Depressed patients in remission show an interaction between variance in the mineralocorticoid receptor NR3C2 gene and childhood trauma on negative memory bias

Janna N. Vrijsen, Susanne Vogel, Alejandro Arias-Vásquez, Barbara Franke, Guillén Fernández, Eni S. Becker, Anne Speckens and Iris van Oostrom

Background Genetic, environmental, and cognitive factors play a role in the development and recurrence of depression. More specifically, cognitive biases have been associated with depression risk genes and life events. Recently, the mineralocorticoid receptor NR3C2 gene, and in particular the rs5534 polymorphism, has been associated with negative memory bias, at least in healthy individuals who experienced severe life adversity. The current study examined the interaction between the rs5534 genotype and different types of adverse life events in a sample of depressed patients in remission.

Materials and methods A total of 298 depressed patients in remission performed an incidental emotional memory task (negative and positive words). Life adversity, childhood trauma, and recent adversity were measured using a self-report questionnaire. NR3C2 rs5534 by life adversity, as well as childhood trauma and recent adversity interactions were analyzed for negative and positive memory bias using analyses of covariance.

Results The significant interaction between rs5534 and childhood trauma on negative memory bias (P = 0.046) indicated that risk ‘A’ allele carriers with childhood trauma tended to show more negative memory bias compared to individuals homozygous for the G allele who had experienced childhood trauma and A allele carriers without childhood trauma. No interaction effects with life adversity or recent adversity were found. Also, no main effect of rs5534 on memory bias was found, although we had insufficient power for this analysis.

Conclusion An association of the NR3C2 gene and childhood trauma with negative memory bias was found in depressed patients in remission, which extends previous findings in a healthy population. Psychiatry Genetics 00:000–000 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Keywords: childhood trauma, cognitive bias, depression, life adversity, memory bias, mineralocorticoid receptor, NR3C2 gene

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Introduction Depression is a complex multifactorial condition with considerable heritability, but genetic studies so far have yielded mixed findings (Sullivan et al., 2000). A potential way to increase the power to detect genetic effects is to investigate the information-processing tendencies of depression (Gottesman and Gould, 2003; Kendler and Neale, 2010). Currently, depressed patients show better memory for negative than for positive information (Matt et al., 1992; Ridout et al., 2003; Mathews and MacLeod, 2005; Gotlib and Joormann, 2010). Upon remission, stress and negative mood reactivate biased processing (McCabe et al., 2000). Moreover, biased memory for emotional information is considered a rather stable cognitive vulnerability factor for depression (Hasler et al., 2004; De Raedt and Koster, 2010). In depressed patients in remission, functional anomalies in relevant brain areas (i.e. ventrolateral prefrontal cortex and cuneus) have been associated with mood regulation by positive memory processing (Foland-Ross et al., 2013). Several recent studies have successfully associated depression candidate genes with biased processing and life adversity (Firk and Markus, 2007; Kwang et al., 2010; Van Oostrom et al., 2012; Gibbs et al., 2013; Woudstra et al., 2013; Asarnow et al., 2014; Vrijsen et al., 2014a). These studies generally found that explicit memory for emotional stimuli was associated with different depression candidate genes (i.e. SLC6A4, BDNF, COMT, PCLO, ADRA2B). For example, the study by Van Oostrom et al. (2012) found less positive memory bias in male BDNF risk allele (Met) carriers who reported adverse childhood events compared with Val/Val homozygotes with childhood adversity. The study by Asarnow et al. (2014) reports more positive memory bias in COMT nonrisk allele (Val) homozygote than in Met-homozygote girls who are at risk for depression because of having a recurrent depressed childhood trauma.
mother. Generally, the interaction between genetic susceptibility and adverse life events is considered an important mechanism in the development of depression as life adversity may modulate genetic effects (Caspi et al., 2003, 2010; Caspi and Moffitt, 2006). Adversity experienced during childhood, when the brain is still developing, may be particularly relevant to cognition (Perry et al., 1995). This is in line with the cognitive models of depression that state that the experience of negative events in childhood often leads to dysfunctional basic assumptions about the self and the world, constituting the biased processing that contributes toward the susceptibility for depression or relapse (Beck, 1976, 2008; Bower, 1981).

A recent study examined the association of the mineralocorticoid receptor NR3C2 gene with negative memory bias in a healthy population (N = 514) using a novel genome-wide association approach (Vogel et al., 2014). The NR3C2 gene codes for the mineralocorticoid receptor, which interacts not only with adolsterone but also, interestingly, in several organs including the brain, with the stress hormone cortisol. Together with the glucocorticoid receptor, the mineralocorticoid receptor regulates the hypothalamus–pituitary–adrenal axis and responds to stress-induced increases in cortisol levels through which it presumably mediates the effects of stress (Joëls et al., 2008). NR3C2 has been associated with emotional memory, anxiety, depression, ruminations, and hopelessness (the latter two being characteristics of depression; Hlavacova et al., 2010; Karst et al., 2010; Otte et al., 2010; Klok et al., 2011a, 2011b). The study by Vogel et al. (2014) implicated the single-nucleotide polymorphism rs5534 as a functional element in the NR3C2 gene to be associated with negative memory bias, especially in individuals who had experienced adverse life events. Individuals homozygous for the ‘A’ allele with high life adversity showed the strongest negatively biased memory processing. Life adversity was assessed using a questionnaire and explicit verbal emotional memory bias was measured using a computer task.

The current study aimed to extend the previously reported interaction between the NR3C2 rs5534 polymorphism and life adversity on negative memory bias in a sample of depressed patients in remission. Examination of interactions between genes and environment in an affected sample is rather novel. A depressed sample in remission can offer insights above and beyond the study of healthy individuals as results can speak to the generalizability of gene–environment interactions. Moreover, selection of a sample of depressed patients in remission offers the opportunity to study genetic risk effects in affected individuals, without current cognitive concomitants or depressive states affecting biased processing and dominating small genetic effects, as in a currently depressed sample (Bhagwagar and Cowen, 2007).

The previous study by Vogel et al. (2014) examined the modulating effect of low versus high life adversity by combining traumatic and more generally adverse events (e.g. ‘sexual abuse’ vs. ‘illness of a close relative’) from different stages of life (i.e. childhood as well as recent events). Besides examining the association between the NR3C2 rs5534 polymorphism and low versus high life adversity on memory bias in an affected sample, the current study aimed to shed light on the differential effect of different types of life adversity on the mineralocorticoid system. The specificity of adverse life events was examined by differentiating between the influence of childhood traumatic events and recent adversity on the association between the NR3C2 rs5534 polymorphism and memory bias. The current study used a different memory task to assess biased explicit memory for verbal stimuli. In contrast to the Vogel et al. (2014) study, a sad mood induction procedure was used to reactivate biased processing and align mood state levels in the depressed sample in remission as depressotypic processing styles re-emerge especially after stress such as a transient sad mood state (Segal and Ingram, 1994). NR3C2 gene A allele carriers who experienced high life adversity, childhood trauma, and/or recent adversity were expected to show the strongest negatively biased memory.

Materials and methods

Participants

This study is part of a larger study, which aims to link cognitive biases to genetic susceptibility for depression (see also Vrijens et al., 2014a, 2014b, 2014c). A total of 337 individuals who experienced one or more depressive episodes in the past and were in remission at the time of testing participated in the study. Of this sample, 314 participants executed the memory task; 15 of these participants did not adhere to the instructions, resulting in unusable data. A total of 320 participants agreed to provide a blood sample; genotyping failed for one participant. Complete genotype, life events, and memory bias data were available for a total of 299 depressed patients in remission. One participant did not provide information on medication use and was excluded, resulting in a sample of 298 patients in remission for the main analyses. The depressed patients in remission were recruited at the Department of Psychiatry of the Radboud University Medical Centre in Nijmegen, the Netherlands, as well as other regional outpatient psychiatric services. Participants were included if they fulfilled the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) (American Psychiatric Association, 1994) for a previous depressive episode. Exclusion criteria were as follows: current depressive episode, current or lifetime bipolar disorder, schizophrenia, and other current or former psychotic disorders, alcohol or substance abuse within the past 6 months, deafness, blindness, neurological disorder, sensorimotor handicaps, and intellectual disability. Patients with a previous major
depressive episode with psychotic features were allowed to participate. Patients with comorbid disorders, such as anxiety disorder, attention deficit hyperactivity disorder, and personality disorder, were included, when not the primary (former) diagnosis. Trained professionals interviewed eligible participants using the Structured Clinical Interview for the DSM-IV Axis-I disorders (SCID-I; First et al., 1996). The SCID-I has been shown to have good reliability (Ske et al., 1991; Williams et al., 1992). A psychiatrist (A.S.) was consulted before inclusion in case of recent recovery from a depressive episode with lingering depressive symptoms. Current use of psychotropic medication that might influence memory bias was assessed by a psychiatrist (A.S.). Depressive symptomatology was measured using the Beck Depression Inventory (BDI-II; Beck et al., 1996). Participants received a gift certificate for their participation. The study had been approved by the Dutch central medical ethics review board (P04.0599C) and was carried out in accordance with guidelines and regulations for human studies.

Measurements
Stressful life events
Stressful childhood events were assessed using an adapted version of the Life Events Questionnaire (Brugha and Cragg, 1990). This version has been used previously in comparable studies (Gerritsen et al., 2011; Van Oostrom et al., 2012; Vogel et al., 2014). Participants were asked to indicate whether they had experienced a set of life events before the age of 16 years, after the age of 16, and/or within the last year. In line with Vogel et al. (2014), a life adversity variable was calculated as the sum of all experienced events. Similar to the study of Vogel et al. (2014), we stratified our sample according to the number of adverse events using a median split into a low life adversity group (below the median of 4 events) and a high life adversity (≥4 events) group.

Furthermore, a variable of childhood traumatic events was calculated. This variable indicated whether or not participants had experienced traumatic events (aggression and/or abuse) before the age of 16 years (no vs. yes). A recent adversity variable was also calculated. This variable reflected whether participants had experienced health problems, health problems of a close one, death of a family member, problems within the romantic relationship, divorce, a conflict at work, monetary problems, or legal issues within the last year (no vs. yes).

Mood induction
Before the task, participants watched a highly emotional negative film segment from the movie 'Sophie’s choice' (Erber and Tesser, 1992). Participants were instructed to allow the emotionality of the film influence their mood as much as possible and to maintain the sad mood state.

Memory bias
Participants were presented sequentially with 12 depression-specific negative and 12 positive words in fixed randomized order, with the restriction that no more than two words of the same valence would be presented consecutively. Words were selected from two databases (Dutch translation of the Affective Norms for English Words database; Bradley and Lang, 1999; Phaf et al., 2006). Each word was presented for 10 s in capital black letters against a white background. To make encoding self-referential, participants were instructed to vividly imagine themselves in a scene with the presented word. Before the onset of the next trial, participants were asked to rate how well they could imagine themselves in the scene on a five-point Likert scale. This task was followed by a short paper-and-pencil distraction task (Raven matrices; Raven, 1958). Upon completion, participants were instructed to return to the computer for an announced free recall test of the 12 depression-specific negative and 12 positive words. Participants were instructed to type in all the words that they could remember within 3 min. Spelling errors were allowed as all responses that did not match exactly with study words were checked manually. The proportion of negative recall (negative memory bias) and the proportion of positive recall (positive memory bias) were calculated. The number of correctly recalled words in a given valence category was divided by the total number of correctly recalled words. For example, a negative memory bias score of 0.25 indicated that 25% of the words that the participant recalled had a depressotypic negative emotional content. This method of scoring ensures that memory bias is not confounded with possible differences in overall memory performance (Gotlib et al., 2004).

Genotyping
Blood was taken by venapuncture and DNA was isolated using standard protocols. Molecular analyses were carried out in a CCKL-accredited laboratory at the Department of Human Genetics of the Radboud University Medical Centre. The NR3C2 rs5534 polymorphism was genotyped using TaqMan analysis (Watson and Li, 2005). The call rate was 99.7% (one missing genotype). The NR3C2 genotype distribution in patients in remission was AA: N = 43 (14.4%), AG: N = 161 (53.8%), and GG: N = 95 (31.8%). Testing for Hardy–Weinberg equilibrium did not show deviations from the expected distribution of genotypes (χ² = 3.65, d.f. = 1, P = 0.056). For reference, the genotype distribution in the Vogel et al. (2014) population was similar: 18.9% AA, 46.5% AG, and 34.6% GG. Because our sample was smaller than that in the study by Vogel et al. (2014) and because no model for the association of the genotype groups with memory bias was present, genotype groups were created on the basis of allele frequency: carriers of at least one risk allele (A homozygotes and heterozygotes) were compared with GG individuals (G homozygotes).
Procedure
The participants were invited for the study by means of an information letter. Before the onset of the experiment, participants were again provided the opportunity to ask questions and they were instructed that they could stop at any time, without specifying a reason. Subsequently, they completed an informed consent form and the questionnaires before performing the mood induction and memory task as described. Finally, participants were debriefed before they were rewarded for their participation.

Statistical analyses
Genotype groups were compared on relevant demographic and clinical variables using t-tests and $\chi^2$ tests (categorical variables). The interaction effect of genotype (AA/AG vs. GG) and life adversity (no vs. yes for all events, childhood trauma, and recent adversity) on the proportion of negative and positive recall was examined using analysis of covariance (ANCOVA). Because of their known effect on cognitive functioning and emotional processing, age, sex, and medication use were included as covariates in the analyses. Because sex differences have been reported for the NR3C2 association with depression (Klok et al., 2011b), we also used an exploratory approach to examine the genotype and life adversity (no vs. yes for all events, childhood trauma, and recent adversity) interaction analyses in male and female participants separately.

Results
Sample descriptives are presented in Table 1. The genotype groups did not differ on age, sex, medication use, depressive symptomatology (BDI-II total score), number of past episodes, the number of adverse life events, or the percentage of individuals who had experienced life adversity, childhood trauma, or recent adversity.

NR3C2 rs5534 genotype main effect
The ANCOVA yielded no main effect of the NR3C2 rs5534 genotype on negative memory bias [$F(1,291) = 0.50$, $P = 0.481$, $f = 0.04$] and also a nonsignificant main effect on positive memory bias [$F(1,291) = 0.001$, $P = 0.970$, $f = 0.00$].

NR3C2 rs5534 genotype–life adversity interaction
Separate $2 \times 2$ ANCOVAs were carried out for negative and for positive memory bias. The genotype (AA/AG vs. GG) × life adversity (<4 vs. ≥4) interaction was nonsignificant for negative [$F(1,291) = 0.22$, $P = 0.639$, $f = 0.03$] and for positive memory bias [$F(1,291) = 0.00$, $P = 0.969$, $f = 0.00$]. The mean negative and positive memory bias scores are presented in Table 2.

NR3C2 rs5534 genotype–childhood trauma interaction
The genotype (AA/AG vs. GG) × childhood trauma (no vs. yes) interaction was significant for negative memory bias [$F(1,291) = 4.03$, $P = 0.046$, $f = 0.12$; see Fig. 1]. The interaction was not significant for positive memory bias [$F(1,291) = 0.37$, $P = 0.544$, $f = 0.03$; see Table 2 for means]. Post-hoc analyses indicated that A allele carriers with childhood trauma tended to show more negative memory bias compared with G allele homozygote patients in remission who experienced childhood trauma [$F(1,110) = 3.82$, $P = 0.053$, $f = 0.19$] and compared with A allele carriers without childhood trauma [$F(1,198) = 2.88$, $P = 0.091$, $f = 0.12$]. It is important to note, however, that these post-hoc effects did not reach the conventional significance level of 0.05 and should hence be interpreted with caution. No effect of childhood trauma was found in G allele homozygotes [$F(1,90) = 1.82$, $P = 0.181$, $f = 0.14$].

NR3C2 rs5534 genotype–recent adversity interaction
The genotype (AA/AG vs. GG) × recent adversity (no vs. yes) interaction was nonsignificant for both negative and positive bias [$F(1,291) = 0.00$, $P = 0.962$, $f = 0.00$ and $F(1,291) = 0.78$, $P = 0.377$, $f = 0.05$], respectively. The mean negative and positive memory bias scores are presented in Table 2.

Effects per sex
The genotype (AA/AG vs. GG) × life adversity (no vs. yes for all events, childhood trauma and recent adversity) yielded nonsignificant findings for all main and interaction

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (SD)/%</th>
<th>Statistical test</th>
</tr>
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<tbody>
<tr>
<td>Genotype AA/AG</td>
<td></td>
<td></td>
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<tr>
<td>Genotype GG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>47.5 (12.0)</td>
<td>$t(297) = 0.36$, $P = 0.717$</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>62</td>
<td>$\chi^2(1, N = 299) = 1.48$, $P = 0.224$</td>
</tr>
<tr>
<td>Medication use (yes)</td>
<td>45</td>
<td>$\chi^2(1, N = 298) = 1.18$, $P = 0.276$</td>
</tr>
<tr>
<td>BDI-II</td>
<td>14.5 (9.9)</td>
<td>$\chi^2(297) = 0.83$, $P = 0.632$</td>
</tr>
<tr>
<td>Number of episodes</td>
<td>3.6 (1.9)</td>
<td>$\chi^2(297) = 0.99$, $P = 0.321$</td>
</tr>
<tr>
<td>Life adversity</td>
<td>4.0 (3.1)</td>
<td>$t(297) = 0.12$, $P = 0.906$</td>
</tr>
<tr>
<td>Life adversity (yes)</td>
<td>92</td>
<td>$\chi^2(1, N = 299) = 0.11$, $P = 0.745$</td>
</tr>
<tr>
<td>Childhood trauma (yes)</td>
<td>36</td>
<td>$\chi^2(1, N = 299) = 1.94$, $P = 0.163$</td>
</tr>
<tr>
<td>Recent adversity (yes)</td>
<td>59</td>
<td>$\chi^2(1, N = 298) = 1.13$, $P = 0.298$</td>
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BDI-II, Beck Depression Inventory-II.
**Table 2** Means and SDs for negative and positive memory bias score per NR3C2 genotype and life events variable (life adversity, childhood trauma, recent adversity) in depressed patients in remission

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Life adversity</th>
<th>Negative memory bias</th>
<th>Positive memory bias</th>
</tr>
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<tbody>
<tr>
<td>AA/AG</td>
<td>No</td>
<td>0.40 (0.17)</td>
<td>0.58 (0.18)</td>
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<tr>
<td>GG</td>
<td>Yes</td>
<td>0.41 (0.16)</td>
<td>0.57 (0.17)</td>
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<tr>
<td></td>
<td></td>
<td>0.39 (0.17)</td>
<td>0.58 (0.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.41 (0.14)</td>
<td>0.57 (0.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.37 (0.17)</td>
<td>0.56 (0.18)</td>
</tr>
</tbody>
</table>

**Discussion**

This study aimed to extend the findings of an earlier study on the interaction between the NR3C2 rs5534 polymorphism with life events on memory bias in healthy individuals (Vogel et al., 2014) to a sample of patients in remission from a major depressive episode. Unlike the Vogel et al. (2014) study, we found no main effect of the NR3C2 rs5534 polymorphism. However, the current study did not have sufficient power to detect this main effect and this may have resulted in false-negative findings. We found evidence for a gene-by-environment interaction that is in accordance with the Vogel et al. (2014) study. Specifically, depressed NR3C2 rs5534 risk allele carriers (AA, AG) in remission who had experienced childhood trauma may show more negative memory bias compared to risk allele carriers without a traumatic childhood and nonrisk allele homozygotes (GG) with childhood trauma. The NR3C2 rs5534 genotype may not interact with traumatic and adverse events that had occurred recently or throughout all stages of life. More studies are needed to discern the different effects of early, recent, and general life adversity. The rs5534 thus interacted specifically with childhood trauma on memory bias in the sample in remission and may be related to the development of stress sensitivity in childhood. This is in accordance with the cognitive models of depression (Beck, 1976, 2008; Bower, 1981) that state that the experience of aggression or abuse during childhood may result in dysfunctional assumptions that engender negatively biased processing of information and increased susceptibility to depression. When examining the effects of sex, the NR3C2 rs5534 by childhood trauma interaction was found in female participants, but not in male participants. This is in line with previous findings on the association between NR3C2 rs5534 and depression, which was restricted to women (Klok et al., 2011). These findings could suggest that NR3C2 rs5534 may be more specifically implied in the development of stress sensitivity in females.

Taken together, the current results and the results of Vogel et al. (2014) indicate that the effect of life adversity may be different in healthy compared with affected individuals. However, because no distinction between type and timing of adverse events was made in the study by Vogel et al. (2014), we do not know whether the results in the healthy sample might have been stronger when examining the interaction with childhood trauma specifically. Examining the interaction in female participants only might also have yielded stronger results, although female participants in the Vogel et al. (2014) study had a stronger positive memory bias than male participants, independent of genotype. It is important to note that no mood induction was used in the study by

effects, except for the genotype × childhood trauma interaction for negative memory bias in female participants \(F(1,187) = 4.11, P = 0.044, f = 0.15\). This interaction has a similar pattern as the interaction in the entire sample of participants.

**Power analysis**

Post-hoc power analyses using the Quanto power calculator (http://hydra.usc.edu/gxe/) showed that the power for the NR3C2 rs5534 genotype main effect and the genotype by childhood trauma interaction was 1, and 99%, respectively. For an NR3C2 rs5534 main effect of this size to be detected (80% chance) as significant at the 5% level, a sample of 6188 participants would be required.
Vogel et al. (2014), and that negative and positive verbal explicit memory bias was examined using a slightly different task. Furthermore, the healthy sample in the study by Vogel et al. (2014) was generally young and highly educated. The current results in a clinical sample with more variations in age and educational level may offer a valuable extension to the previous study.

The rs5534 polymorphism may influence the regulation of mineralocorticoid expression through which it in turn might affect the excitability and structural integrity of the amygdala and hippocampus (Gass et al., 2000; Groeneweg et al., 2011; Klok et al., 2011a). This has been associated with fear, anxiety, and mood disorders in general and negative memory bias in particular (Bremner et al., 2000; Frodl et al., 2002; Gerritsen et al., 2011). As proposed by Vogel et al. (2014), this is a hypothetical pathway through which this polymorphism affects emotional memory processing and hence acts as a susceptibility factor for depression. It could be speculated that differences in cortisol secretion might render young NR3C2 rs5534 A allele carriers more vulnerable to severely stressful events and might influence the development of emotional processing styles. This may be reflected by subtle depression-related neurobiological abnormalities, which also appear to persist after remission (Davidson et al., 2002; Leppanen, 2006; Kempton et al., 2011).

Our results should be viewed in the context of some strengths and limitations. A major strength is that we studied the presence of a previously reported (Vogel et al., 2014) gene–environment interaction using a slightly different memory task and in an independent affected sample. This is presumed to be informative of the robustness of such an interaction (Moffitt et al., 2006). Furthermore, we extended earlier findings by studying the effect of different adverse life events from a developmental perspective. A limitation is the measurement method of the childhood events as negative bias might have affected participants’ recall. The Life Events Questionnaire assesses the occurrence of several factual events during predetermined periods of life. Assessments of such specific events are presumed to minimize distortion of recall because, in general, adults’ recall of specific childhood events seem fairly accurate (Brewin et al., 1993). Another limitation is related to the sample size and the limited power to find a main effect of NR3C2. The high power of the gene by childhood trauma interaction might have been driven by a strong effect childhood trauma. Although it had sufficient power, the gene-by-childhood trauma interaction was not strong and might have been an incidental finding because multiple statistical tests were carried out without statistical correction. Our results thus provide not more than a first indication of the association between a polymorphism in the NR3C2 gene, stress sensitivity, and bias in depressed patients in remission. Replications using larger samples are needed for substantiation of the findings.

Conclusion
The current results complement the previously reported NR3C2 gene and life adversity interaction on negative memory bias by the inclusion of an affected sample. Although in need for substantiation, the results may indicate that especially female NR3C2 rs5534 risk allele carriers who had experienced childhood trauma develop depressorotypic information-processing styles that render them more susceptible for depression. This study underscores the importance of repeating genetic studies in clinical samples to gain information on state-specific and trait-specific features of the interaction and providing an indication of the generalizability of the association.

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Conflicts of interest
There are no conflicts of interest.

References


