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Subtle gene–environment interactions driving paranoia in daily life

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It has been suggested that genes impact on the degree to which minor daily stressors cause variation in the intensity of subtle paranoid experiences. The objective of the present study was to test the hypothesis that catechol-*O*-methyltransferase (COMT) Val[158]Met and brain-derived neurotrophic factor (BDNF) Val[66]Met in part mediate genetic effects on paranoid reactivity to minor stressors. In a general population sample of 579 young adult female twins, on the one hand, appraisals of (1) event-related stress and (2) social stress and, on the other hand, feelings of paranoia in the flow of daily life were assessed using momentary assessment technology for five consecutive days. Multilevel regression analyses were used to examine moderation of daily life stress-induced paranoia by COMT Val[158]Met and BDNF Val[66]Met genotypes. Catechol-*O*-methyltransferase Val carriers displayed more feelings of paranoia in response to event stress compared with Met carriers. Brain-derived neurotrophic factor Met carriers showed more social-stress-induced paranoia than individuals with the Val/Val genotype. Thus, paranoia in the flow of daily life may be the result of gene–environment interactions that can be traced to different types of stress being moderated by different types of genetic variation.

Keywords: Brain-derived neurotrophic factor, catechol-O-methyltransferase, paranoia, psychoses, risk factors, schizophrenia, stress, twins

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Paranoid thoughts in healthy individuals [subclinical paranoia (Combs & Penn 2004; Fenigstein & Vanable 1992)] represent a common and psychometrically accessible phenomenon, with at least 10–15% of the general population regularly experiencing them (Freeman & Garety 2006). It has been suggested that paranoid thoughts in healthy individuals are on the same continuum as paranoid delusions in psychotic patients (Combs & Penn 2004; Fenigstein & Vanable 1992). Studies using momentary assessment technology (Delespaul 1995; DeVries 1992) have shown that individuals display stable differences in their tendency to respond with paranoid and other psychotic experiences to small daily life stressors and that some of this variation may represent the behavioural expression of genetic risk for severe psychotic disorders (Myin-Germeys *et al.* 2005a), mediated possibly by underlying abnormal dopamine reactivity (Myin-Germeys *et al.* 2005b).

The enzyme catechol-*O*-methyltransferase (COMT) plays a critical role in the degradation of dopamine. The gene contains a functional polymorphism (Val[158]Met) with two common variants (Val and Met), corresponding to high and low COMT activity, respectively. Increased COMT activity may result in increased levels of mesolimbic dopamine signalling and increased risk for delusions and hallucinations (Akil *et al.* 2003; Bilder *et al.* 2004). Given the fact that stress similarly affects subcortical dopamine release (Pruessner *et al.* 2004; Wand *et al.* 2007), synergistic COMT–stress interactions may be hypothesized.

Brain-derived neurotrophic factor (BDNF) is likely to play a role in stress-related disorders, such as anxiety and depression (Chen *et al.* 2006; Duman 2004; Hashimoto 2007; Santarelli *et al.* 2003). Extensive literature documents that stress (acute, chronic, physical or social stress such as social isolation and social defeat) decreases BDNF expression in the hippocampus (Duman & Monteggia 2006; Kozlovsky *et al.* 2007). A Val[66]Met functional polymorphism in the gene encoding BDNF has been the focus of much recent investigation. The Valine (Val) variant is associated with higher neuronal BDNF secretory activity than the methionine (Met) variant (Chen *et al.* 2004). Met carriers may be more sensitive to stress-induced BDNF depletion and may thus experience more extreme behavioural responses to stress compared with Val/Val subjects. Meta-analyses yield conflicting results as to whether BDNF Val[66]Met is associated with schizophrenia (Gratacòs *et al.* 2007; Kanazawa *et al.* 2007; Xu *et al.* 2007), which may be indicative of underlying heterogeneity caused by gene–environment interaction (Van Os & Sham 2003). Given the close association between anxiety and paranoia (Combs & Penn 2004; Freeman & Garety 2004; Freeman *et al.* 2005; Martin & Penn 2001), it is attractive to speculate that BDNF–stress interactions may underlie symptoms of paranoia.

The aims of this study were to investigate the potential moderating effects of COMT and BDNF polymorphisms on

feelings of paranoia in response to stress. Given the fact that stressful environmental exposures associated with schizophrenia differ in the degree to which they may induce 'social defeat'-type psychological effects (Bjorkqvist 2001) in the realm of interpersonal interactions (Collip *et al.* 2008), two types of stressors were included in the current investigation: the first associated with events and the other with social interactions.

Materials and methods

Subjects

The study sample consisted of 621 participants, aged 18–61 years, who were taking part in an ongoing longitudinal, general population twin study on gene–environment interactions in psychiatric disorders. Most participants (twins) were recruited from the East-Flanders Prospective Twin Survey. This population-based survey has prospectively recorded all multiple births in the province of East-Flanders since 1964 (Derom *et al.* 2006; Loos *et al.* 1998). Zygosity was determined through sequential analysis based on sex, fetal membranes, blood groups and DNA fingerprints. The project was approved by the local ethics committee, and all participants gave written informed consent. Participants were white and of Belgian origin.

Experience sampling method

The experience sampling method (ESM) is a momentary assessment technique to assess subjects in their daily living environment and has been extensively validated for the use of immediate effects of stressors on mood (Csikszentmihalyi & Larson 1987; Delespaul 1995; DeVries 1992; Myin-Germeys *et al.* 2001; Wichers *et al.* 2007). Subjects received a digital wristwatch and a set of ESM self-assessment forms collated in a booklet for each day. The wristwatch was programmed to emit a signal (beep) at an unpredictable moment in each of ten 90-min time blocks between 0730 and 2230 h on five consecutive days. After each beep, subjects were asked to fill in the ESM self-assessment forms previously handed to them, collecting reports of thoughts, current context (activity, persons present and location), appraisals of current situation and mood. All self-assessments were rated on 7-point Likert scales. Trained research assistants with ample experience in momentary assessment techniques explained the ESM procedure to the participants during an initial briefing session, and a practice form was completed to confirm that subjects understood the rating scales. Subjects could call a telephone number in case they had questions or problems during the ESM sampling period. Subjects were instructed to complete their reports immediately after the beep, thus minimizing memory distortion, and to record the time at which they completed the form. To verify whether subjects had completed the form within 15 min of the beep, the time at which subjects indicated that they completed the report was compared with the actual time of the beep. All reports not filled in within 15 min after the beep were excluded from the analysis because previous work (Delespaul 1995) has shown that reports completed after this interval are less reliable and consequently less valid. In addition, subjects with less than 17 valid reports (of 50) were excluded from the analysis as previous work has shown that measures of individuals with less than 30% of completed reports are less reliable (Delespaul 1995).

Measures

Event stress and social stress in daily life

Appraisals of minor daily events, situational contexts and feelings of paranoia were collected at each beep within the ESM framework. For the measurement of event-related stress, subjects were asked to report the most important event that happened between the current and the previous beep. This event was subsequently rated on a 7-point bipolar scale (from -3 = very unpleasant, 0 = neutral to 3 = very pleasant). The scale was reversed so that higher scores represent higher disliking the event (event stress). Social stress was measured by asking subjects whether they were alone at the time of the beep. If not alone, they were asked whether they liked the company they were in at that moment. This was rated on a 7-point Likert scale [from 'not at all' (1) to 'very much' (7)]. The scale was reversed so that higher scores represent higher disliking of being in that company (social stress). To validate the measure of social stress, the association between the ESM item whether they liked the company they were with and another ESM item 'I would like this situation to be different' was calculated, yielding a significant correlation between the two ($r = 0.52$, $P < 0.001$).

Paranoia

The paranoia scores were derived from the ESM reports as described previously (Myin-Germeys *et al.* 2003, 2005a; Thewissen *et al.* 2008). They were assessed by the ESM item 'I feel suspicious' [from 'not at all' (1) to 'very' (7)].

To test whether the effects of social and event stress on paranoia level were independent of negative affect, the ESM-negative mood items (feeling insecure, lonely, anxious, guilty, down; hereafter 'negative affect') were entered separately into the model. These ESM items were rated on 7-point Likert scales [from 'not at all' (1) to 'very' (7)].

Genotyping

Placental tissue for DNA analysis was available for 156 participants, blood samples for 14, and buccal cell samples for 208, using a sterile swab specifically designed for the collection of buccal cell samples for DNA testing (Omni Swabs; Whatman plc, Brentford, UK).

Genomic DNA was extracted using QIAamp DNA Mini Kits (Qiagen, Venlo, the Netherlands) according to the appropriate protocol for each sample type. Catechol-*O*-methyltransferase $Val^{158}Met$ and BDNF $Val^{66}Met$ genotypes were determined by KBioscience (Hertz, UK) using their proprietary allelic discrimination assay (for details, see http://www.kbioscience.co.uk).

For every monozygotic (MZ) twin in the sample with genotypic data, the same genotypic data were included for the co-twin, under the assumption that both twins had identical genotypes.

Statistical analysis

ESM data have a hierarchical structure. Thus, multiple observations (level 1) were clustered within subjects (level 2), who were part of twin pairs (level 3). Multilevel random regression analysis is the method of choice to deal with data consisting of observations at more than one level in terms of unit of analysis by taking the variability associated with each level of nesting into account (Snijders & Bosker 1999). Thus, multilevel random regression analysis models both fixed and random effects. The fixed effects are interpreted similarly as standard regression coefficients and are estimated directly; the random effects portion of the model is specified by considering the nesting of the data. The XTMIXED command in STATA 10.0 (StataCorp 2007) was used to conduct multilevel linear regression analyses.

First, the increase in feelings of paranoia following event stress and social stress was assessed. Second, moderation of the stress-induced paranoia response by COMT (Val/Val, Val/Met, Met/Met) was examined, fitting the two-way interaction term between COMT genotype and stress in the model of paranoia. The same was carried out for the BDNF polymorphism. Effect sizes of interactions between the COMT and the BDNF variants on the one hand and event and social stress appraisals on the other were calculated by applying and testing the appropriate linear combinations using the STATA LINCOM command. Main effects and interactions were assessed by Wald test (Clayton & Hill 1993).

As subjects can differ in the number of beeps that they are actually in other people's company, all analyses for social stress were controlled for the number of observations each person contributed to the analyses to take into account possible systematic differences in appraisal of social events through, for example personality differences. All variables included in the analyses were standardized (by dividing the variables by their between-subject standard deviation), yielding standardized effect sizes.

Results

Sample

The total sample consisted of 621 white subjects, of which 610 participated in the ESM procedure. Thirty-one subjects were excluded because they had missing or less than 17 valid ESM self-reports, thus leaving 579 subjects with ESM measurements for feelings of paranoia. Subjects with less than 17 valid ESM self-reports did not differ in mean scores for event and social stress ($t = -0.34$, $P = 0.73$; $t = -1.35$, $P = 0.18$, respectively). However, there was a significant difference in reported paranoia scores ($t = -3.29$, $P = 0.001$), excluded subjects scoring higher. However, it is unclear whether these differences represent true differences in feelings of paranoia because the self-reports of the excluded subjects are less reliable. Also, in order for the difference in paranoia score to have biased the results, additional differential attrition for the stress scores would have been necessary as well, and this was not the case. Thus, a true difference in paranoia as a function of attrition would have affected generalizability of the findings rather than causing bias. Mean age of these subjects was 27.7 years (SD = 7.9 years, range 18–61 years). Of these subjects, 552 were female members of MZ and dizygotic twin pairs and 27 were non-twin sisters. A majority of 62% had a college or university degree, 36% completed secondary education and 1% had primary education only. The majority were currently employed (64% employed, 30% student, 3% unemployed and 3% homemaker). The mean score on the ESM paranoia item was 1.16 (SD = 0.63, range 1–7); mean score for event stress was −1.10 (SD = 1.56, range −3 to 3) and mean score for social stress was −5.39 (SD = 1.47, range −7 to −1). Eight subjects had incomplete ESM measurements with respect to event stress.

Of the 579 subjects with ESM measures of paranoia, COMT Val^{158}Met and BDNF Val^{66}Met genotype were available for 461 and 473, respectively. The frequencies of the three COMT genotypes were 24.5% Val/Val, 53.7% Val/Met and 21.8% Met/Met comparable with previous reported frequencies (Henquet *et al.* 2006; Stefanis *et al.* 2004) and in Hardy–Weinberg equilibrium ($\chi^2 = 3.02$, df = 1, $P = 0.08$). The COMT Met/Met variant was the reference category.

The frequencies of the three BDNF genotypes were 64.1% Val/Val, 30.7% Val/Met and 5.2% Met/Met comparable with previous reported frequencies (Lang *et al.* 2005; Oroszi *et al.* 2006; Schule *et al.* 2006) and in Hardy–Weinberg equilibrium ($\chi^2 = 1.51$, df = 1, $P = 0.22$). As the BDNF Met/Met genotype group was very small ($n = 23$), statistical analyses were not conducted separately in this group of subjects, as they would be underpowered. The Met/Met group was not simply added to the Val/Met group because differential pathophysiological mechanisms with regard to mental health outcomes may apply to each genotype (Chen *et al.* 2004). The Val/Val variant was the reference category.

Stress-induced paranoia response in the flow of daily life

In 5189 observations of a total of 20 837 (24.9%), subjects indicated that they were alone and thus not in the company of other persons. These observations were therefore not informative with respect to social stress and were not used in the present analyses for social stress.

Event stress was correlated significantly with social stress ($r = 0.27$, df = 569, $P < 0.001$). Both event stress ($\beta = 0.08$, $P < 0.001$) and social stress ($\beta = 0.06$, $P < 0.001$) were significantly and positively associated with feelings of paranoia, indicating that experiencing stressful situations are associated with elevated levels of feeling suspicious. When controlling for negative affect, the association for event stress was reduced but remained highly significant ($\beta = 0.02$, $P = 0.001$), whereas the association with social stress was reduced more and became non-significant ($\beta = 0.01$, $P = 0.07$).

Moderation of stress sensitivity by COMT

Event stress

There were no significant main effects of COMT genotype on feelings of paranoia or on event stress. There was evidence that COMT genotype moderated event-related stress sensitivity. Thus, while COMT Val/Met carriers did not differ significantly from Met/Met carriers ($\beta = 0.001$, $P = 0.94$) and this effect remained non-significant after controlling for negative affect ($\beta = -0.005$, $P = 0.67$), COMT Val/Val carriers reported significantly more feelings of paranoia in association with event stress compared with Met/Met carriers ($\beta = 0.05$, $P = 0.002$). This effect was essentially unchanged after controlling for negative affect ($\beta = 0.05$, $P = 0.001$). In Table 1, unadjusted beta-coefficients are given, stratified by values of event stress relative to the reference category (Fig. 1). The greatest degree of separation in effect size between Val/Val and Met/Met was in the highest categories of unpleasant ($\chi^2 = 4.83$, df = 1, $P = 0.03$) and very unpleasant appraisals of events ($\chi^2 = 29.18$, df = 1, $P < 0.001$).

Social stress

Catechol-*O*-methyltransferase had a significant main effect on social stress. Catechol-*O*-methyltransferase Val/Val ($\beta = -0.15$, $P = 0.04$) and Val/Met carriers ($\beta = -0.15$, $P = 0.02$) reported significantly less social stress than Met/Met carriers. This effect remained significant after controlling for negative affect (Val/Met: $\beta = -0.16$, $P = 0.01$; Val/Val: $\beta = -0.16$, $P = 0.02$). Catechol-*O*-methyltransferase genotype did not interact with social stress in the model of paranoia (Val/Met: $\beta = 0.02$, $P = 0.10$; Val/Val: $\beta = 0.01$, $P = 0.41$), and this remained so after controlling for negative affect (Val/Met: $\beta = 0.004$, $P = 0.74$; Val/Val: $\beta = 0.01$, $P = 0.40$).

Moderation of stress sensitivity by BDNF

Social stress

There were no significant main effects of BDNF genotype on paranoia, event or social stress. Brain-derived neurotrophic factor interacted with social stress in the model of paranoia. Thus, BDNF Val/Met carriers showed significantly more feelings of paranoia to stressful social situations than BDNF Val/Val carriers ($\beta = 0.04$, $P < 0.001$). This effect was reduced ($\beta = 0.02$, $P = 0.07$) when the analysis was controlled for

Table 1: Beta-coefficients and *P*-values of interaction term 'event stress' × 'COMT Val158Met genotype' on paranoia score, separate for each value of event stress relative to the reference category

		Met/Met		Val/Met		Val/Val	
		β-coefficient	*P*-value	β-coefficient	*P*-value	β-coefficient	*P*-value
Event stress							
'Very pleasant'	−3	—	—	—	—	—	—
	−2	−0.054	0.307	0.027	0.418	0.062	0.250
	−1	0.093	0.128	0.066	0.073	−0.008	0.888
'Neutral'	0	0.079	0.155	0.066	0.054	0.102	0.052
	1	0.117	0.180	0.073	0.195	0.157	0.057
	2	0.180	0.058	0.281	<0.001	0.492	<0.001
'Very unpleasant'	3	0.246	0.008	0.381	<0.001	0.996	<0.001

negative affect. In Table 2, unadjusted beta-coefficients are given, stratified by values of social stress relative to the reference category (Fig. 2). Again, most separation was towards higher values of stress; differences in effect size between the Val/Val and the Val/Met variants were significant for unpleasant ($\chi^2 = 4.12$, df $= 1$, $P = 0.04$) and very unpleasant ($\chi^2 = 12.77$, df $= 1$, $P = 0.0004$) appraisals of company.

Event stress

Brain-derived neurotrophic factor genotype did not interact with event stress in the model of paranoia ($\beta = 0.05$, $P = 0.33$), and this remained so after controlling for negative affect ($\beta = -0.01$, $P = 0.66$).

Discussion

The present study found that minor stressful events in general as well as social stressful daily life situations are associated with an increase in feelings of paranoia in the flow of daily life, in line with previous research (Malla *et al.* 1990; Myin-Germeys *et al.* 2005a; Norman & Malla 1991). The results confirm that paranoia is a highly dynamic and fluctuating mental state, variation of which is strongly associated with environmental stimuli (Freeman *et al.* 2008; Thewissen *et al.* 2008).

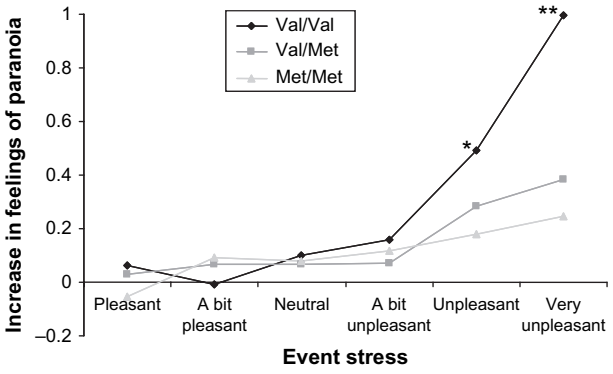

Figure 1: Effect sizes of event stress on feelings of paranoia: effect sizes of the paranoia response of event stress levels 'pleasant' to 'very unpleasant, relative to the paranoia response of the reference category 'very pleasant', stratified by COMT Val158Met genotype. $*P < 0.05$ and $**P < 0.001$ indicate that the difference between COMT Met/Met and COMT Val/Val is significant for the given category of event stress.

Catechol-O-methyltransferase, BDNF, stress and paranoia

There were no main effects for the COMT Val[158]Met polymorphism on feelings of paranoia. This is in accordance with two recent meta-analyses that found no or little evidence for an association between the COMT Val[158]Met polymorphism and the familial vulnerability to psychoses (Fan *et al.* 2005; Munafo *et al.* 2005). Absence of genetic main effects is possible in the presence of strong gene–environment interactions, which can reduce the power of non-stratified molecular genetic studies to such an extent that detection of association becomes all but impossible (Van Os & Sham 2003). Thus, the influence of COMT Val[158]Met on psychosis phenotypes may be better understood in terms of gene–environment interactions rather than in terms of genetic main

Table 2: Beta-coefficients and *P*-values of interaction term 'social stress' × 'BDNF Val66Met genotype' on paranoia score, separate for each value of social stress relative to the reference category

		Val/Val		Val/Met	
		β-coefficient	*P*-value	β-coefficient	*P*-value
Social stress					
'I like much'	1	—	—	—	—
	2	−0.010	0.723	−0.012	0.767
	3	0.0672	0.019	0.038	0.380
	4	0.100	<0.001	0.123	0.006
	5	0.167	0.003	0.348	<0.001
	6	0.185	0.009	0.424	<0.001
'Not at all'	7	0.0853	0.114	0.459	<0.001

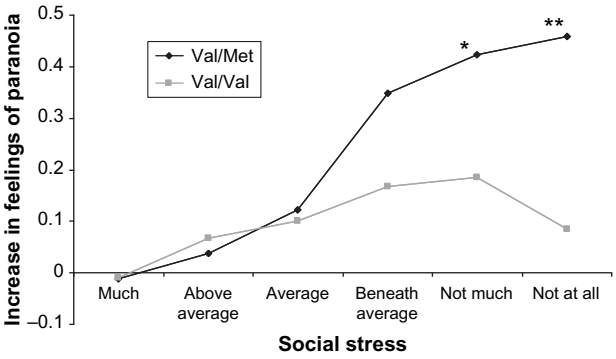

Figure 2: Effect sizes of social stress on feelings of paranoia: effect sizes of the paranoia response of social stress levels of liking the company much to not liking the company at all relative to the paranoia response of the reference category of liking the company very much, stratified by BDNF Val66Met. Brain-derived neurotrophic factor Met/Met is omitted from the analyses because of small group size. $*P < 0.05$ and $**P < 0.001$ indicate that the difference between BDNF Val/Val and BDNF Val/Met is significant for the given category of event stress.

effects. The results showed that COMT moderated the effect of event stress on feelings of paranoia, with Val/Val carriers showing more feelings of paranoia in response to unpleasant events compared with Met/Met carriers, even after controlling for other forms of negative affect. The findings are in agreement with those described by Stefanis *et al.* (2007), who reported that environmental stressful changes associated with induction into compulsory military service led to an increase in psychotic symptoms, the effect being larger in Val carriers than in Met/Met subjects. Our findings do not agree with another previous study (Van Winkel *et al.* 2008), which showed that Met/Met patients showed the largest increase in ESM delusional ideation in reaction to ESM event stress, whereas there were no significant interactions between COMT and ESM event stress in control subjects. However, the study sample was predominantly male and consisted of cannabis users with a psychotic disorder and non-psychotic cannabis users, which limits comparability with the present results.

In contrast to the results for event stress, COMT did not moderate the effect of social stress on feelings of paranoia. However, there was a significant gene–environment correlation (genetic control of exposure to the environment) for the COMT genotype in relation to social stress. Met/Met carriers had higher social stress scores than Val carriers. These results suggest that while Val carriers may have a lower tendency to appraise social company as unpleasant, they are prone to experience more paranoid feelings in response to stressful events.

In contrast to the COMT Val^{158}Met polymorphism, there was no interaction between BDNF Val^{66}Met and event-related stress reactivity. Rather, BDNF Val^{66}Met interacted with social stress in its effect on feelings of paranoia. Thus, the effects of BDNF Val^{66}Met on behaviour may also be understood in terms of gene–environment interactions. The different findings for the COMT and BDNF polymorphism suggest that both may impact on paranoia through different pathways, the first by acting on stressful events and the second by acting on stressful social situations. High levels of COMT may result in enhanced reactivity of dopamine neurons in response to environmental stimuli so that exposure to even minor stressors can result in an excessive dopamine response (Laruelle 2000; Myin-Germeys *et al.* 2005b). Catechol-*O*-methyltransferase activity is thought to be particularly important for the regulation of prefrontal dopamine levels and to influence mesolimbic dopaminergic activity only indirectly by controlling prefrontal feedback mechanisms (Deutch *et al.* 1990; Tunbridge *et al.* 2006). The presence of the high-activity Val allele results in increased metabolism of dopamine in the prefrontal cortex and to decreased tonic inhibition of downstream projections, leading to increased phasic dopamine in mesolimbic areas. Environmental risk factors may disrupt the inhibitory influence the prefrontal cortex has on mesolimbic activity, leading to an enhanced responsiveness of mesolimbic dopamine signalling to stress (Deutch *et al.* 1990). Stimulus-independent release of dopamine may take over the normal process of contextually driven salience attribution, resulting in aberrant assignment of salience to environmental events and internal representations (Kapur 2003). Myin-Germeys *et al.* (2005b) have shown that sensitization of the dopamine system may indeed underlie psychotic reactivity to daily life stressors in individuals at elevated genetic risk for psychosis. Cougnard *et al.* (2007) suggested that relatively common, subclinical developmental psychotic experiences may become abnormally persistent when synergistically combined with environmental risk factors, which may impact on sensitization, such as cannabis, childhood trauma or urbanicity.

The results of the present study suggest that the effect of COMT on event stress reactivity may be relatively independent of negative affect. In contrast, the interaction between BDNF and social stress was reduced after controlling for negative affect, suggesting mediation by negative affect. Brain-derived neurotrophic factor is associated with stress-related disorders, such as anxiety and depression (Chen *et al.* 2006; Duman 2004; Hashimoto 2007; Santarelli *et al.* 2003). A prenatal genetic manipulation of the BDNF gene causing fetal BDNF depletion results in depressive, aggressive and anxiety-related behaviours in adult mice (Chan *et al.* 2006). This behavioural effect may be mediated by BDNF signalling through amygdaloid structures. Experimentally reduced BDNF expression in the central and medial amygdala in rats resulted in increased anxiety-like behaviour (Pandey *et al.* 2006). Berton *et al.* (2006) showed that repeated exposure to social defeat stress sensitizes the ventral tegmental area-nucleus accumbens pathway in mice only when BDNF function is intact, and BDNF deletion requires repeated exposure to social defeat stress to result in social avoidance behaviour. This suggests that the effect of BDNF would mainly come to the fore during negative social situations, Met carriers showing a greater degree of anxious responses to these minor social stressors, which in turn could lead to feelings of paranoia. In line with this hypothesis was the finding by Wichers *et al.* (in press), using the same sample, that BDNF Val^{66}Met Met carriers showed an increased negative affective response to social stress, but not event

stress, compared with Val/Val subjects. Thus, there may be two pathways leading to feelings of paranoia. Individuals may come to experience paranoid ideas through abnormal dopamine sensitization, mediated by the COMT Val^{158}Met polymorphism. Alternatively, negative affect can lead to increased feelings of paranoia and may be mediated by genes such as BDNF that are involved in depression.

Clinical significance

Stress exposures alone, and in interaction with genetic vulnerability, showed statistically significant associations with daily life stress sensitivity. However, the question rises to what extent these effects represent clinically meaningful findings. Generally, effect sizes of around 0.2 are considered relevant but low and those around 0.8 high (Cohen 1988). In the current study, the overall effect sizes vary but are generally low (less than 0.2). However, when examining the beta-coefficients for each of the separate values of stress (Tables 1 and 2), effect sizes for the COMT Val/Val and the BDNF Val/Met carriers are clinically meaningful for the highest levels of stress. Furthermore, the results of the current study were derived from data reflecting daily life context of repetitive events (unlike effects reported in most unilevel studies) indicating cumulative impact over time. For example, the findings indicate that the genetic vulnerability for psychotic reactivity to minor stressors is not present only once in a single event but impacts repeatedly in daily life person–context interactions.

Limitations

Several methodological issues need to be considered. First, the measures of event-related stress and paranoia are based on paper-and-pencil self-report. Therefore, concerns exist about the lack of control over participant compliance with the ESM protocol (Broderick *et al.* 2004; Kudielka *et al.* 2003). In particular, fixed time sampling protocols may be problematic and can bias results. However, the present study did not use a fixed time sampling frame, and our ESM procedure was validated in a previous study (Jacobs *et al.* 2005). Part of the same sample as described in the present analysis (Jacobs *et al.* 2005) was instructed to take, during the ESM procedure, saliva samples at each of the 10 unpredictable moments during the five consecutive days. Participants recorded collection times, unaware that compliance with the sampling protocol was investigated by means of electronic monitoring devices. Results showed that compliance was high (more than 90%), and inclusion of the inaccurately timed samples did not distort the data (Jacobs *et al.* 2005). Therefore, results from the ESM procedure in the present study can be considered valid.

Second, the assessment of paranoia contained only one item ('I feel suspicious'). Nevertheless, paranoia is the most common abnormal belief found in patients with psychosis and psychometrically accessible in healthy volunteers (Garety & Hemsley 1987; Jorgensen & Jensen 1994).

Third, the present analyses are cross-sectional, making it impossible to assess causality. Feelings of paranoia may be a reaction to event-related or social stressors, or feeling suspicious may bias a person to interpreting (social) events as being more unpleasant (more stressful). Possibly, paranoid beliefs arise from minor daily stressors as well as generate negative evaluations of (social) events. However, even if the direction of association was reversed, what holds is that the COMT and BDNF genotypes have an impact on the associations between daily stressors and feelings of paranoia.

Fourth, the sample consisted of female participants only. A previous study (Bolger *et al.* 1989) showed that women reported more distress in relation to daily stressors than men. Consistent with these findings, Myin-Germeys *et al.* (2004) showed a significant increase in emotional reactivity to daily stress in women compared with men. Sex differences in feeling suspicious are also expected because previous research found higher levels of positive schizotypy in females compared with males (Jackson & Claridge 1991; Maric *et al.* 2003; Raine 1992), and there is evidence that sex differences in patients with schizophrenia are particularly present for persecutory delusions (Goldstein *et al.* 1990). Last, there are studies that suggest that there may be sex differences with respect to COMT (Alsobrook *et al.* 2002; Kates *et al.* 2006; Zinkstok *et al.* 2006). Women have been shown to have markedly lower COMT activity than men (Boudikova *et al.* 1990; Floderus *et al.* 1981), presumably because of down-regulation of COMT by oestrogens (Jiang *et al.* 2003; Xie *et al.* 1999). Analogue to the high-activity Val allele being associated with increased feelings of paranoia, male populations may therefore show higher levels of paranoia. Therefore, the present findings cannot necessarily be extrapolated to a male population.

The present study included only a single variant of the COMT and BDNF genes. Although the COMT Val158Met polymorphism is the most frequently investigated COMT polymorphism capturing most of the genetic functional variation, some studies suggest that the Val158Met polymorphism may not capture all functional variation in COMT (Meyer-Lindenberg *et al.* 2006; Shifman *et al.* 2002, 2004). Haplotypes defined by several polymorphism gene sites may be provide better measures than single nucleotide polymorphisms for analysis of genetic variations (Nackley *et al.* 2006). Catechol-*O*-methyltransferase haplotypes can modulate protein expression by altering messenger RNA secondary structure (Nackley *et al.* 2006), and recent studies have shown that COMT haplotypes may be more strongly associated with schizophrenia risk or endophenotypes for schizophrenia than the Val158Met polymorphism alone (Diaz-Asper *et al.* 2008; Meyer-Lindenberg *et al.* 2006; Shifman *et al.* 2002, 2004). Likewise, BDNF haplotypes may capture more of the genetic variation than the Val66Met polymorphism alone, although this remains to be determined (Gratacòs *et al.* 2007).

Finally, multiple testing was not taken into account because we tested a limited number of main hypotheses, and outcomes were correlated across analyses, obviating the need for conservative corrections such as Bonferroni. The probability of false-positive results is low in the present study: more tests were significant than might be expected by chance alone. Thus, of the 20 multilevel regression analyses performed, 8 showed a P-value of <0.05, while only 1 significant finding would have been expected by chance alone.

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