stressors at onset were the patients both homozygous for the long*SERTPR allele and for the Val*COMT allele (50.0% of patients carrying this genotype).

To sum up, COMT showed the most effective association with onset of mood disorders after exposure to adverse events, independently from sex and diagnosis of patients. SERTPR also showed positive associations with onset after stressors, although weaker than COMT and only significant among females and UP. Finally the interaction between COMT and SERTPR on onset connected to adversities was statistically significant.

Discussion

We investigated our large sample of mood-disorder patients for life stressors at onset of illness, together with their genotype at four genetic loci. Although a number of limitations characterize the present work, as discussed below, this is the first time, to our knowledge, that these candidate genes have been tested for their involvement in ‘gene x environment’ interactions in relation to both BP and UP depression.

Our findings about stressful life events are in line with previous research. First, the occurrence of life stressors at first lifetime mood-disorder episode was high (65.74%) in our patient sample. This is in line with the idea that stressors are a risk factor for the onset of mood disorders (Paykel, 2003). Second, we replicated the finding that life stressors may be more likely to be associated with onset of mood disorders among women than among men (Nazroo et al., 1997). However, in our sample this was mainly due to onset during peripartum in females. Third, we replicated the finding that life stressors are more likely to be associated with onset of UP than onset of BP (Paykel, 1994, 2003).

Using our large patient population, we were able to test the moderating effect of genotype on the association between life stressors and mood disorders. Two findings stand out. First, we found that, among UP patients, carriers of the short allele of SERTPR were significantly more likely to have been exposed to stressful life events. The positive association between the short SERTPR and the occurrence of stressors at onset indirectly confirms the finding of Caspi et al. (2003) regarding a ‘gene x environment’ interaction in the development of depressive symptoms, as well as the involvement of SERTPR in this interaction. On the basis of previous evidence, the effect of SERTPR on the development of affective disorders may be mediated by the modulation of anxiety-related traits (Lesch et al., 1996; Schinka et al., 2004; Sen et al., 2004) and sensitivity to stress (Caspie et al., 2003; Hariri et al., 2002a, 2005).

The effect of SERTPR was slightly more significant in females than in males. This finding is in line with the work of Eley et al. (2004). However, other studies found the interaction in both males and females (Kendler et al., 2005). Further research is required to clarify the role of gender in the observed associations.

To our knowledge, the SERTPR has been never tested in BP patients, regarding an interaction with life events in onset of the disorder. We did not observe an effect of SERTPR neither in relation to manic onset nor to depressive onset of BP. As such, the effect of SERTPR may be limited to the development of UP depressive illness. This finding should be considered preliminary until replicated.

In addition, we found that the Met variant of COMT was significantly associated with the exposure to adverse events and its effect was even stronger than that observed for SERTPR. The low-activity Met allele, which presumably allows more DA to become available at the synapse, has been associated with personality traits marked by negative emotionality, such as harm avoidance and neuroticism (Eley et al., 2003; Enoch et al., 2003; Stein et al., 2005), and anger-related traits associated with violent suicide (Rujescu et al., 2003). The Val/Val genotype has instead been associated with extraversion (Reuter and Hennig, 2005).

Overall these findings may be useful to explain the association of the Met/Met genotype with the occurrence of stressors at onset: we hypothesize that Met/Met subjects, being characterized by higher harm avoidance and neuroticism, may have a greater risk to develop a mood disorder when exposed to life stressors. It should be noted that the effect of COMT was independent from sex and diagnosis, which resulted on the effect of SERTPR in our sample. However, the low sample size of patients genotyped for COMT, compared to that of subjects genotyped for SERTPR, may not have allowed us to find positive effects for these variables.

In our opinion, it is noticeable that the two genetic variants associated with adverse events at onset were those labelled as ‘low activity’ and both producing an excess of monoamines in the synaptic cleft: 5-HT by reduced serotonin transporter and DA by the unstable form of catechol-O-methyltransferase. A significant interaction between COMT and SERTPR genotypes on
stressors at onset was also observed, thus the cooccurrence of dysregulation in monoaminergic systems, resulting in an excess of synaptic monoamines, may act synergically in abnormal responses to stress and in the precipitation of affective disorder. We hypothesize that this should mostly occur in subjects still susceptible for the disorder, because of the conjunction of other genetic and psychosocial features (Caspì et al., 2003). SERTPR as well as COMT may not be directly involved in mood disorders, but they could act as moderators of the depressogenic influence of stressful life events, which are well known to be risk factors for the appearance of these psychiatric illnesses.

Alternatively, one may also point to the fact that the 1/1 SERTPR and the Val/Val COMT both resulted more frequently in subjects who developed a mood disorder not preceded by adverse events. This is a different way to look at the matter. However, there are no data to support this point of view, since, in this case, the 1/1 and Val/Val genotypes should have been more frequently associated with the disorder per se. Conversely, the s/s SERTPR genotype did show the major associations with mood disorders (Lotrich and Pollock, 2004), while no positive associations were found for any COMT genotype (Gutierrez et al., 1997; Kunugi et al., 1997; Serretti et al., 2003).

In our sample, an excess of the short SERTPR allele was observed among patients. This is consistent with findings from a recent meta-analysis (Lotrich and Pollock, 2004) but not with others (Furlong et al., 1998; Lasky-Su et al., 2005). In our sample, the excess of the s/l genotype may support a positive association between the short allele and major depression, but, on the other hand, and in line with our previous observations, the short SERTPR may be in excess in our depressed patients because it increases depressogenic traits (Lesch et al., 1996) and abnormal reactions to stressors (Caspì et al., 2003). Further, the excess of the short allele in our sample may be related to the particularity of our sample, which was primarily collected for previous pharmacogenetic studies (Smeraldi et al., 1998; Zanardi et al., 2000). In fact, the short SERTPR has been repeatedly associated with poor response to selective serotonin reuptake inhibitors (SSRIs). Thus, our sample may over-represent the s/l genotype because we oversampled severe and non-responder patients for the aims of our pharmacogenetic investigations. This characterization of our sample may not only have biased the genetic balance of the sample, regarding SERTPR, but also that of the other polymorphisms. However, we did not observe deviations from Hardy–Weinberg equilibrium for the other genes considered. On the other hand the inclusion of non-responders, severe and mainly hospitalized patients, may have reduced the representativeness of our sample, in particular regarding the main findings about genetic × environment interactions.

Four other main limitations characterize the present work. First, its overall retrospective approach could have biased data collection towards unreliable estimates of clinical variables, including adverse events at onset (Keller et al., 1987). However, it is not apparent why this should produce spurious evidence of gene × environment interactions. Second, although life events were collected according to the LEDS (G. W. Brown and T. O. Harris, unpublished data), the specific type of event, except for peripartum, as well as the number of life events, were not recorded in our database. The availability of such data could be relevant to the investigation of the impact of genes on response to particular stressors. For example, it has been shown that the number and intensity of stressors influence the gene × environment interaction in depression (Caspì et al., 2003; Kendler et al., 2005). Further, we did not consider other sources of stress associated with depression, such as childhood maltreatment (Caspì et al., 2002, 2003), social support (Kaufman et al., 2004) or other lifetime traumas (Kendler et al., 1993). Third, the present work did not allow evaluation of the independent effects of the exposure to stressors alone or the genotype alone. On the other hand, the ‘case-only’ design has been reported to result in greater precision in estimating interactions than control-case investigations (Piegorsch et al., 1994). Finally, the ‘case-only’ design requires the assumption that exposure is independent from genotype, but genetic influences on exposure to adverse life events in mood-disorder patients have been hypothesized (Kendler et al., 1993). On the other hand, both Caspi et al. (2003) and Kendler et al. (2005) did not report an influence of SERTPR on exposure to stressors.

Ethnic origin is a frequent cause of stratification bias, but our sample was composed of subjects mainly collected in the North of Italy with Italian antecedents for at least two generations. Italy is characterized by a substantial genetic homogeneity, even if genetic heterogeneity has been evidenced for some isolated populations, such as Sardinia (Cavalli-Sforza, 1994; Gasparini et al., 1997). However, no subjects from Sardinia were included in the present study.

In conclusion, the present study supports previous evidence of an effect of SERTPR on abnormal responses to stressful events and SERTPR is hypothesized here to lead to the onset of mood disorders via its influence on the reaction to adversities. Further, our
data suggest an important role of this variant in females and as a factor risk for major depression but not mania and BP. In addition, we found the Met variant of COMT even more associated with stressors than the short SERTPR variant, having a great effect both in females and males, and representing a risk factor for both major depression and BP. Prospective studies are recommended to investigate the role of these genetic variants in the onset of both UP and BP depression.

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Statement of Interest

None.

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