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[a], Susanne Vogel[b,c], Alejandro Arias-Vásquez[a,b,c,d], Barbara Franke[a,c,d], Guillén Fernández[b,c], Eni S. Becker[e], Anne Speckens[a] and Iris van Oostrom[a]

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. *Psychiatr Genet* 00:000–000**

Psychiatric Genetics 2015, **00**:000–000

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

Departments of [a]Psychiatry, [b]Cognitive Neuroscience, [c]Donders Institute for Brain, Cognition and Behaviour, [d]Human Genetics, Radboud University Medical Center and [e]Behavioural Science Institute, Radboud University Nijmegen, Nijmegen, The Netherlands

Correspondence to Janna N. Vrijsen, PhD, Department of Psychiatry, Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands
Tel: +31 24 36 10685; fax: +31 24 36 19561;
e-mail: janna.vrijsen@radboudumc.nl

Received 28 January 2014 **Revised** 3 October 2014 **Accepted** 20 January 2015

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

0955-8829 DOI: 10.1097/YPG.0000000000000081

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 gene-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, rumination, 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 Vrijsen *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 (Skre *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 unannounced 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 ($\chi^2=3.65$, $d.f.=1$, $P=0.056$). 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 χ^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 2×2 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 1 Means (SDs) and/or number of occurrences and statistical tests comparing the depressed patients in remission genotype groups on demographic and clinical variables

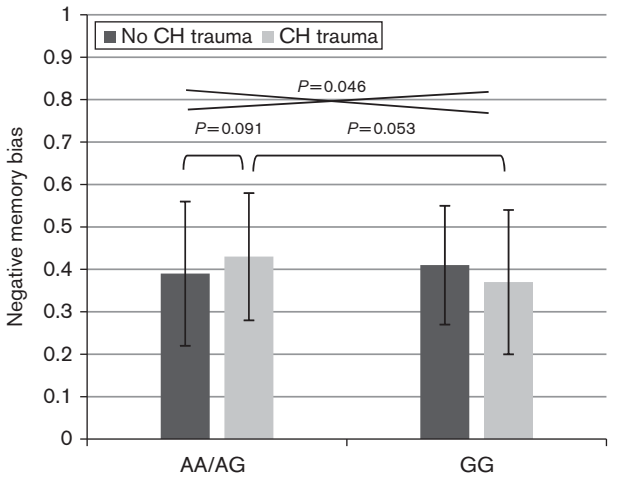
	Mean (SD)/%		
Variables	Genotype AA/AG	Genotype GG	Statistical test
Age	47.5 (12.0)	48.0 (11.5)	$t(297) = 0.36$, $P = 0.717$
Sex (female)	62	70	$\chi^2(1, N = 299) = 1.48$, $P = 0.224$
Medication use (yes)	45	52	$\chi^2(1, N = 298) = 1.18$, $P = 0.276$
BDI-II	14.5 (9.9)	13.8 (9.6)	$t(297) = 0.63$, $P = 0.532$
Number of episodes	3.6 (1.9)	3.4 (1.8)	$t(297) = 0.99$, $P = 0.321$
Life adversity	4.0 (3.1)	4.1 (3.1)	$t(297) = 0.12$, $P = 0.906$
Life adversity (yes)	92	91	$\chi^2(1, N = 299) = 0.11$, $P = 0.745$
Childhood trauma (yes)	36	44	$\chi^2(1, N = 299) = 1.94$, $P = 0.163$
Recent adversity (yes)	59	65	$\chi^2(1, N = 299) = 1.13$, $P = 0.288$

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

		Mean (SD)	
Genotype	Life adversity	Negative memory bias	Positive memory bias
AA/AG	No	0.40 (0.17)	0.58 (0.18)
	Yes	0.41 (0.16)	0.57 (0.17)
GG	No	0.40 (0.15)	0.58 (0.16)
	Yes	0.40 (0.16)	0.56 (0.18)
Genotype	Childhood trauma	Negative memory bias	Positive memory bias
AA/AG	No	0.39 (0.17)	0.58 (0.19)
	Yes	0.43 (0.15)	0.57 (0.15)
GG	No	0.41 (0.14)	0.57 (0.15)
	Yes	0.37 (0.17)	0.58 (0.19)
Genotype	Recent adversity	Negative memory bias	Positive memory bias
AA/AG	No	0.42 (0.16)	0.57 (0.17)
	Yes	0.39 (0.17)	0.58 (0.18)
GG	No	0.41 (0.14)	0.59 (0.14)
	Yes	0.39 (0.16)	0.56 (0.19)

Fig. 1



NR3C2 genotype × childhood (CH) trauma interaction with negative memory bias score as a dependent variable in depressed patients in remission. Error bars represent SDs.

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.

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.*, 2011b). 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

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 depressotypic 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.

Acknowledgements

The authors thank the participants for their time and effort.

Conflicts of interest

There are no conflicts of interest.

References

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders*, 4th ed. Washington, DC: American Psychiatric Association.

Asarnow LD, Thompson RJ, Joormann J, Gotlib IH (2014). Children at risk for depression: memory biases, self-schemas, and genotypic variation. *J Affect Disord* **159**:66–72.

Beck AT (1976). *Cognitive therapy and the emotional disorders*. New York: International Universities Press.

Beck AT (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *Am J Psychiatry* **165**:969–977.

Beck AT, Steer RA, Brown GK (1996). *Beck Depression Inventory manual*, 2nd ed. San Antonio, TX: Psychological Corporation.

Bhagwagar Z, Cowen PJ (2007). It's not over when it's over: persistent neurobiological abnomalities in recovered depressed patients. *Psychol Med* **38**:307–313.

Bower GH (1981). Mood and memory. *Am Psychol* **36**:129–148.

Bradley MM, Lang PJ (1999). Affective norms for English words (ANEW): instruction manual and affective ratings. Technical Report C-1, The Center for Research in Psychophysiology, University of Florida.

Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS (2000). Hippocampal volume reduction in major depression. *Am J Psychiatry* **157**:115–118.

Brewin CR, Andrews B, Gotlib IH (1993). Psychopathology and early experiences: a reappraisal of retrospective reports. *Psychol Bull* **113**:82–98.

Brugha TS, Cragg D (1990). The list of threatening experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatr Scand* **82**:77–81.

Caspi A, Moffitt TE (2006). Gene-environment interactions in psychiatry: joining forces with neuroscience. *Nat Rev Neurosci* **7**:583–590.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, *et al.* (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **301**:386–389.

Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE (2010). Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry* **167**:509–527.

Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K (2002). Depression: perspectives from affective neuroscience. *Annu Rev Psychol* **53**:545–574.

De Raedt R, Koster EH (2010). Understanding vulnerability for depression from a cognitive neuroscience perspective: a reappraisal of attentional factors and a new conceptual framework. *Cogn Affect Behav Neurosci* **10**:50–70.

Erber R, Tesser A (1992). Task effort and the regulation of mood: the absorption hypothesis. *J Exp Soc Psychol* **28**:339–359.

Firk C, Markus CR (2007). Review: serotonin by stress interaction: a susceptibility factor for the development of depression? *J Psychopharmacol* **21**:538–544.

First MB, Spitzer RL, Gibbon M, Williams JBW (1996). *Structured clinical interview for DSM–IV Axis I disorders-clinician version (SCID-CV)*. Washington, DC: American Psychiatric Press.

Foland-Ross LC, Cooney RE, Joormann J, Henry ML, Gotlib IH (2013). Recalling happy memories in remitted depression: a neuroimaging investigation of the repair of sad mood. *Cogn Affect Behav Neurosci* **14**:818–826.

Frodl T, Meisenzahl E, Zetzsche T, Bottlender R, Born C, Groll C*, et al.* (2002). Enlargement of the amygdala in patients with a first episode of major depression. *Biol Psychiatry* **51**:708–714.

Gass P, Kretz O, Wolfer DP, Berger S, Tronche F, Reichardt HM*, et al.* (2000). Genetic disruption of mineralocorticoid receptor leads to impaired neurogenesis and granule cell degeneration in the hippocampus of adult mice. *EMBO Rep* **1**:447–451.

Gerritsen L, Tendolkar I, Franke B, Vasquez AA, Kooijman S, Buitelaar J*, et al.* (2011). BDNF Val66Met genotype modulates the effect of childhood adversity on subgenual anterior cingulate cortex volume in healthy subjects. *Mol Psychiatry* **17**:597–603.

Gibbs AA, Bautista CE, Mowlem FD, Naudts KH, Duka T (2013). Alpha 2B adrenoceptor genotype moderates effect of reboxetine on negative emotional memory bias in healthy volunteers. *J Neurosci* **33**:17023–17028.

Gotlib IH, Joormann J (2010). Cognition and depression: current status and future directions. *Annu Rev Clin Psychol* **6**:285–312.

Gotlib IH, Kasch KL, Traill S, Joormann J, Arnow BA, Johnson SL (2004). Coherence and specificity of information-processing biases in depression and social phobia. *J Abnorm Psychol* **113**:386–398.

Gottesman II, Gould TD (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* **160**:636–645.

Groeneweg FL, Karst H, de Kloet ER, Joëls M (2011). Rapid non-genomic effects of corticosteroids and their role in the central stress response. *J Endocrinol* **209**:153–167.

Hasler G, Drevets WC, Manji HK, Charney DS (2004). Discovering endophenotypes for major depression. *Neuropsychopharmacology* **29**:1765–1781.

Hlavacova N, Bakos J, Jezova E (2010). Eplerenone, a selective mineralocorticoid receptor blocker, exerts anxiolytic effects accompanied by changes in stress hormone release. *J Psychopharmacol* **24**:779–786.

Joëls M, Karst H, de Rijk RH, de Kloet ER (2008). The coming out of the brain mineralocorticoid receptor. *Trends Neurosci* **31**:1–7.

Karst H, Berger S, Erdmann G, Schutz G, Joëls M (2010). Metaplasticity of amygdalar responses to the stress hormone corticosterone. *Proc Natl Acad Sci USA* **107**:14449–14454.

Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S*, et al.* (2011). Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatry* **68**:675–690.

Kendler KS, Neale MC (2010). Endophenotype: a conceptual analysis. *Mol Psychiatry* **15**:789–797.

Klok MD, Alt SR, Irurzun Lafitte AJ, Turner JD, Lakke EA, Huitinga I*, et al.* (2011a). Decreased expression of mineralocorticoid receptor mRNA and its splice variants in postmortem brain regions of patients with major depressive disorder. *J Psychiatr Res* **45**:871–878.

Klok MD, Giltay EJ, Van der Does AJ, Geleijnse JM, Antypa N, Penninx BW*, et al.* (2011b). A common and functional mineralocorticoid receptor haplotype enhances optimism and protects against depression in females. *Transl Psychiatry* **1**:e62.

Kwang T, Wells TT, McGeary JE, Swann WB, Beevers CG (2010). Association of the serotonin transporter promoter region polymorphism with biased attention for negative word stimuli. *Depress Anxiety* **27**:746–751.

Leppanen JM (2006). Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Curr Opin Psychiatry* **19**:34–39.

Mathews A, MacLeod C (2005). Cognitive vulnerability to emotional disorders. *Annu Rev Clin Psychol* **1**:167–195.

Matt GE, Vazquez C, Campbell WK (1992). Mood-congruent recall of affectively toned stimuli: a meta-analytic review. *Clin Psychol Rev* **12**:227–255.

McCabe SB, Gotlib IH, Martin RA (2000). Cognitive vulnerability for depression: deployment of attention as a function of history of depression and current mood state. *Cogn Ther Res* **24**:427–444.

Moffitt TE, Caspi A, Rutter M (2006). Measured gene-environment interactions in psychopathology. *Perspect Psychol Sci* **1**:5–27.

Otte C, Hinkelmann K, Moritz S, Yassouridis A, Jahn H, Wiedemann K*, et al.* (2010). Modulation of the mineralocorticoid receptor as add-on treatment in depression: a randomized, double-blind, placebo-controlled proof-of-concept study. *J Psychiatr Res* **44**:339–346.

Perry B, Pollard R, Blakley T, Baker W, Vigilante D (1995). Childhood trauma, the neurobiology of adaptation, and 'use-dependent' development of the brain: how 'states' become 'traits'. *Inf Ment Health J* **16**:271–291.

Phaf RH, van der Leij AR, Stienen BMC, Bierman D (2006). *Positive, neutral and negative words at minimal presentation levels: ordering by perceptual clarification, Technical Report*. Amsterdam, The Netherlands: Universiteit van Amsterdam.

Raven JC (1958). *Standard progressive matrices*. London: H. K. Lewis.

Ridout N, Astell AJ, Reid IC, Glen T, O'Carroll RE (2003). Memory bias for emotional facial expressions in major depression. *Cogn Emot* **17**:101–122.

Segal ZV, Ingram RE (1994). Mood priming and construct activation in tests of cognitive vulnerability to unipolar depression. *Clin Psychol Rev* **14**:663–695.

Skre I, Onstad S, Torgersen S, Kringlen E (1991). High interrater reliability for the Structured Clinical Interview for DSM–III–R Axis I (SCID-I). *Acta Psychiatr Scand* **84**:167–173.

Sullivan PF, Neale MC, Kendler KS (2000). Genetic epidemiology of major depression: review and metaanalysis. *Am J Psychiatry* **157**:1552–1562.

Van Oostrom I, Franke B, Rijpkema M, Gerritsen L, Arias-Vasquez A, Fernandez G*, et al.* (2012). Interaction between BDNF Val66Met and childhood stressful life events is associated to affective memory bias in men but not women. *Biol Psychol* **89**:214–219.

Vogel S, Gerritsen L, Van Oostrom I, Arias-Vásquez A, Rijpkema M, Joëls M*, et al.* (2014). Linking genetic variants of the mineralocorticoid receptor and negative memory bias: interaction with prior life adversity. *Psychoneuroendocrinology* **40**:181–190.

Vrijsen JN, Becker ES, Arias-Vásquez A, van Dijk MK, Speckens A, van Oostrom I (2014a). What is the contribution of different cognitive biases and stressful childhood events to the presence and number of previous depressive episodes? *Psychiatry Res* **217**:134–142.

Vrijsen JN, van Oostrom I, Arias-Vásquez A, Franke B, Becker ES, Speckens A (2014b). Association between genes, stressful childhood events and processing bias in depression vulnerable individuals. *Genes Brain Behav* **13**:508–516.

Vrijsen JN, van Oostrom I, Isaac L, Becker ES, Speckens A (2014c). Coherence between attentional and memory biases in sad and formerly depressed individuals. *Cognit Ther Res* **38**:334–342.

Watson DE, Li B (2005). TaqMan applications in genetic and molecular toxicology. *Int J Toxicol* **24**:139–145.

Williams JB, Gibbon M, First MB, Spitzer RL, Davis M, Borus J*, et al.* (1992). The Structured Clinical Interview for DSM–III–R (SCID): multisite test–retest reliability. *Arch Gen Psychiatry* **49**:630–636.

Woudstra S, van Tol MJ, Bochdanovits Z, van der Wee NJ, Zitman FG, van Buchem MA*, et al.* (2013). Modulatory effects of the piccolo genotype on emotional memory in health and depression. *PLoS One* **8**:e61494.