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Original article

Outgroup emotion processing in the vACC is modulated by childhood trauma and CACNA1C risk variant

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Abstract

A high frequency of outgroup contact—as experienced by urban dwellers and migrants—possibly increases schizophrenia risk. This risk might be further amplified by genetic and environmental risk factors, such as the A-allele of rs1006737 within the calcium voltage-gated channel subunit alpha1 C gene and childhood interpersonal trauma (CIT). Both have been related to ventral anterior cingulate cortex (vACC) functioning. We investigated vACC functioning, during ingroup and outgroup emotion perception in relation to rs1006737 and CIT. Group membership was manipulated through a minimal group paradigm. Thus, in our functional magnetic resonance imaging study, a group of healthy Caucasian participants ($n = 178$) viewed video-recorded facial emotions (happy *vs* angry) of actors artificially assigned to represent the ingroup or the outgroup. Rs1006737 and CIT were related to brain activation for group and emotion specific processing. The group–emotion interaction in the vACC showed reduced sensitivity to emotional valence for outgroup member processing. Specifically for the angry outgroup condition, we found a gene by environment interaction in vACC activity. We speculate that the increased schizophrenia risk in migrants and urban dwellers could therefore be facilitated via this pathophysiological pathway.

Key words: anterior cingulate cortex; minimal group paradigm; outgroup; environment; genetics

Introduction

Urban dwellers and migrants live in highly complex social structures with equally complex intergroup relations. Both have an increased risk for schizophrenia (Cantor-Graae and Selten, 2005; Das-Munshi *et al.*, 2012; Vassos *et al.*, 2012). Minority migrant groups experience increased psychosis risk when they stand out from their social environment, for example, through a different skin colour (Akdeniz *et al.*, 2014a), particularly when living in neighborhoods where own-group density is lower (Das-Munshi *et al.*, 2012), implicating a relevance of outgroup confrontation in this context. Especially humans with genetic and other environmental risks, such as the A-allele of rs1006737

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within the calcium voltage-gated channel subunit alpha1 C (CACNA1C) gene and childhood interpersonal trauma (CIT) might be sensitive to frequent outgroup confrontation. In this context, the ventral anterior cingulate cortex (vACC) has been suggested to be an important converging zone of genetic and environmental risk factors for schizophrenia (Tost and Meyer-Lindenberg, 2012; Akdeniz *et al*., 2014a). Indeed, alterations in vACC structure or functioning have been associated not only with ethnic-minority status (Akdeniz *et al*., 2014b) and urban upbringing (Lederbogen *et al*., 2011) but also with ingroup/outgroup processing (Volz and Kessler, 2009), the risk allele at rs1006737 within the CACNA1C gene (Wang *et al*., 2011), and experience of CIT (Van Harmelen *et al*., 2010). However, evidence about the exact interplay between rs1006737 and CIT regarding ingroup/outgroup processing is missing.

Numerous behavioral studies have shown the differential cognitive and emotional processing of ingroup and outgroup members, i.e. the misperception of emotional facial expressions in members of a different race (Elfenbein and Ambady, 2002), the misperception of non-verbal cues (gaze, posture gestures) (Hugenberg and Bodenhausen, 2004; Dovidio *et al* ., 2006) and difficulties with theory of mind tasks (Adams *et al*., 2010). However, the cognitive processing and correlated brain activation for the membership of groups delineated by sex or race are liable to uncontrolled effects, such as emotional stereotypes, which are independent of a 'pure' group effect (Wheeler and Fiske, 2005). Hence, it is impossible to differentiate the effect of prejudice or stereotypes from pure effect of group membership when the group is modulated by ethnicity. Studies on the effects of group membership using different ethnicities are confronted with this bias (Cikara and Van Bavel, 2014). To circumvent this bias, ingroup *vs* outgroup classification can be achieved using the well-established minimal group paradigm (MGP), creating artificial ad hoc groups (e.g. using two different coloured arm bands; Taijfel, 1970; Tajfel *et al*., 1971; Cikara and Van Bavel, 2014). MGP effects on behavior have been demonstrated widely in social psychology experiments (Tajfel *et al*., 1971; Diehl, 1990). These advantages make the MGP especially suitable for investigating the association of neural ingroup/outgroup processing with genetic and environmental risk factors for schizophrenia, such as rs1006737 and CIT. The neural correlates of ingroup/outgroup membership have been demonstrated using functional magnetic resonance imaging (fMRI), which has shown a relevance of the ACC and the medial prefrontal cortex in the processing of racial (Eres and Molenberghs, 2013; Cikara and Van Bavel, 2014) and minimal group membership (Volz and Kessler, 2009). The latter study of Volz and colleagues was the first who used fMRI to investigate neural processing in group-related tasks based on a modified version of the MGP. In this study, participants distributed money between ingroup members (ingroup trial), between outgroup members (outgroup trial) or between ingroup and outgroup members (mixed trial). Comparative intergroup evaluation processes (mixed group trials *vs* same group trials) elucidated a network including the vACC, dorsomedial prefrontal cortex, temporoparietal junction and precuneus. Moreover, the vACC is part of a facial emotion processing network, which also processes happy and angry facial expressions (Fusar-Poli *et al*., 2013). Yet, the influence of group membership on neural activation in the vACC for emotional facial expressions has not been investigated, and the relevance of genetic and environmental factors in this context is unknown.

CACNA1C has been repeatedly identified as a susceptibility gene for bipolar disorder, major depressive disorder, schizophrenia and schizotypal traits (Ferreira *et al*., 2008; Sklar *et al*., 2008; Green *et al*., 2010; Nyegaard *et al*., 2010; Roussos *et al*., 2013; Ripke *et al*., 2014, 2013; Takahashi *et al*., 2015; Rao *et al*., 2016; Starnawska *et al*., 2016). *CACNA1C* encodes the pore-forming alpha-1c sub-unit of the L-type voltage-gated calcium channel and plays an important role in dendritic development, synaptic plasticity, learning and memory formation (Bhat *et al*., 2012). Rs1006737 risk variant carriers have been shown to demonstrate vACC dysfunction while performing episodic memory tasks that correlates with activation patterns in first-degree relatives of patients with bipolar disorder, major depression or schizophrenia (Erk *et al*., 2014). Neural activation for facial emotion perception in the vACC is altered in patients with schizophrenia (Taylor *et al*., 2012). However, the influence of rs1006737 on neural vACC activation for facial emotion processing in the interplay with environmental risk factors remains unknown. CIT is an epidemiologically validated environmental risk factor for schizophrenia and affective disorders (Gilbert *et al*., 2009; Matheson *et al*., 2012) and is associated with hyper-reactivity of the amygdala during the presentation of threat-related faces, implicating a dysfunction of the regulatory effect of prefrontal areas on limbic structures (Dannlowski *et al*., 2012). In line with this assumption, the experience of CIT is associated with reduced vACC grey matter volume (Van Harmelen *et al*., 2010; Dannlowski *et al*., 2012) and an impaired emotional regulation during the perception of negative emotional stimuli (New *et al*., 2009).

In summary, ingroup/outgroup perception—being related to migration and urban upbringing—and the schizophrenia risk factors rs1006737 and CIT are associated with structural and functional alterations in the vACC. Although suspected, no study has yet investigated how genetic and environmental factors converge in the vACC in this specific context.

In this study, we investigated the neural correlates of group-dependent (ingroup *vs* outgroup) facial emotion processing and their relation to rs1006737 and CIT. Therefore, we used a MGP in an autochthonous German sample. We hypothesized (1) an interaction of neural activation for the processing of emotional valence (happy *vs* angry) and group membership (ingroup *vs* outgroup) in the vACC. We further hypothesized (2) a moderation of vACC function in response to group-dependent (ingroup *vs* outgroup) emotion processing by rs1006767 and CIT.

Materials and methods

Subjects

Study participants were 198 healthy, right-handed, Caucasian German native speakers of central European decent aged 19–39 years (M: 24.04 years; SD: 3.25 years, 50% males). We excluded 18 subjects due to head movement exceeding one voxel size (3.6 mm) during fMRI scanning, one subject due to insufficient engagement in post-scanning behavioural tasks, and one because of an incidental finding of a brain pathology leaving 178 subjects for the final analysis. One participant was excluded from genetic analysis due to a missing blood sample. Our study was approved by the local ethics committee, according to the Declaration of Helsinki, and all participants gave written informed consent prior to the commencement of the study.

DNA extraction and genotyping

Genomic DNA was prepared from whole blood samples according to standard procedures. Rs1006737 was genotyped using a TaqMan 5' nuclease assay. Accuracy was assessed by duplicating 15% of the sample, and reproducibility was 100%. Fifteen

subjects were rs1006737 homozygous A, while 91 were heterozygous GA, and 71 were homozygous G. The allele frequencies did not deviate from the Hardy–Weinberg equilibrium ($P = 0.23$). Genetic risk was defined by A-allele carrier status for rs1006737 (AA/AG vs. GG).

Measuring childhood trauma and schizotypal traits

Childhood trauma was measured via the Trauma History Questionnaire (THQ) (Green, 1996). This 27-item self-report instrument determines possible exposure to a wide range of traumata. We focused on traumatic events with an interpersonal-interaction component such as being a victim of robbery or of sexual or physical abuse (10 items). Our sample was divided into groups of those with at least one self-reported traumatic event and those with no traumatic events before the age of 18. Schizotypal traits were assessed using the Schizotypal Personality Questionnaire-Brief (SPQ-B), a 22-item instrument with adequate reliability and validity (Raine and Benishay, 1995).

Behavioural data analysis

All non-fMRI data were analysed using SPSS 20.0.0 for Windows (SPSS, Chicago, IL). The interaction of CIT and the rs1006737 risk allele was tested, as a proof of concept, regarding schizotypal traits as a proxy for schizophrenia risk (Vollema *et al.*, 2002) using general estimation equations (GEE) with a multi-factorial design.

fMRI task and procedure

MGP manipulation. In order to create ad-hoc minimal groups, subjects completed a false psychological test where they answered questions regarding personality and problem-solving strategies. They were told that the purpose of this test was to identify strategies for solving a problem. After completing the test, which took about 5–10 min, participants were told that they were either a 'conclusive' problem solver with a 'holistic approach' or a 'sequential' problem solver with an 'analytical approach'. In fact, these problem-solver types do not exist, and subjects had been randomly assigned to one of these groups before the experiment. To increase group identification, the participants had to read a short text with a further description of the two 'personality types'. Before and after the fMRI session, participants were asked to indicate the degree of identification with the own problem-solver type (ingroup) and the other problem-solver type (outgroup) on a computer screen, which was assessed on a 7-point Likert scale. This manipulation strategy has also been used elsewhere (Ruckmann *et al.*, 2015).

Stimuli. We used 5 s video clips presenting dynamic facial expressions that had been described and validated previously among another groups of subjects (Kircher *et al.*, 2013; Pohl *et al.*, 2013). Briefly, in these video clips professional actors depicted emotional facial expressions for anger and happiness. The video clips were framed with a coloured strip (either blue or green) according to the actor's (false) identity as either a sequential or conclusive problem solver, enabling participants to make ingroup/outgroup associations.

fMRI stimulus setup. We used a block design with two conditions: 'facial expression' (happy *vs* angry) and 'group' (participants observing ingroup vs. outgroup, with groups coded by coloured blue or green video). Half of the actors were ingroup members, while the other half were outgroup members. In both groups, sex was equally distributed. Each condition was presented in six blocks consisting of four video clips. Each block was introduced with an instruction slide (2 s) followed by a white fixation cross (5 s) and encompassed four video clips (5 s) presenting the same facial expression. In addition, there were six blocks where only a white fixation cross was presented as a low-level baseline (25 s); these were also introduced through instruction slides (2 s). For a complete description of the paradigm, including conditions of no interest and permutation strategies, see Supplementary Material.

fMRI data acquisition. Imaging was conducted on a 3 T MRI scanner (MAGNETOM Trio, Siemens, Erlangen, Germany) equipped with a 12-channel head coil. Echo-planar T2*-weighted images were acquired (TR = 2250 ms, TE = 30 ms, flip angle 90°, FOV = 230 mm, distance factor = 20%) using 36 slices in an oblique axial orientation (slice order = ascending, voxel size = 3.6 mm^3, interslice gap = 0.72 mm).

fMRI data analysis. Data were analysed using SPM8 standard routines and templates (Wellcome Department of Imaging Neuroscience, London, UK). Five initial brain volumes of each run were excluded. The remaining images were realigned to the mean image and then normalized to the standard Montreal Neurological Institute (MNI) template with volume units of 2 mm × 2 mm × 2 mm and finally smoothed with an 8 mm Gaussian filter at full-width at half maximum (FWHM). The following analyses were based on an ordinary least-squares estimation method using a general linear model. At the single-subject level, regressors were created from the time course of each condition and convoluted with a canonical hemodynamic response function. Movement parameters from realignment were integrated in the model as regressors of no interest. The low-level baseline condition was not included in the model. High-pass filtering (cut-off period of 128 s) was applied. First- and second-order time modulation was used for each condition and integrated as additional regressors in the model. For each subject, we calculated the t-contrast of the interaction (ingroup/outgroup) by emotion (happy/angry). Group analyses were performed by entering the resulting contrasts into a one-sample *t*-test (SPM8), where subjects were treated as random variables. Here, an *F*-contrast was calculated (as direction of effects were unknown) revealing the activation of the latter interaction at the group level in the ACC region of interest (ROI). In addition, this interaction was tested in an exploratory whole-brain analysis (see Supplementary Material).

ACC ROI was defined using the Wake Forest PickAtlas (www.fmri.wfubmc.edu), and the extraction and calculation of percent signal change (PSC) for each condition (ingroup happy, ingroup angry, outgroup happy and outgroup angry) was performed using the MarsBaR toolbox (http://marsbar.sourceforge.net/) for SPM8. All analyses were controlled for factors being unequally distributed among the four groups (CIT *vs* no CIT and A-allele carrier at rs1006737 *vs* no A-allele carrier at rs1006737) by including the respective information as covariates of no interest in the model (see Supplementary Material). All results were corrected for multiple comparisons at $P < 0.05$ family-wise error (FWE) on a voxel level with minimum cluster size of 50 voxels.

Contrasts of interest. To test the hypothesis that social categorization as either ingroup or outgroup has an effect on the neural processing of different emotional facial expressions in the ACC,

we calculated an interaction analysis of the emotion (happy *vs* angry) and group membership (ingroup *vs* outgroup) factors using the ACC ROI.

Following our second hypothesis—that ACC functioning is sensitive to a gene—environment interaction between the schizophrenia risk factors rs1006737 and CIT—we used the extracted PSC for each subject and condition. GEEs with a multifactorial design were performed in SPSS to test the 2×2×2×2 interaction of group, emotion, rs1006737 and trauma.

Results

MPG manipulation

In a post-fMRI debriefing, all participants correctly remembered their own problem-solver type, its associated colour and the faces of group members presented to them during scanning. Identification with the own group (ingroup) was significantly higher than with the other group (outgroup) both before and after fMRI scanning (before fMRI scanning: identification with IG = 4.93; identification with OG = 3.42; $P < 0.001$; after fMRI scanning: identification with IG = 5.21; identification with OG = 2.98; $P < 0.001$). Interestingly, the difference in identification between the ingroup and outgroup was significantly higher after scanning than before (before fMRI scanning: difference identification with IG > OG = 1.52; after fMRI scanning: difference identification with IG > OG = 2.24; $P < 0.001$), validating participants' engagement with the fMRI task.

Personality characteristics

The SPQ-B total score showed acceptable internal consistency (Cronbach's α: 0.663). There was a significant interaction between the rs1006737 genotype and CIT for schizotypal personality ($P = 0.043$, Wald $\chi^2 = 4.01$), indicating that the most prominent schizotypal traits were in the group with both genetic and environmental risk factors (see Table 1). There was no main effect of rs1006737 or CIT on the SPQ-B. In a post hoc analysis, SPQ-B total score was not associated with vACC neural activity.

fMRI results

In the ACC ROI analyses, we found a significant interaction between the MPG group (ingroup/outgroup) and emotion (happy/angry), suggesting that group membership influences the processing of facial emotions in the vACC (MNI xyz = 8, 42, 0; F = 23.71; cluster size k = 423 voxels; df = 177; $P<0.001$; FWE corrected). This interaction effect was confirmed by exploratory whole-brain analyses (see Supplementary Figure S1 and Supplementary Table S1). The bar graphs in Figure 1 illustrate the PSC for activity in the ACC ROI and indicate that emotional valence modulated vACC activation for ingroup members only—there was a stronger deactivation for angry than for happy facial ingroup emotion. There were no significant main effects of MPG group membership or emotional facial expression in the ACC ROI. For the respective results of the whole-brain analyses, see Supplementary Material.

Table 1. Sample characteristics

	rs-1006737 genotype				
	GG no CIT ($n = 34$)	GG CIT ($n = 37$)	AG/AA no CIT ($n = 55$)	AG/AA CIT ($n = 52$)	P
Sex ratio (m/f)	22/12	12/25	32/23	24/28	0.028[a]
Age (years)	24.2 ± 3.0	24.6 ± 3.2	24.5 ± 3.7	23.2 ± 2.8	0.114[b]
SPQ-B*	3.7 ± 2.9	3.5 ± 2.6	3.2 ± 2.5	4.7 ± 3.0	0.038[b]
THQ	5.6 ± 6.08	8.8 ± 8.7	6.1 ± 6.0	8.7 ± 6.0	0.040[b]
CIT	–	2.1 ± 1.3	–	1.75 ± 0.8	0.208[c]

Note: Values represent mean ± standard deviation; SPQ-B, Schizotypal Personality Questionnaire-Brief; THQ, Trauma History Questionnaire; CIT, Childhood Interpersonal Trauma.
[a]Pearson χ^2 for differences in frequencies.
[b]One-way ANOVA for mean differences.
[c]Two-sample t-test.
*P = <0. 05 for interaction of rs1006737 (GG *vs* GA/AA) and childhood interpersonal trauma (yes *vs* no).

Gene–environment interaction

There was a significant interaction for neural processing within the vACC between the factors rs1006737 (GG *vs* GA/AA), CIT (yes *vs* no), emotional valence (happy *vs* angry) and group membership (ingroup *vs* outgroup; Wald $\chi^2 = 4.753$, $P < 0.05$; see Figure 2). The bar graphs in Figure 2 illustrate the PSC for the activity in the vACC for the 16 conditions (2×2×2×2). There was a main effect of trauma for the processing of happy ingroup members (green bars on the far left; post-hoc interaction Wald $\chi^2 = 5.2$, $P < 0.05$). Most interestingly, there was an interaction between rs1006737 and trauma for vACC activity in response to the angry outgroup (blue bars on the far right; post-hoc interaction Wald $\chi^2 = 9.1$, $P < 0.01$; see Figure 2). Importantly, these results remained significant when using a continuous variable for CIT (see Supplementary Material). We found no main effects for rs1006737 and CIT in terms of vACC activation across conditions (for both, $P > 0.2$) and no effect of genetic and environmental risk factors for facial expressions in the angry ingroup or happy outgroup (for all, $P > 0.2$).

Discussion

Genetic and environmental factors contribute to the development of schizophrenia. However, the specific neural pathways and interactions of different risk factors remain to be further clarified (Van Os *et al.*, 2014). Here, we investigated the neural correlates of ingroup vs. outgroup processing in a large group of healthy subjects using fMRI by applying a MGP with emotional facial expressions as video stimuli. In line with our hypotheses, we found (1) an interaction of neural activation for the processing of emotional valence (happy *vs* angry) and group membership (ingroup *vs* outgroup) in the vACC. We further revealed (2) an interaction of vACC activation during group-dependent (ingroup *vs* outgroup) emotion processing for the risk factors CIT and rs1006737. Specifically for angry outgroup emotion processing, there were different effects of trauma depending on genetic predisposition.

The interaction of the two factors, emotional valence and group membership, was driven by differences in vACC activation in terms of the emotional valence of a presented face (angry or happy) for encounters with ingroup members only. This was reflected by a stronger deactivation for angry compared to happy facial expressions for ingroup members. The vACC is a key region in the fronto-limbic emotion regulatory system (Etkin *et al.*, 2011). A distinction of the emotional valence on a neural level in this region might reflect a higher emotional relevance of the ingroup. Indeed, previously the vACC has been found to be activated during the processing of self-related stimuli (Heatherton, 2011). However, at the same time, reduced

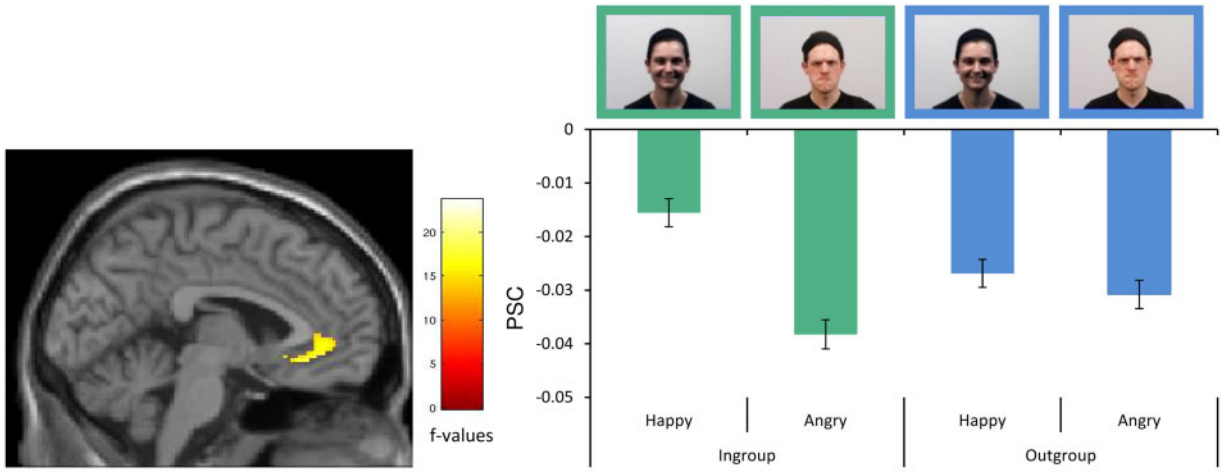

Fig. 1. Interaction of Emotion and Group. The interaction of group (ingroup *vs* outgroup) and emotion (happy *vs* angry) factors in the ACC ROI is driven by differences in emotional ingroup processing. PSC = percent signal change. Sex was equally distributed among the ingroup and outgroup and all actors depicted all facial expressions.

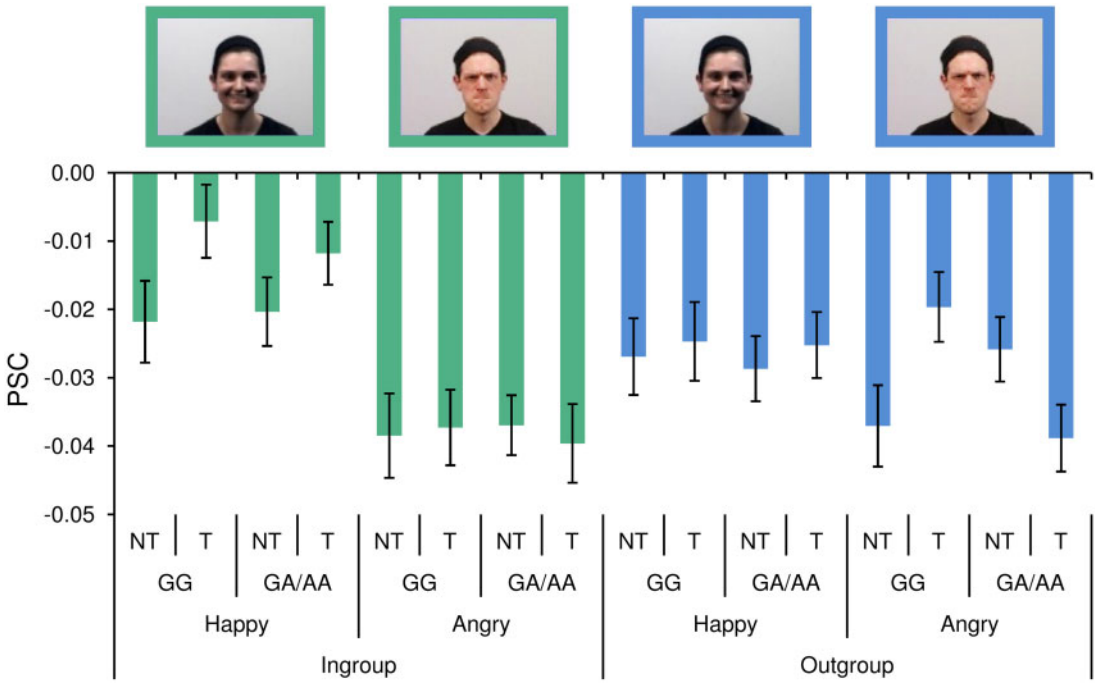

Fig. 2. Interaction of rs1006737 and childhood trauma with emotion and group. At the condition level, there is significant interaction between rs1006737 and trauma, particularly for processing angry outgroup emotions. T = childhood trauma; NT = no childhood trauma; GG or GA/AA of rs1006737 (A=risk allele); PSC = percent signal change. Sex was equally distributed among the ingroup and outgroup and all actors depicted all facial expressions.

emotional discrimination for outgroup members in this region also reflects an indifference for opposite emotional signals of outgroup members on a neural level, which might become relevant in situations where confrontation with outgroup members is frequent—as in urban dwellers or migrants. Indeed, misperception of emotions has been shown for faces not belonging to the subject's own race (Elfenbein and Ambady, 2002). However, here we showed for the first time similar results on a neural level using a MGP and therefore, we experimentally avoided ethnic bias. Such an indifference regarding outgroup emotional signals might also have consequences on a behavioural level. In the study by Volz and colleagues, neural vACC activation has been associated with altered behaviour towards the (minimal) outgroup in terms of a discrimination of the outgroup in a money distribution game (Volz and Kessler, 2009). Hence, altered vACC activation regarding group membership is related to an intergroup bias in both processing of emotional signals and behavior.

With our study, we were able to show that the processing of ingroup/outgroup emotional signals in the vACC furthermore interacts with the genetic and environmental risk factors rs1006737 and CIT, respectively. We found a significant fourfold interaction of the (within-subject) factors group and emotion and the (between-subject) factors rs1006737 and CIT. This was driven by a significant interaction of rs1006737 and CIT specifically for angry outgroup emotions. Depending on rs1006737 risk allele carrier status (GG *vs* GA/AA) CIT was related to an increased (GG) or decreased (GA/AA) vACC activation during

angry outgroup processing (see Figure 2). This inverted effect of CIT results in a similar vACC activation for angry outgroup facial expressions in subjects with no risk factors (GG + NT) and the subjects with both risk factors (GA/AA + T). Hence, we cannot interpret this interaction as a simple combined effect of both risk factors. Regarding the vACC in its interplay with the limbic system, CIT and rs1006737 both are related to alterations on various levels. Functional fronto-limbic connectivity for emotional facial expressions is reduced in individuals carrying the rs1006737 risk allele (Wang *et al.*, 2011) and altered in a complex manner in individuals with aversive childhood experience (Williams *et al.*, 2006). On a brain structural level, CIT and rs1006737 have opposite effects in the vACC: rs1006737 risk allele is associated with increased vACC volume (Wang *et al.*, 2011) while childhood emotional maltreatment and traumatic experiences are associated with reduced vACC volume (Cohen *et al.*, 2006; Van Harmelen *et al.*, 2010; Baker *et al.*, 2013). Increased vACC volume in rs1006737 risk allele carriers might reflect a compensatory mechanism of inefficient neuroplasticity (Wang *et al.*, 2011) whilst CIT negatively affects neurogenesis as well as production of neurotrophic factors through a stress-induced release of glucocorticoids and pro-inflammatory cytokines (Cattaneo *et al.*, 2015). A history of trauma induces changes and aberrant functioning of the hypothalamic pituitary-adrenal axis (Miller *et al.*, 2007) which is associated with depression or schizophrenia and other psychotic disorders (Krishnan and Nestler, 2008; Walker *et al.*, 2008). At the same time L-type voltage-gated calcium channels in the limbic system encoded by *CACNA1C* are involved in the regulation of the hypothalamic pituitary-adrenal axis by exhibiting glucocorticoid-mediated increases in calcium currents (Karst *et al.*, 2002; Chameau *et al.*, 2007). Furthermore, given the effects of rs1006737 on neuroplasticity and memory formation in frontal and mesolimbic structures (Erk *et al.*, 2010; Wang *et al.*, 2011; Bhat *et al.*, 2012), trauma and rs1006737 are likely to converge in brain structure and functioning on multiple levels in a complex manner. Hence, the inverted effect in vACC activation of CIT depending on rs1006737 risk allele carrier status for angry outgroup processing, revealed by our study, is likely to be a result of a complex interaction in neuroplasticity and connectivity of the vACC and converging effects of both risk factors in associated brain regions. Future studies have to disentangle the complex network(s) in which the inverted effect by CIT on angry outgroup emotion processing is embedded. Our results substantiate that relevant effects of genetic and environmental (risk) factors on a neural level evolve through their interaction and remain hidden when examining them in isolation. However, with this study, we could for the first time reveal an interaction of gene (rs1006737) and environment (CIT) in vACC ingroup/outgroup processing.

Ingroup/outgroup processing is especially relevant for individuals moving in complex social structures with a variety of groups—such as urban dwellers and migrants. Indeed, urban dwellers and migrants both show relevant alterations in vACC functioning—urban living and upbringing has been associated with differences in vACC functioning in response to social evaluative stress (Lederbogen *et al.*, 2011). An ethnic minority group exhibited increased heart rate and increased subjective emotional response as well as differences in vACC functioning and connectivity in response to social stress compared to an autochthon control group (Akdeniz *et al.*, 2014b). Another study revealed a reduced vACC volume and, in addition, a negative correlation of early urbanicity and vACC volume in male migrants (Akdeniz *et al.*, 2017). The causal influence of migration and urban living on schizophrenia risk is not yet fully understood (Cantor-Graae and Pedersen, 2013; Heinz *et al.*, 2013; Van Os *et al.*, 2014). Based on our results, we speculate that the ubiquitous encounter of outgroup members, experienced by migrants and urban dwellers, is—in combination with genetic and additional environmental risk—in itself a risk factor for schizophrenia (Abed and Abbas, 2011).

An incidental finding was the association of CIT with a lower vACC deactivation for happy ingroup facial expressions resulting in an increased difference between neural activation for happy and angry ingroup processing. In the past, childhood maltreatment was related to an increased difference between vACC activation for happy and sad facial expressions (Dannlowski *et al.*, 2013). Furthermore, childhood maltreatment is associated with an attention bias away from happy facial emotions depending on attachment style (Davis *et al.*, 2014). However, our finding implies an intergroup bias in this context, which should be further investigated in the future.

The subgroup with combined risk, presence of rs1006737 risk allele and experience of CIT (GA/AA + T), showed higher schizotypal traits than the other groups. This finding shows that in our sample the interaction of rs1006737 and CIT is in fact associated with higher schizophrenia vulnerability (Vollema *et al.*, 2002). Importantly, schizotypal traits were not associated with vACC functioning, indicating that the effects described above are not confounded by variability in schizotypal traits in our sample but can be traced back to the interaction of rs1006737 and CIT.

Several limitations of this study have to be noted. During fMRI scanning, the participants only watched videos and no behavioral data, self-report data or physiological measures were collected to not distort the automatic response to the presented faces. Hence, there are no additional data from the scanner with which to correlate our imaging results. Further, although happy and angry facial expressions represent two contrary emotions, there are plenty of other emotions and nuances of facial expressions.

With this study, we demonstrate that distinction of opposite emotional signals regarding neural activity in the vACC—a major hub of emotional processing and regulation—depends on group membership. Furthermore, we confirm the putative role of the vACC as a converging zone of genetic and environmental risk factors of schizophrenia by demonstrating the modulation of vACC functioning in response to negative outgroup emotion by childhood interpersonal trauma and rs1006737 risk allele carrier status. On a neurophysiological basis, gene–environment interactions are still poorly understood and the investigation of these effects is in its early stages (Van Os *et al.*, 2014). There is huge potential in this research area for increasing our understanding of the pathogenesis of psychiatric disorders. With our work, we took a step in this direction by revealing for the first time that a gene–environment interaction of schizophrenia risk factors influences facial emotion processing depending on group membership.

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Supplementary data

Supplementary data are available at *SCAN* online.

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