

ADRA2B genotype modulates effects of acute psychosocial stress on emotional memory retrieval in healthy young men

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ABSTRACT

Previous studies have shown that acute psychosocial stress impairs retrieval of declarative memory with emotional material being especially sensitive to this effect. A functional deletion variant of the ADRA2B gene encoding the $\alpha 2B$ -adrenergic receptor has been shown to increase emotional memory and neural activity in the amygdala. We investigated the effects of acute psychosocial stress and the ADRA2B allele on recognition memory for emotional and neutral faces. Forty-two healthy, non-smoker male volunteers (30 deletion carriers, 12 noncarriers) were tested with a face recognition paradigm. During encoding they were presented with emotional and neutral faces. One hour later, participants underwent either a stress ("Trier Social Stress Test (TSST)") or a control procedure which was followed immediately by the retrieval session where subjects had to indicate whether the presented face was old or new. Stress increased salivary cortisol concentrations, blood pressure and pulse and impaired recognition memory for faces independent of emotional valence and genotype. Participants showed generally slower reaction times to emotional faces. Carriers of the ADRA2B functional deletion variant showed an impaired recognition and slower retrieval of neutral faces under stress. Further, they were significantly slower in retrieving fearful faces in the control condition. The findings indicate that a genetic variation of the noradrenergic system may preserve emotional faces from stress-induced memory impairments seen for neutral faces and heighten reactivity to emotional stimuli under control conditions.

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1. Introduction

Acute psychosocial stress triggers a fast response inducing the release of noradrenaline and a slow response inducing the release of glucocorticoids. In humans, it has been shown that elevated levels of glucocorticoids impact on a variety of cognitive functions, especially learning and memory (reviewed in (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007)). This influence depends critically on the timing of the stressor relative to the memory phase (Schwabe, Wolf, & Oitzl, 2010). Acute stress or administration of stress hormones before memory encoding improves later retrieval while administration of stress or stress hormones before retrieval often impairs performance (reviewed in (Wolf, 2008)).

For example, rats showed impaired spatial long-term memory when receiving a footshock prior to retention. This stress induced deficit could be abolished by blocking corticosterone synthesis (de Quervain, Roozendaal, & McGaugh, 1998). In humans, several

studies provide evidence for impairments of memory when the stressor is applied prior to retrieval (Kuhlmann, Piel, & Wolf, 2005; Tollenaar, Elzinga, Spinhoven, & Everaerd, 2008). Impairments were mainly demonstrated in tasks using verbal material and free recall (Buchanan, Tranel, & Adolphs, 2006; Smeets, Otgaar, Candel, & Wolf, 2008). The stress-induced impairments are in line with the finding that pharmacological enhancement of glucocorticoid levels prior to retrieval reduced cued recall of word pairs learned 24 h earlier and decreased neural activity in the medial temporal lobe (de Quervain et al., 2003).

Emotional memory is especially prone to acute psychosocial stress. In humans, emotional memory has often been studied by using emotional and neutral verbal material which volunteers had to recall 24 h later. Using such an approach, Kuhlmann et al. (2005) and Smeets et al. (2008) Smeets (2011) provide evidence that the stress induced impairment of verbal memory retrieval is stronger for emotional than for neutral words. Stress induced memory impairments are however also evident with shorter delays between encoding and retrieval. Buchanan and colleagues found stress-induced impairments in free recall of moderately arousing words 1 h after encoding. Similar impairments were reported by Merz et al. for socially relevant information (Buchanan et al., 2006; Merz, Wolf, & Hennig, 2010).

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Several studies investigated the interaction between glucocorticoids and noradrenaline with respect to encoding of emotional memories. These findings suggest that an interaction of these two endogenous modulators impacts on neural activity in hippocampus and amygdala, increasing memory for emotional items (Kukolja, Klingmuller, Maier, Fink, & Hurlmann, 2011; van Stegeren, Roozendaal, Kindt, Wolf, & Joels, 2010). Whether changes in noradrenergic activity also impact on retrieval of emotional memories is less well understood. While some studies, like (Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009) did not find any evidence for impaired memory after blockade of noradrenergic activity with propranolol prior to retrieval, others found that the drug reduced retrieval of emotional material, an effect which was still evident 24 h later in the absence of the drug (Kroes, Strange, & Dolan, 2010). De Quervain, Aerni, and Roozendaal (2007) and de Quervain et al. (2007) further investigated the interaction of propranolol administration and acute stress on recall of emotionally arousing words. They found that noradrenergic blockade alone did not affect recall of emotional or neutral words, but prevented the impairment of emotional memory induced by cortisone treatment.

Additional evidence for a role of noradrenaline in emotional memory comes from genetic studies. A functional deletion variant of the *ADRA2B* gene which is characterised by a loss of three glutamic acid residues (301–303) in the third intracellular loop encoding the α_2B subunit of the noradrenaline receptor, acts as a loss-of-function variant and increases noradrenaline availability. Behaviorally it has been shown that deletion carriers have enhanced memory for emotional pictures and it was suggested that this effect is due to an emotional arousal-induced activation of noradrenergic neurotransmission (de Quervain, Aerni, et al., 2007; de Quervain, Kolassa, et al., 2007). fMRI data suggest that deletion carriers exhibit increased neural activity in the amygdala during encoding of emotional pictures (Rasch et al., 2009). Further, acute stress induced by showing short movie clips with highly aversive content, increased phasic amygdala responses to dynamically morphing emotional faces in deletion carriers but not in non-carriers. This suggests that stress modulates amygdala processing in a genotype specific way (Cousijn et al., 2010). However, whether acute stress shows different effects on emotional memory as a function of *ADRA2B* receptor polymorphism is still unknown.

The present study aimed to investigate whether acute psychosocial stress differentially impacts on recognition of neutral and emotional material as a function of *ADRA2B* genotype. Participants performed a recognition memory task for neutral and negative emotional faces and were exposed to the Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993) prior to memory retrieval. We expected to find impaired memory retrieval after stress, especially with respect to emotional faces. Further, we expected a genotype specific modulation of memory retrieval.

2. Materials and methods

2.1. Participants

Forty-five young, healthy men between 18 and 30 years of age (23.63 ± 0.44) and a body mass index between 18 and 25 participated in this study. None of them suffered from any acute or chronic disease or took medication. The study was approved by the ethics committee of the University of Oldenburg, and subjects provided written informed consent. Data of one participant were excluded because of a high number of missed responses (50% missed), and data of two participants were excluded due to technical failure. Of the remaining 42 subjects, 21 subjects were heterozygous and 9 subjects were homozygous carriers of the deletion variant of *ADRA2B*. 12 subjects did not carry the deletion variant.

As in related studies (Cousijn et al., 2010; Rasch et al., 2009), we treated homozygote and heterozygote carriers of the deletion variant of *ADRA2B* ($n = 30$) as one group (deletion carriers).

2.2. Design and procedure

We combined a standardised psychosocial stress protocol with a face recognition memory task which consisted of an encoding and retrieval phase separated by 75 min (including a 60-min-break and a 15-min psychosocial stress test). Due to the high difficulty level of the task we refrained from a longer delay between encoding and retrieval. Stress or a respective control procedure was applied in a within subject cross over design prior to retrieval. Stress and control sessions were separated by approx. 1 week. Testing took place between 8:30 a.m. and 2:30 p.m. Behavioural, physiological and subjective data were collected in order to measure stress effects and potential stress by genotype interactions.

2.3. Psychosocial stress

We used the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), which is a standardised and well established treatment to induce psychosocial stress in a laboratory setting. After an anticipatory preparation period, participants had to perform a free speech in front of a committee (fictitious job interview), followed by a mental arithmetic task (counting backwards from 2043 in steps of 17). Each of the three periods lasted 5 min whilst participants were video and voice recorded for potential post-analysis. This protocol is a combination of social-evaluative threat and an uncontrollable situation, which is consistently associated with a significant cortisol increase in saliva and blood (Dickerson & Kemeny, 2004). The uncontrollable and evaluative aspects were omitted in the control condition, where participants had to perform a free speech (about a recently experienced motion picture or book) and an easy mental arithmetic task (counting forwards from zero in steps of 15) in an empty room without committee and recording (description of the placebo TSST see (Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009)).

2.4. Face recognition memory task

We used a face recognition memory task since emotional faces strongly activate the amygdala (Dolcos, LaBar, & Cabeza, 2005) and since neutral and emotional stimuli are well comparable in terms of visual input.

2.4.1. Face databases and preparation

Neutral and emotional faces were selected from several databases such as KDEF (Lundqvist, Flykt, & Oehman, 1998), Nimstim (Tottenham et al., 2009), 2D facial emotional stimuli (Gur et al., 2002), Ekman (Ekman & Friesen, 1976), MITCBL face recognition database (Weyrauch et al., 2004), PICS and Essex face database (see acknowledgement). The hair was removed and faces were converted to grey scale and a size of 85 (width) \times 127 (height) pixels with Corel DRAW Graphics Suite 12. All faces were presented on a grey background. Even though faces were already classified in the databases used we performed another rating of the final set of faces used in this study by a separate set of volunteers. Ratings were made according to type of emotion (fear, disgust, neutral, other) and emotional expressiveness (rated from 1 to 4) according to (Goeleven, Raedt, Leyman, & Verschuere, 2008, Treese, Brinkmann, & Johansson, 2003). Emotional faces were rated on average by 53.57% of volunteers as fearful, 32.86% of volunteers as disgust, 13.57% of volunteers as showing another negative emotion. On average, 63.5% of volunteers rated the faces as showing a

strong emotional expression. Neutral faces were rated by all of volunteers as neutral.

2.4.2. Memory task paradigm

During encoding, participants were presented randomly with 100 faces with either emotional or neutral expression (half emotional and half neutral). Each face was displayed for 2 s, with an inter-stimulus-interval (ISI) from 2 to 12 s. Participants had to press one of two buttons to indicate the gender of the displayed face. One hour after encoding, participants were exposed to either the TSST or the control condition which was followed by the retrieval phase. During retrieval, participants were presented randomly with 150 emotional and neutral faces: 100 faces from the encoding session (old) and 50 new faces (again half emotional and half neutral). Each face was displayed for 2.5 s, with an ISI of 2–12 s. Subjects had to indicate whether the displayed face was an old face or a new face, by pressing the corresponding button. Participants were instructed and trained prior to the task. Training consisted of an encoding-training session with 15 faces and a retrieval-training session with 25 faces, which were not used in the experiment. The paradigm was piloted in a separate set of volunteers ($n = 20$) involving remember/know judgments to investigate whether the recognition of faces is primarily based on recollection or familiarity (Rajaram, 1993). From all faces correctly identified as old, 62.7% obtained a remember response whereas 37.3% obtained a know response. Remember responses were faster than know responses (mean \pm SEM 1526 \pm 48 ms and 2142 \pm 76 ms respectively). Since several subjects reported difficulties in deciding whether they remember or know a face, remember/know judgments were not used in the experiment.

2.5. Physiological and subjective measures

Salivary concentrations of free cortisol, blood pressure, pulse and subjective mood ratings were collected at four time points: (i) prior to the encoding phase, (ii) prior to the start of the TSST/control condition, (iii) directly afterwards and (iv), after completion of the retrieval session (i.e., approx. 40 min after TSST). Saliva was collected using Salivette collection devices (Sarstedt AG & Co., Nümbrecht, Germany), which were stored afterwards at -20°C until biochemical analysis. Biochemical analysis was performed by the lab of Prof. Dr. C. Kirschbaum, Dresden, Germany. Salivary levels of free cortisol were measured using a luminescenceimmunoassay (IBL GmbH, Hamburg, Germany). Inter- and intra-assay variations were below 15%. Affective responses were assessed with the German version of the Multidimensional Mood State Questionnaire (MDBF) (Steyer et al., 1997) after collection of saliva samples. The questionnaire consists of 24 items with a five-point rating scale each. These 24 items rely on three underlying dimensions: good mood-bad mood, alertness-tiredness, calmness-nervousness.

2.6. Genotyping

DNA was extracted from oral epithelium cells according to (Walsh, Metzger, & Higuchi, 1991). Genotyping was performed according to (Rasch et al., 2009) by the 'Institut für Polymorphismus- und Mutationsanalytik', Homburg, Germany.

2.7. Statistical analysis

Accuracy and median reaction times were calculated for each trial type and condition in each subject. Responses were classified as hits (old face presented and correctly recognised as old), correct rejections (new face presented and correctly recognised as new), false alarms (new face presented and erroneously identified as old) and misses (old face presented and not recognised). We fo-

cused our statistical analysis on four measures: (i) hit rate and (ii) reaction time (RT) for hits and two measures of classical signal detection theory, (iii) d' and (iv) response bias (criterion c). Data were analysed with two repeated measures ANOVAs. The first ANOVA tested for genotype independent effects as a function of the within-subject-factors condition (stress/control) and emotion (emotional/neutral). The second ANOVA tested for genotype specific effects using three factors: the within-subject-factors condition and emotion and the between-subject-factor genotype (*ADRA2B* deletion carriers/non-carriers). Since a significant genotype effect on blood pressure during retrieval was found, we included systolic blood pressure changes ($\text{BP}_{\text{stress}}(\text{after retrieval} - \text{after TSST}) - \text{BP}_{\text{control}}(\text{after retrieval} - \text{after TSST})$) as a covariate into our analyses. Note that results were not different when the covariate was not entered into the analysis. Significant effects were followed by post-hoc t -tests (paired t -tests for comparison between control and stress condition, unpaired t -tests for comparison between genotypes). Physiological and mood effects were analysed with either paired-samples t -test (independent of genotype), or repeated measures ANOVA with the factor time point (prior to TSST, after TSST and after scanning), condition (stress/control) and genotype (carrier/non-carrier). All statistical analyses were performed using SPSS 18.0 (SPSS GmbH, Munich, Germany).

3. Results

3.1. Genotype independent effects of psychosocial stress

3.1.1. Physiological and mood effects

Strong responses to acute psychosocial stress as implemented by the TSST were evident in cortisol and cardiovascular measures as well as in mood ratings (Fig. 1). A within group comparison after TSST or the respective control treatment revealed significantly higher salivary cortisol concentrations in the stress as compared to the control group ($t(41) = 7.13, p < 0.001$). Blood pressure and pulse were significantly increased after the TSST (systolic pressure: $t(41) = 3.31, p < 0.01$; diastolic pressure: $t(41) = 2.51, p < 0.05$; pulse: $t(41) = 2.54, p < 0.05$).

After TSST treatment, subjects reported decreased mood (good-bad mood scale: stress: 28.07 ± 0.85 , control: 33.86 ± 0.67 , $t(41) = -6.04, p < 0.001$) and increased nervousness (calm-nervous scale: stress: 24.40 ± 0.93 , control: 31.86 ± 0.62 , $t(41) = -8.15, p < 0.001$). No significant differences were found for alertness (alert-tired scale: stress: 29.95 ± 0.81 , control: 29.88 ± 0.81 , $t(41) = 0.09, p = 0.932$).

3.1.2. Face recognition memory

We first tested whether psychosocial stress prior to retrieval impacts on face recognition memory independent of genotype. We found a significantly reduced sensitivity of face recognition memory under stress (main effect of condition $F(1,40) = 4.66, p = 0.038$, see Fig. 2A). There was a tendency for reduced hit rates under stress ($F(1,40) = 3.91, p = 0.055$, see Fig. 2B). D' -prime values and hit rates did neither show a main effect of emotion ($F(1,40) = 0.016, p = 0.901$ and $F(1,40) = 0.107, p = 0.745$ respectively) nor a condition by emotion interaction ($F(1,40) = 0.097, p = 0.757$ and $F(1,40) = 0.574, p = 0.453$ respectively). In other words, we found a stress-induced impairment of face recognition which was similar for neutral and emotional faces. Note that the response criterion c was not significantly modulated by stress or emotion ($F(1,35) = 0.164, p = 0.688$; $F(1,35) = 0.288, p = 0.595$; data not shown).

Reaction time analysis revealed a main effect of emotion with slower RTs to correctly remembered emotional faces as compared to neutral faces ($F(1,40) = 7.06, p = 0.011$, see Fig. 2C). There was

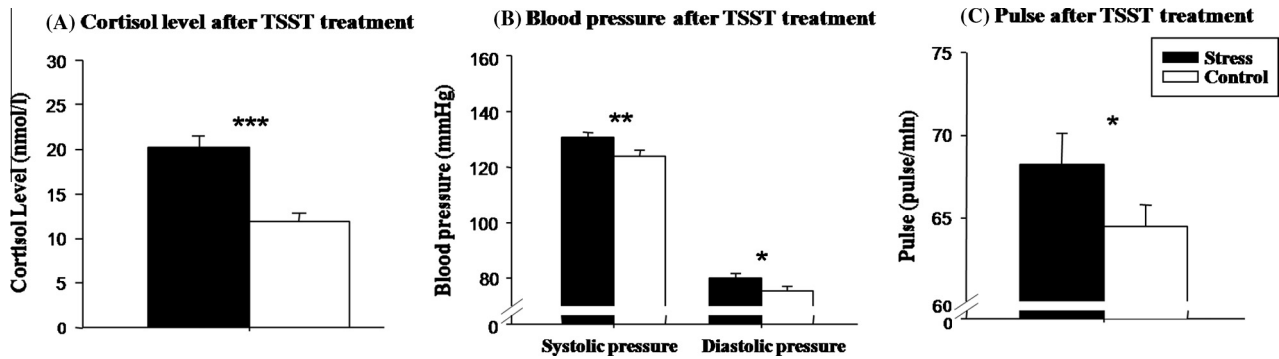


Fig. 1. Effects of psychosocial stress on salivary cortisol concentrations (A), blood pressure (B) and pulse (C) after the stress and control procedure. (Mean and SEM, $0.01 < p \leq 0.05$; $0.001 < p \leq 0.01$; $***p \leq 0.001$).

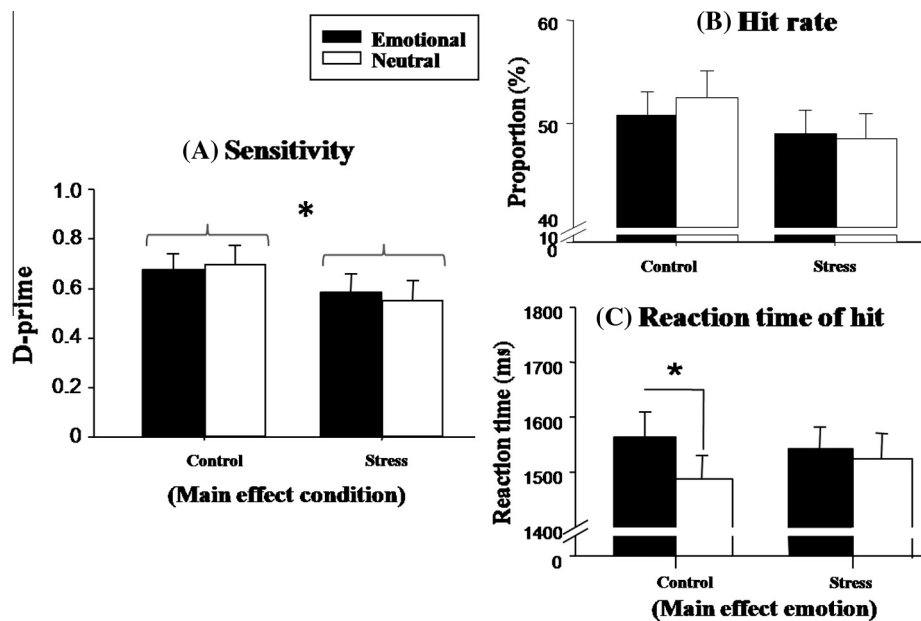


Fig. 2. Genotype independent effects of acute psychosocial stress on face recognition memory (mean and SEM). A. Effects on sensitivity (d-prime). Stress prior to retrieval impaired accuracy for both emotional and neutral faces (*ANOVA $p < 0.05$). B. Effects on hit rate. C. Effects on speed of face recognition memory. Retrieval of emotional faces took longer than retrieval of neutral faces (significant main effect of emotion) which was primarily evident in the control condition (* t -test $p < 0.05$), the condition by emotion interaction was however not significant.

neither a main effect of condition ($F(1,40) = 0.112$, $p = 0.740$) nor a condition by emotion interaction ($F(1,40) = 1.053$, $p = 0.311$). However, post-hoc t -tests revealed that the slower reaction times in retrieving emotional faces were primarily evident in the control condition ($t(41) = 2.06$, $p = 0.046$), but not in the stress condition ($t(41) = 0.983$, $p = 0.332$).

3.2. Effects of psychosocial stress as a function of ADRA2B genotype

3.2.1. Physiological and mood effects

There was no significant difference in cortisol concentrations or mood ratings as a function of *ADRA2B* genotype. However, stress-induced cardiovascular effects differed as a function of genotype (see Fig. 3). While increases of systolic blood pressure were observed in both genotypes after TSST, non-carriers showed prolonged cardiovascular responsivity with elevated blood pressure values even after 40 min after the start of the TSST (time by condition by genotype interaction: $F(1,40) = 5.70$, $p < 0.05$; post-hoc t -test ($t(40) = -3.43$, $p \leq 0.001$).

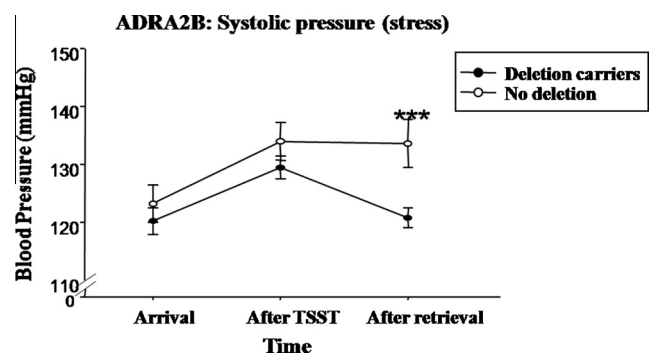


Fig. 3. Systolic blood pressure as a function of time, condition and genotype. Non-carriers of the *ADRA2B* deletion show a prolonged cardiovascular response to stress (*** t -test $p < .001$).

3.2.2. Face recognition memory

In a second step, we analysed the effects of stress on face recognition memory as a function of genotype. The stress induced reduction of d-prime values shown above was not modulated by *ADRA2B*

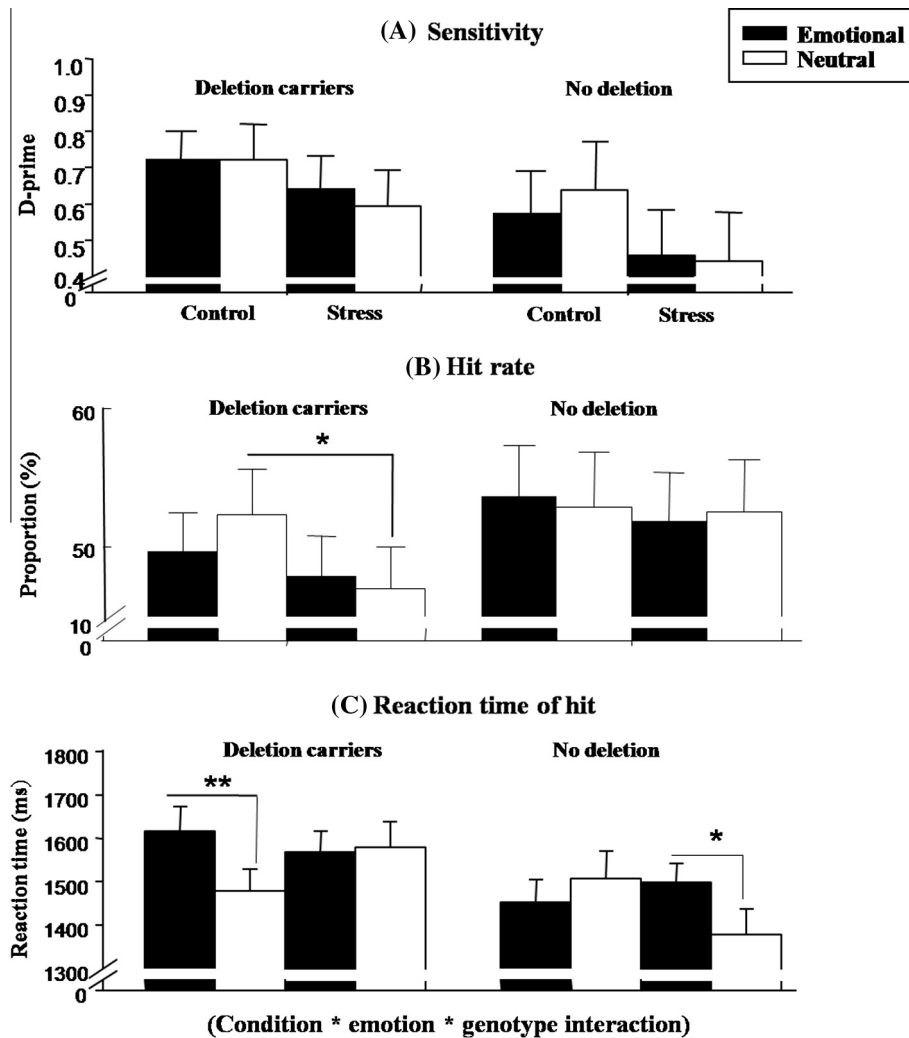


Fig. 4. Effects of acute psychosocial stress on face recognition memory as a function of *ADRA2B* genotype (mean and SEM). A. Effects on sensitivity (d-prime). Sensitivity of face recognition memory did not reveal any genotype effects. B. Effects on hit rate. In deletion carriers, hit rate was significantly impaired for neutral faces in the stress condition. C. Effects on speed of face recognition memory. RT data revealed a significant genotype by condition by emotion interaction. Deletion carriers showed a slower reaction time to emotional faces under control conditions which was not observed under stress or in non-carriers under control conditions (**t*-test $p < 0.05$, ***t*-test $p < 0.01$).

genotype (main effect of genotype $F(1,34) = 0.001$, $p = 0.982$; genotype by condition interaction $F(1,34) = 2.465$, $p = 0.125$; genotype by emotion interaction $F(1,34) = 0.635$, $p = 0.431$; genotype by condition by emotion interaction $F(1,34) = 0.091$, $p = 0.765$, see Fig. 4A). There was also no significant genotype-dependent effect on hit rate (main effect of genotype $F(1,39) = 0.988$, $p = 0.326$; genotype by condition interaction $F(1,39) = 0.273$, $p = 0.605$; genotype by emotion interaction $F(1,39) = 0.162$, $p = 0.689$; genotype by condition by emotion interaction $F(1,39) = 0.345$, $p = 0.560$). However, post-hoc *t*-test showed a decreased hit rate for neutral faces under stress as compared to control in deletion carriers ($t(29) = -2.28$, $p = 0.030$). Non-carriers showed no significant differences in hit rate for neutral faces under stress as compared to control ($t(11) = -0.110$, $p = 0.914$). Note that the response criterion *c* was not modulated by genotype (data not shown).

Analysis of reaction time data revealed a genotype by condition by emotion interaction ($F(1,39) = 7.429$, $p = 0.010$ see Fig. 4C), no other interactions or main effects were significant (main effect of genotype $F(1,39) = 1.395$, $p = 0.245$; genotype by condition interaction $F(1,39) = 2.177$, $p = 0.148$; genotype by emotion interaction $F(1,39) = 0.003$, $p = 0.960$). Post hoc *t*-tests revealed that *ADRA2B* deletion carriers showed slower RTs to emotional faces in the

control condition ($t(29) = 2.92$, $p = 0.007$). This effect was abolished under stress, due to an increase of RTs to neutral faces, which showed a trend for significance ($t(29) = 1.98$, $p = 0.058$ compared against control and $t(40) = 1.97$, $p = 0.055$ compared against non-carriers). In contrast, non-carriers did not yield differential reaction times to emotional or neutral faces in the control condition but showed higher reaction times to emotional as compared to neutral faces under stress ($t(11) = 2.55$, $p = 0.027$). This was due to slower RTs to neutral faces under stress which showed a trend for significance ($t(11) = -1.91$, $p = 0.082$).

4. Discussion

We provide evidence that acute psychosocial stress impairs recognition memory for faces. Further, we show that a deletion variant of the gene coding the α_2B adrenergic receptor reduces hits to neutral faces under stress, an effect which was not present in non-deletion carriers. Reaction time data supports this evidence by showing a trend for slower retrieval of neutral faces under stress in deletion carriers. Hence, in deletion carriers emotional faces may be preserved from stress-induced memory impairments

seen for neutral faces. Additional genotype-specific effects were found in the control condition. Here, reaction time data provides evidence for slower retrieval of emotional faces in deletion carriers.

4.1. Genotype independent effects

The significant effect of psychosocial stress on salivary cortisol and subjective mood ratings replicates results of many prior studies and confirms that the employed psychosocial stress protocol (TSST) successfully induced a neuroendocrine and subjective stress response (Dickerson & Kemeny, 2004). Our behavioural results are in line with previous evidence showing impairments in memory performance when stress is applied prior to retrieval (Cousijn et al., 2010; Dolcos et al., 2005; Kuhlmann et al., 2005; Merz et al., 2010; Smeets, Jellic, & Merckelbach, 2006). While previous studies used words, pictures, movie clips or socially relevant information as stimuli, we here provide first evidence that psychosocial stress also impacts on recognition of faces. This finding may be of relevance for eyewitness testimonies and suggests that post-crime interrogations should avoid psychosocial stress (Morgan et al., 2007).

In contrast to studies using words or pictures, we could not replicate the often found enhanced memory for emotional items, nor a recognition bias (Buchanan, 2007; Maratos, Allan, & Rugg, 2000; Windmann & Kutas, 2001). Further, we did not find any evidence for an emotion specific stress-induced impairment in recognition memory. Rather, stress-induced decreases in recognition memory were present for both, neutral and emotional faces. There are only few studies which used face stimuli to investigate the effects of emotional valence on recognition memory. One study reported increased recognition of negative emotional faces (Keightley, Chiew, Anderson, & Grady, 2011), while others were unable to find emotional effects on accuracy measures of face recognition (Johansson, Mecklinger, & Treese, 2004) or even found an impairment (Harvey, Bodnar, Sergerie, Armony, & Lepage, 2009; Sergerie, Lepage, & Armony, 2007).

There are several reasons for the much weaker effect of emotion on recognition memory for faces. First, retrieval of faces is more difficult than retrieval of objects or words and it has been suggested that different brain areas and cognitive processes contribute to retrieval of faces as compared to words (Galli & Otten, 2011). Second, in face memory paradigms, memory retrieval is tested using measures of recognition rather than free recall. While free recall relies on recollection, recognition memory consists of two distinct processes, recollection and familiarity, the latter being less modulated by emotion (Kensinger & Corkin, 2003). Kuhlmann et al. (2005) suggested that stress effects on free recall are sometimes stronger than on cued recall, which is supported by findings of Merz et al. (2010), who observed significant impairments after stress for both recognition and free recall, but with stronger effects on free recall. In contrast, cortisone administration was found to impact only on measures of free recall but not recognition (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000).

Another factor which may have contributed to the lack of emotional modulation of recognition memory and the lack of an emotion by stress interaction is the rather short delay between encoding and retrieval. Most studies showing stress-induced impairments in memory retrieval, which were specific to emotional material, used delays of 24 h or longer in order to reliably separate retrieval from consolidation processes (Kuhlmann et al., 2005; Quesada, Wiemers, Schoofs, & Wolf, 2012; Smeets, 2011; Tollenaar et al., 2008). However even studies with short delays between encoding and retrieval found memory impairments (Merz et al., Buchanan et al.). A first fMRI study on stress and memory retrieval also reported reduced hippocampal activity during the retrieval of material learned 1 h prior to cortisol application (Oei et al., 2007). In contrast, improvements of memory retrieval

for emotional items are seen when stress or stress hormones are applied before or immediately after encoding, thus affecting consolidation (Cahill & Alkire, 2003; Kuhlmann & Wolf, 2006). Payne and colleagues (Payne et al., 2007) were able to show that the beneficial effects of stress prior to encoding were specific to emotional items, recall of neutral items was even impaired. We cannot exclude that our stress intervention, which was applied 1 h after encoding affected both, consolidation and retrieval. However, since we found impairments rather than improvements of memory, and since some prior studies also used short intervals, we think that a stronger action on retrieval processes is more likely.

Although facial emotion did not modulate accuracy measures, correct recognition of emotional faces took longer than recognition of neutral faces, an effect which was also found, at least numerically, in other studies using face stimuli (Johansson et al., 2004; Keightley et al., 2011; Sergerie et al., 2007). The effect was especially prominent in the control condition and numerically reduced under stress. In contrast to accuracy-related measures, reaction times are continuous response measures which may be more sensitive than categorical response measures (Jou, Matus, Aldridge, Rogers, & Zimmerman, 2004). Reaction time measures have been used previously in memory paradigms and were shown to correlate with confidence ratings (Jou et al., 2004; Ratcliff & Murdock, 1976). Faster reaction times thus may reflect the greater ease to retrieve memories with stronger representations. However, with respect to emotional material, a second process could influence reaction times. (Williams, Moss, Bradshaw, & Mattingley, 2005) have shown that visual search times to fearful faces are slower than to other emotional faces and speculate that fearful faces signal a potential threat in the environment, which directs attention away. Since we did not find any significant differences in accuracy measures for retrieval of emotional vs. neutral faces, we suggest that the significant increase in reaction times to emotional faces found here and by others could be explained by this second process which may be related to shifting attention away from the presented face.

4.2. Genotype dependent effects

Psychopharmacological studies provide evidence that noradrenaline interacts with other neurotransmitters, neuromodulators and stress hormones (Wust et al., 2004) in the amygdala and hippocampus to enhance long-term memory consolidation (McGaugh & Roozendaal, 2009), especially for emotional events (Cahill, Prins, Weber, & McGaugh, 1994). Furthermore, the noradrenergic system is also necessary for retrieval of recent memory (Murchison et al., 2004), and the coordinated action of noradrenergic neurons in locus coeruleus and amygdala activates forebrain fronto-hippocampal networks that are essential for memory retrieval (Sara, 2009; Sterpenich et al., 2006). Blocking noradrenergic activity with the β -adrenergic receptor antagonist propranolol abolished the declarative memory enhancement for emotional items, an effect which was still found on the following days, in the absence of the drug (Kroes et al., 2010). Studies investigating the interaction of propranolol and stress reported that propranolol alone did neither affect recall of emotional nor neutral words, but blocked the psychosocial stress-induced memory enhancement for emotional words (Schwabe et al., 2009) and a cortisone-induced impairment of recalling emotionally arousing words (de Quervain, Aerni, et al., 2007; de Quervain, Kolassa, et al., 2007). A similar result was also reported with regard to long-term spatial memory retrieval in rats (Roozendaal, Hahn, Nathan, de Quervain, & McGaugh, 2004). Thus, there is ample of evidence that the noradrenergic system modulates effects of stress on emotional memory and it is reasonable to assume that a genetic variation which impacts on noradrenergic neurotransmission may affect stress-induced effects on emotional memory.

Human genetic studies provide evidence that a genetic variation of noradrenergic neurotransmission, the *ADRA2B* deletion, enhances emotional memory, both for negative and positive scenes (de Quervain, Aerni, et al., 2007; de Quervain, Kolassa, et al., 2007). fMRI data suggests that this effect is related to an increased activation of the amygdala (Rasch et al., 2009) and inferior frontal gyrus (Urner et al., 2011) during successful emotional memory encoding in deletion carriers. Note however, that even though this indicates an effect of *ADRA2B* genotype on encoding, differences in noradrenergic neurotransmission are also present at retrieval and may impact on performance.

In contrast to the results of de Quervain, Aerni, et al. (2007) and de Quervain, Kolassa, et al. (2007), we did not find any evidence for enhanced emotional memory in deletion carriers of the *ADRA2B* polymorphism which may be due to our much smaller group size and the different stimulus material used. The *ADRA2B* deletion has also been investigated in relation to acute and chronic stress, irrespective of memory. Cousijn et al. (2010) induced acute stress via aversive movie clips and provide evidence for stronger phasic amygdala activity in deletion carriers under stress - even though stress induced increases in tonic amygdala activity were not modulated by genotype (Cousijn et al., 2010). Our accuracy data does not yield strong evidence for genotype specific effects of stress. The only significant finding was a reduction in hit rate for neutral items under stress which was found in deletion carriers only. This co-occurred with a tendency for slower RTs when retrieving neutral items in deletion carriers under stress, which may indicate difficulties in retrieving neutral memories. Hence, deletion carriers may be specifically prone to stress induced impairments in retrieval of neutral items while emotional items are preserved from stress induced impairments.

The reaction time data further suggest that deletion carriers showed a slower reaction to emotional faces under control conditions which was not observed under stress or in non-carriers under control conditions. If slower reaction times in retrieving emotional faces are primarily driven by a shift of attention to a potential threat in the environment, which is signaled by the emotional face, then our finding suggests an increase in emotional reactivity in deletion carriers which would be in line with increased amygdala activations found by Cousijn et al. (2010) and Rasch et al. (2009). Individual differences in selective attention to angry faces which were related to stress-induced cortisol reactivity were reported by Roelofs, Bakvis, Hermans, van Pelt, and van Honk (2007).

4.3. Blood pressure

We found a genotype-dependent effect of stress on blood pressure. Non-carriers of the *ADRA2B* deletion showed prolonged cardiovascular responsivity to the stressor. It is known that *ADRA2B* is important in the regulation of blood pressure, cardiovascular function and lipid metabolism, and a study in Chinese men has shown that *ADRA2B* non-carriers have higher blood pressure while studies of Caucasians yielded in consistent results (Zhang et al., 2005). We here report a relation between *ADRA2B* genotype and cardiovascular response to psychosocial stress, which was evident as prolonged recovery of systolic blood pressure in non-carriers of the *ADRA2B* deletion. Note that the initial cardiovascular response to the stressor was similar in both groups. Increases in systolic blood pressure and increases in plasma noradrenaline have also been described after administration of progesterone and naturally fluctuating progesterone levels were shown to modulate stress induced cortisol responses and emotional memory (Childs, Van Dam, & de Wit, 2010; Felmingham, Fong, & Bryant, 2012). Altered stress reactivity might translate into a heightened vulnerability for cardiovascular and psychiatric disorders in non-carriers.

4.4. Molecular mechanisms

Traditionally effects of stress on emotional memory have been linked to β adrenergic noradrenaline receptors. A recent animal study which used both, a pharmacological challenge and a genetic manipulation, revealed a complex interaction between stress, β adrenergic noradrenaline receptors and memory retrieval (Schutsky, Ouyang, Castelino, Zhang, & Thomas, 2011). Other animal studies indicate that glucocorticoids regulate α_2 adrenergic receptors in the brain (Flugge, 1999). The deletion of the α_2 adrenergic receptor encoding gene *ADRA2B*, which was studied here, has a pronounced effect on receptor phosphorylation leading to a loss of agonist-promoted desensitization, which evokes a partial uncoupling of the receptor from functional interaction with G proteins (Gi/o). Increases in stress hormones after acute psychosocial stress may thus influence α_2 receptors in a genotype specific way. Although the relationship between α_2 receptors and memory retrieval is unclear, one can assume that a change of α_2 receptors might mediate downstream molecular factors which could interact with β receptors and therefore suggest that genetic variations in *ADRA2B* might change the sensitivity to stress induced physiological and behavioural effects.

In summary, our study is the first to show that psychosocial stress prior to retrieval impairs recognition memory for both neutral and emotional faces. We provide evidence that the deletion variant of the *ADRA2B* gene decreases memory recognition for neutral items under stress and increases the speed of retrieving emotional information from memory under control conditions. The latter finding may indicate an attentional bias to emotional information in this group.

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Faces from Essex face database are downloaded from the website of Dr. Libor Spacek (<http://cswww.essex.ac.uk/mv/allfaces/index.html>) and faces from PICS database are downloaded from Psychological Image Collection at Stirling (<http://pics.psych.stir.ac.uk/>).

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