



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

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ARTICLE INFO

Article history:

Received 12 October 2012

Revised 20 March 2013

Accepted 22 March 2013

Available online 12 April 2013

Keywords:

Humans

Face recognition

Emotional memory

Stress

ADRA2B

Cortisol

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

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