

A deletion variant of the $\alpha 2b$ -adrenoceptor is related to emotional memory in Europeans and Africans

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Emotionally arousing events are recalled better than neutral events. This phenomenon, which helps us to remember important and potentially vital information, depends on the activation of noradrenergic transmission in the brain. Here we show that a deletion variant of *ADRA2B*, the gene encoding the $\alpha 2b$ -adrenergic receptor, is related to enhanced emotional memory in healthy Swiss subjects and in survivors of the Rwandan civil war who experienced highly aversive emotional situations.

Enhanced memory for emotional events is a well recognized phenomenon which has obvious adaptive value in evolutionary terms, as it is vital to remember both dangerous and favorable situations¹. Studies in animals and humans investigating the mechanisms underlying the memory enhancing effect of emotional arousal have indicated that this effect depends critically on the activation of noradrenergic transmission in the brain²⁻⁶. Furthermore, it has been shown that a pharmacological stimulation of noradrenergic transmission with the $\alpha 2$ adrenergic receptor antagonist yohimbine potentiates the memory enhancing effect of emotional arousal⁷.

A common variant of *ADRA2B* consists of an inframe deletion of three acidic residues (Fig. 1). Specifically, glutamic acid residues 301-303 in the third intracellular loop of the receptor, which are part of a large glutamic acid stretch (glu12, amino acids 297-309), are absent in about 30% of Caucasians and in about 12% of African Americans⁸. This deletion is accompanied by such *in vitro* functional consequences as reduced receptor mediated inhibition of adenylyl cyclase, greater EC₅₀ and decreased agonist promoted phosphorylation and receptor desensitization⁸. Because pharmacological manipulation of $\alpha 2$ adrenergic receptors affects memory for emotionally arousing information in humans⁷, we hypothesized that the deletion polymorphism of *ADRA2B* is related to interindividual differences in enhanced memory for emotional information.

Memory testing and genotyping were carried out in 435 young Swiss adults (322 females, 113 males; median age, 21 years; range, 18-28 years). Subjects were presented with ten neutral, ten positive and ten negative photographs in a random order. The photographs were taken from the international affective picture system (IAPS)⁹ and were presented for 4 s each. Immediately following the presentation of each photograph, subjects were asked to rate it for valence and arousal using the IAPS rating scales⁹. Delayed free recall was tested 10 min after presentation. To document recall, subjects had to describe in writing each picture with a few words. The descriptions were rated for recall success independently by two trained investigators (the inter rater reliability was > 99%). Attention and concentration were assessed with the d2 cancellation test¹⁰ and working memory was assessed with the digit span task¹¹. All subjects gave written informed consent and the study was approved by the ethics committees of the Canton of Zurich, Switzerland, of the University of Konstanz, Germany, and of the Mbarara University of Science & Technology, Uganda.

Study participants showed a high degree of interindividual variability in memory enhancement for emotional information (Fig. 2). For positive photographs there was a mean increase in recall performance of 57% relative to neutral photographs ($P < 0.0001$), and for negative photographs there was a mean increase of 55% relative to neutral photographs ($P < 0.0001$). Deletion carriers showed significantly increased memory enhancement for emotional information compared with noncarriers (carriers, $N = 214$, $78\% \pm 7\%$; noncarriers, $N = 221$, $43\% \pm 6\%$; $F = 12.1$, degrees of freedom = 1, error degrees of freedom = 430, $P = 0.0005$). Heterozygous and homozygous carriers of the deletion were treated statistically as one group because of the relative small number of homozygous carriers. Genotype frequencies were in Hardy Weinberg equilibrium, and corresponded to the frequencies typically observed in Caucasians⁸. A one way ANOVA comparing the

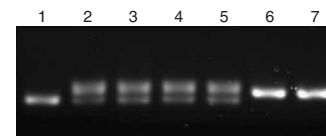


Figure 1 PCR products from carriers and noncarriers of the deletion were identified by their different sizes (that is, 200 versus 209 base pairs). Lane 1, homozygous deletion carrier; lanes 2-5, heterozygous deletion carriers; lanes 6 and 7, noncarriers of the deletion. PCR products were stained with ethidium bromide and run on a 3% agarose gel. The forward primer: 5' AGAAGGAGGGTGTGGGG 3' and reverse primer: 5' ACCTATAGCACCCACGCCCT 3' were used, with an annealing temperature of 58 °C. Reactions were run in duplicate and rated by two blinded investigators.

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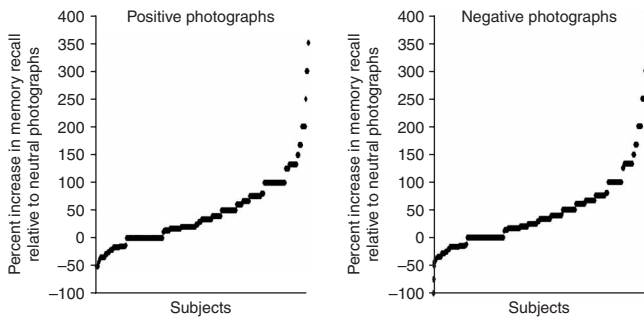


Figure 2 Interindividual variability in enhanced memory for emotional information (Swiss sample). The figures illustrate the percent increase in memory recall of positive (left) and negative (right) photographs relative to neutral photographs. Each subject is represented by a dot, and values are ordered from lowest (left side of each of the graphs) to highest (right side of each of the graphs).

recall performance for neutral photographs between genotype groups showed no statistically significant difference (carriers, $N = 214$, 4.7 ± 0.1 [mean recalled pictures \pm s.e.m.]; non carriers, $N = 221$, 4.9 ± 0.1 ; $F = 2.8$, degrees of freedom = 1, error degrees of freedom = 433, $P = 0.1$). A repeated measures ANOVA revealed that the interaction genotype \times emotional valence was statistically significant ($P < 0.05$), further indicating the specificity of the association of the deletion variant with enhanced memory for emotional information. Correcting for gender did not influence the genotype effect. The deletion dependent increase in memory enhancement applied to photographs of both positive (carriers, $77\% \pm 8\%$; noncarriers, $43\% \pm 7\%$; $F = 8.8$, degrees of freedom = 1, error degrees of freedom = 430, $P = 0.003$; **Fig. 3a**) and negative emotional content (carriers, $79\% \pm 7\%$; noncarriers, $43\% \pm 6\%$; $F = 13.7$, degrees of freedom = 1, error degrees of freedom = 430, $P = 0.0002$; **Fig. 3a**). The deletion did not exert any effect on the increase in arousal ratings for emotional versus neutral photographs (positive photographs: carriers, $271\% \pm 34\%$ [mean increase \pm s.e.m.]; noncarriers, $267\% \pm 32\%$; $F = 0.007$, degrees of freedom = 1, error degrees of freedom = 431, $P = 0.9$; negative photographs: carriers, $380\% \pm 46\%$; noncarriers, $375\% \pm 43\%$; $F = 0.006$, degrees of freedom = 1, error degrees of freedom = 431, $P = 0.9$; **Fig. 3b**). We therefore conclude that the genotype dependent differences in enhanced memory for emotional information were not due to genotype dependent differences in emotional arousal. Consistent with this finding, it has been reported that a pharmacological manipulation of noradrenergic transmission affects the formation of emotional memory without affecting emotional arousal ratings³. Together, these findings suggest that the *ADRA2B* genotype did not affect emotional arousal itself, but rather affected emotional arousal induced activation of noradrenergic transmission and, thereby, the formation of emotional memory. Furthermore, we did not observe genotype dependent differences in attention or working memory performance ($P = 0.4$ and $P = 0.3$, respectively).

Enhanced memory for emotionally arousing events may have adaptive value in evolutionary terms. However, extremely aversive, in

particular life threatening, events can lead to an excessive and persisting emotional memory of the traumatic event which can result in intrusive and distressing re-experiencing (traumatic memory). Studies in twins indicate that the heritability of re-experiencing traumatic events ranges from 23% to 51%, suggesting that naturally occurring genetic variations have an important impact on this trait¹². We therefore hypothesized that deletion carriers would have increased emotional memory for traumatic events reflected in increased re-experiencing symptoms. We tested this hypothesis in 202 refugees who had fled from the Rwandan civil war and were living in the Nakivale refugee camp in Uganda at the time of investigation (100 females, 102 males; median age, 34 years; range, 29–41 years). All subjects had experienced multiple, highly aversive situations and were examined by trained experts with a structured interview based on the Post-traumatic Diagnostic Scale¹³ with the help of trained interviewers chosen from the refugee community. Traumatic events were assessed using a checklist of 31 war- and nonwar-related traumatic event types (for example, injury by a weapon, rape, accidents). The population consisted of 133 subjects fulfilling the diagnostic criteria of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* for post-traumatic stress disorder (PTSD) and 69 subjects without PTSD or a history of PTSD. Deletion carriers had a significantly higher score for re-experiencing symptoms per traumatic event type than did non-carriers (carriers, $N = 42$, 0.47 ± 0.05 [mean number \pm s.e.m.]; noncarriers, $N = 160$, 0.31 ± 0.03 ; degrees of freedom = 1, error degrees of freedom = 198, $P = 0.003$; **Fig. 3c**), whereas the deletion was not significantly associated with hyperarousal or avoidance symptoms ($P > 0.1$). The association of the deletion with increased traumatic memory was independent of the presence of PTSD ($P = 0.8$ for the interaction of genotype \times PTSD diagnosis) and the genotype was equally distributed across the diagnostic groups. Correcting for gender did not influence the genotype effect on traumatic memory. Genotype frequencies were in Hardy-Weinberg equilibrium and corresponded to the frequencies typically observed in populations of Sub-Saharan African origin⁸.

Noradrenergic transmission is known to modulate both short-term memory processes⁴ and long-term memory consolidation⁶ of emotionally arousing information. In the Swiss cohort of healthy young individuals, the genotype-dependent difference was observed as early as 10 min after learning, suggesting that short-term memory processes were already affected. Furthermore, the genotype was also related to

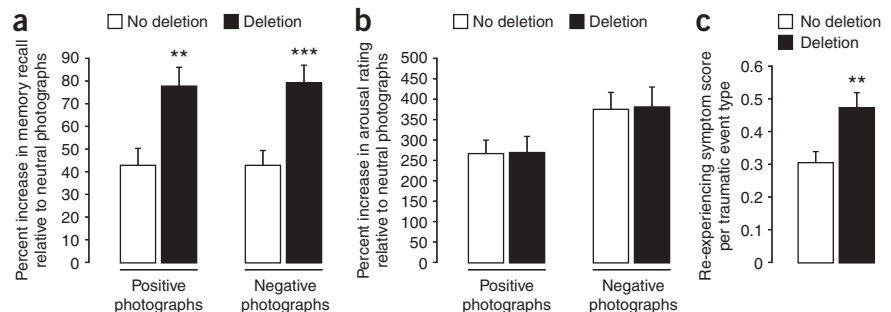


Figure 3 Enhanced memory for emotional information in relation to the deletion variant of the $\alpha 2b$ adrenergic receptor in European and African populations. (a) Percent increase in memory recall of positive and negative photographs relative to neutral photographs in the Swiss sample (mean \pm s.e.m.). (b) Percent increase in arousal ratings of positive and negative photographs relative to neutral photographs in the Swiss sample (mean \pm s.e.m.). (c) Re-experiencing symptom score per traumatic event type in relation to the deletion variant of the $\alpha 2b$ adrenergic receptor in the Rwandan sample (mean \pm s.e.m.). ** $P < 0.01$ and *** $P < 0.001$.

long term traumatic memories in individuals who experienced life threatening situations. The deletion of three glutamic acid residues of the $\alpha 2b$ adrenergic receptor studied here reportedly alters the function of the receptor and results in reduced inhibition of adenylyl cyclase, greater EC_{50} , but also results in decreased agonist promoted phosphorylation and receptor desensitization⁸. Because these *in vitro* data suggest that the deletion may exert both agonistic and antagonistic effects, an *a priori* assumption of the genotype effect on the phenotype is not possible. In the present study, we found that the deletion exerted a phenotypic effect similar to that of the $\alpha 2$ adrenergic receptor antagonist yohimbine: potentiation of the memory enhancing effect of emotional arousal through a stimulation of noradrenergic transmission⁷. These data suggest that the deletion variant acts primarily as a loss of function polymorphism of the $\alpha 2b$ adrenergic receptor in the regulation of emotional memory.

Taken together, we show that a genetically anchored alteration in the noradrenergic system is related to enhanced emotional memory in healthy young Swiss subjects. Furthermore, we found that the same genetic alteration is related to increased traumatic memory in a Sub Saharan African population of civil war refugees who experienced multiple and highly aversive emotional situations. The present findings suggest that the price for the deletion related enhancement of emotional memory may be enhanced intrusive and distressing emotional memory for traumatic events. Consistent with the idea that a genetically anchored alteration in the noradrenergic system is related to traumatic memory, recent studies have indicated that the noradrenergic system is a promising target for pharmacological treatment of PTSD¹⁴. Future studies are necessary to reveal additional genetic variations related to enhanced memory for emotional information and to address their potential relationship to anxiety disorders.

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AUTHOR CONTRIBUTIONS

D.J.-F.d.Q. and A.P. designed the study, conducted the phenotypic and genetic experiments, and wrote the manuscript. I.T.K., V.E., P.L.O., F.N. and T.E. conducted the phenotypic experiments in the African population and wrote the manuscript.

COMPETING INTERESTS STATEMENT

The authors declare no competing financial interests.

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