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Deletion variant in the *ADRA2B* gene increases coupling between emotional responses at encoding and later retrieval of emotional memories

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ABSTRACT

A deletion variant of the *ADRA2B* gene that codes for the α2b adrenoceptor has been linked to greater susceptibility to traumatic memory as well as attentional biases in perceptual encoding of negatively valenced stimuli. The goal of the present study was to examine whether emotional enhancements of memory associated with the *ADRA2B* deletion variant were predicted by encoding, as indexed by the subjectively perceived emotional salience (i.e., arousal) of events at the time of encoding. Genotyping was performed on 186 healthy young adults who rated positive, negative, and neutral scenes for level of emotional arousal and subsequently performed a surprise recognition memory task 1 week later. Experience of childhood trauma was also measured, as well as additional genetic variations associated with emotional biases and episodic memory. Results showed that subjective arousal was linked to memory accuracy and confidence for *ADRA2B* deletion carriers but not for non-carriers. Our results suggest that carrying the *ADRA2B* deletion variant enhances the relationship between arousal at encoding and subsequent memory for moderately arousing events.

1. Introduction

There is evidence that emotionally salient events are typically remembered more vividly than everyday ones (Kensinger & Corkin, 2003; Sharot, Martorella, Delgado, & Phelps, 2007). Yet individuals differ in the degree to which emotional salience enhances memory (Hamann, Ely, Grafton, & Kilts, 1999; Todd, Palombo, Levine, & Anderson, 2011) as well as in their susceptibility to intrusive memories associated with post-traumatic stress disorder (PTSD) (Yehuda & LeDoux, 2007). Individual differences may also partly explain conflicting findings in the literature, with some studies reporting that memory is enhanced for emotionally arousing relative to neutral events [e.g., (Brown & Kulik, 1977; Ochsner, 2000)], and other studies failing to find such an effect (Sharot, Verfaellie, & Yonelinas, 2007).

The modulation hypothesis (McGaugh, 2002) proposes that increased norepinephrine (NE) activity in the basolateral amygdala (BLA) elicited by an affectively salient event enhances encoding of the event. Such arousal related activity at encoding further interacts with the influence of NE on longer-term memory consolidation processes to enhance memory for salient events (Cahill & Alkire, 2003; Roozendaal & McGaugh, 2011). This hypothesis is supported by findings that in rats, administration of NE into the BLA both prior to and following encoding of an event is associated with enhanced memory (for review see Roozendaal et al. (2009) and Roozendaal and McGaugh (2011)). In humans, the influence of arousal on both encoding and post-encoding processes has been demonstrated by injecting epinephrine or exposing participants to emotionally arousing images prior or subsequent to encoding (Anderson, Wais, & Gabrieli, 2006; Cahill & Alkire, 2003; Cahill, Gorski, & Le, 2003; Cahill, Prins, Weber, & McGaugh, 1994; Schwarze, Bingel, & Sommer, 2012). We have recently shown that, in humans, enhanced arousal at encoding is associated with the experience of emotion enhanced perceptual vividness (EEV), which in turn predicts the vividness of later memory (Todd, Talmi, Schmitz, Susskind, & Anderson, 2012).

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Recently a deletion variant of the *ADRA2B* gene, which codes for the α2b adrenoceptor, has been linked to the emotional enhancement of memory. The deletion variant, which is associated with greater extracellular NE availability (Small, Brown, Forbes, & Liggett, 2001), predicts greater capacity for emotionally enhanced memory as well increased propensity for intrusive traumatic memory in Rwandan genocide survivors (de Quervain et al., 2007). There is also evidence that *ADRA2B* genotype influences affective biases in initial encoding. Deletion carriers have been found to show greater amygdala activation when viewing negatively-valenced scenes (Rasch et al., 2009) and enhanced perceptual encoding of negative words in comparison with non-carriers (Todd et al., 2013). An outstanding question concerns whether the emotionally enhanced memory experienced by deletion carriers reflects the emotional enhancement of initial encoding, as the modulation hypothesis would predict. The aim of the present study was to investigate genetic influences on the relation between responses to affectively salient stimuli at encoding and in subsequent memory.

Genotyping was performed on healthy young adults who viewed positive arousing, negative arousing, and neutral scenes and rated their subjective level of emotional arousal in response to the scenes. Participants were given a surprise recognition memory task 1 week later. As episodic memory and working memory are highly correlated (Kane & Engle, 2000; Unsworth, 2007), and personality—in particular neuroticism—has been linked to our genes of interest (Canli, 2008), working memory and personality were measured as control variables. Participants were also genotyped for additional genetic variations associated with emotional biases (*5HTTLPR* and *COMT*) and episodic memory (*BDNF*, *KIBRA*, and *ApoE*) [for review see (Todd et al., 2011)]. Because genetic variations often interact with life experience to influence behavioral outcomes (Hyde, Bogdan, & Hariri, 2011), we also measured history of trauma exposure in childhood. If NE release during encoding is related to both the experience of arousal and later expression of enhanced memory, we expected that there would be a stronger relation between subjectively rated arousal at encoding and memory for *ADRA2B* deletion carriers over non-carriers after controlling for relevant variables/genes. This would further suggest a mutual enhancement of encoding and post-encoding processes by the perceived affective salience of emotional events during encoding. Based on previous findings of greater amygdala response (Rasch et al., 2009) and rapid perceptual encoding for negative images in deletion carriers (Todd et al., in press), we expected to find an advantage for negatively arousing images.

2. Materials and methods

2.1. Participants

288 participants (203 female) of Caucasian descent were recruited from the University of Toronto as part of the DNA Affect and Memory Project (DAMP), a collaborative project looking at genetic influences on attention and memory. Participation was either for financial compensation of $40 or for credit in a first-year psychology course, in addition to $10. Participants were between the ages of 18 and 35 (mean age = 21.0) with normal or corrected-to-normal vision. Participants reporting a history of significant head injuries, stroke, epilepsy, brain surgery learning disabilities, and diagnosis of psychopathology were excluded. The study was approved by the University of Toronto Research Ethics Board.

2.2. Materials

Experimental tasks were presented using E-prime Version 1.2 (Psychology Software Tools, Pittsburgh, PA). For the emotional memory task, sixty images were selected from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 1997) database (20 positive arousing, 20 neutral, and 20 negative arousing). Positive and negative images were balanced for arousal and valence, and neutral images were controlled for number of faces in comparison to the negative images. The Child Trauma Questionnaire (Bernstein et al., 1994) was administered to investigate the influence of traumatic life experience on measures of interest—specifically the childhood physical abuse scale. The Big Five Inventory (Benet-Martinez & John, 1998) was also administered to control for individual differences in personality. Because genetic variation has been consistently associated with neuroticism (Canli, 2008) we were particularly interested in the neuroticism sub-scale.

2.3. Procedure

Ethics approval was obtained from University of Toronto and the Centre for Addiction and Mental Health. Before coming in to the lab, participants were instructed to complete a series of questionnaires through a website. On this website, participants gave informed consent and completed the Big Five Inventory and our own demographics questionnaire. Although history of anxiety and depression were listed as exclusion criteria for participants entering the study, this questionnaire included the following questions as a means of more effective screening: "Have you ever suffered from significant anxiety that interfered with your functioning? If yes, please indicate treatment received (psychotherapy, antidepressant medication, hospitalization)". The same questions were asked for depression. Tasks described here were part of a larger battery of tasks administered as part of the DAMP project.

2.3.1. Emotional memory task

In each trial, following a 750 ms fixation cross, participants viewed an IAPS image which was presented for 2000 ms. Participants then rated the previously viewed image for valence (on a nine-point scale from 'very negative' to 'very positive') and arousal (on a nine-point scale from 'not at all arousing' to 'very arousing'). Participants completed a total of 30 trials (10 per valence category in random order).

The effects of positive vs. negative arousal on memory can differ at longer and shorter delays (Ochsner, 2000). Thus, in order to measure effects on long-term memory processes, we asked participants to complete an online memory task 1 week following in-lab data collection. Participants rated each of the 30 images they were presented a week previously as well as 30 images they had not seen (image sets were counter-balanced across participants) in terms of how certain they were that they had or had not seen the image previously. Images were rated for confidence on a six-point scale, with one being 'certain it is new' and six being 'certain it is old'. Recognition memory was calculated by binning trials labeled old and new to calculate hits and false alarms.

2.4. Control tasks

2.4.1. Working memory

To control for individual differences in working memory associated with episodic memory capacity [e.g., (Ranganath, Johnson, & D'Esposito, 2003)] participants performed a k-estimate task. In this task, arrays of 1, 2, 3, 4, or 6 colored squares were presented for 150 ms. After a delay of 1200 ms, a single colored square was presented in one of the positions of the previous stimuli, and participants were asked to determine whether it was the same color as the square that was in the same position previously. There were 30 trials of each array size for a total of 150 trials. Over the course of several studies we have found that the 4-square array is most sensitive to individual differences in personality (e.g., neuroticism)

and behavior. Thus, for each participant a score was calculated based on proportions of hits and misses for *k*4 as a measure of individual capacity for visuospatial working memory.

2.5. Genotyping

A saliva sample (~2 mL) was collected from each subject in an Oragene OG-500 DNA kit (DNA Genotek, Ottawa, ON). DNA was extracted as per manufacturer's instructions and diluted to 20 ng/μL working concentration.

For the *ADRA2B* 9 bp deletion locus, total genomic DNA (60 ng) was combined with 1X MBI Fermentas PCR buffer containing KCl, 1.5 mM $MgCl_2$ (MBI Fermentas), 0.0325 μg each primer (forward primer sequence: 5′ HEX-CAGAAGGAGGGTGTTTGTGG; reverse primer sequence: 5′ CCACTGCCCACCTATAGCAC), 0.2 mM each dNTP (MBI Fermentas) and 0.6 U Taq polymerase (MBI Fermentas) to a total volume of 15 μl in a 96-well PCR plate. The PCR reactions were subjected to an initial denaturation for 5 min at 95 °C, followed by 30 cycles of amplification in an AB 2720 thermal cycler: denaturing for 30 s at 95 °C, annealing for 30 s at 60 °C and extension for 30 s at 72 °C, and a final extension at 72 °C for 10 min. Similarly for the SLC6A4 LPR (*5HTTLPR*), 40 ng total genomic DNA was combined with 1X MBI Fermentas PCR buffer containing $(NH_4)_2SO_4$, 1.5 mM $MgCl_2$ (MBI Fermentas), 0.0325 μg each primer (Cook et al., 1997; forward primer labeled with 5′ HEX fluorescent tag), 0.16 mM each dNTP (MBI Fermentas) and 1 U Taq polymerase (MBI Fermentas) to a total volume of 25 μL in a 96-well PCR plate. The PCR reactions were subjected to an initial denaturation for 3 min at 95 °C, followed by 40 cycles of amplification in an Eppendorf Mastercycler Pro S thermal cycler: denaturing for 30 s at 95 °C, annealing for 30 s at 61 °C and extension for 1 min at 71 °C, and a final extension at 72 °C for 10 min. Five microliters of the PCR product was combined with 1X New England Biolabs Buffer 2, 10 U MspI restriction enzyme (New England Biolabs) in a total volume of 30 μL was digested overnight at 37 °C. For both *ADRA2B* and the LPR, the final products were electrophoresed on an AB 3130-*Avant* Genetic Analyzer as per manufacturer's directions, and product sizes determined by comparison to GeneScan 500 ROX size standard using GeneMapper (version 4.0).

For *COMT*, *BDNF*, *KIBRA*, and *ApoE*, a total of five single nucleotide polymorphisms (SNPs) across the four genes were genotyped using TaqMan pre-designed assays (LifeTechnologies, Burlington, ON): Val158Met in the *COMT* gene (rs4680; assay ID C__25746809_50); *BDNF* Val66Met (rs6265; assay ID C__11592758_10); rs17070145 in the *KIBRA* gene (assay ID C__33286269_10); and the *ApoE* 112 (rs429358; assay ID C___3084793_20) and 158 polymorphisms (rs7412; C____904973_10). For each reaction, 20 ng genomic DNA were amplified as per manufacturer's directions scaled to a total volume of 10 μL in an Applied Biosystems (AB) 2720 thermal cycler. Post-amplification products were analyzed on the ABI Prism 7500 Sequence Detection System using the allelic discrimination option and genotype calls were determined manually by comparison to six No Template Controls. For the *ApoE* markers, the 112 and 158 genotypes were combined to determine the individual's *ApoE* ε diplotype.

Genotyping of 10% of samples from each run were replicated for quality control purposed for each marker.

3. Results

All genotype frequencies fell within the Hardy–Weinberg equilibrium: *ADRA2B* (284 individuals) $X^2 = 0.07$, $p > .05$; *5HTTLPR* (285 individuals) $X^2 = 0.16$, $p > .05$; *COMT* (288 individuals) $X^2 = 0.59$, $p > .05$, *BDNF* (288 individuals) $X^2 = 0.59$, $p > .05$, *KIBRA* (288 individuals) $X^2 = 0.95$, $p > .05$, *ApoE* rs429358 (288 individuals) $X^2 = 0.28$, $p > .05$; ApoE rs7412 (288 individuals) $X^2 = 0.28$, $p > .05$. Based on previous research (de Quervain et al., 2007; Rasch et al., 2009) homozygote and heterozygote *ADRA2B* deletion carriers were treated as a single group due to the low number of homozygotes. Similarly, homozygote and heterozygote carriers of the *5HTTLPR* short allele, the *COMT* val allele, the *KIBRA* T allele, *BDNF* and *ApoE* variants other than *ApoE*4, were also treated as a single group.

Because of a relation between anxiety/depression and several genes of interest (Canli, 2008), 72 participants were further excluded from analysis for previous diagnosis or treatment for anxiety or depression, which was revealed by self-report via the demographics questionnaire. We were unable to obtain reliable genotyping for *ADRA2B* for a further 12 participants, 16 participants were excluded for other missing data, and 2 participants for corrected recognition memory scores of less than 0, leaving a final *N* of 186 (133 female). Participants were grouped into *ADRA2B* deletion carriers ($n = 102$) and non-carriers ($n = 84$).

3.1. Analyses of covariance: Inclusive models

To examine the influence of *ADRA2B* on emotional modulation of recognition memory, while accounting for the influence of other relevant genes and control variables, mixed-model ANCOVAs were employed. Positive and negative arousing trials were included as separate valence categories as previous research suggests that differently valenced stimuli can have differing influences on memory at longer delays (Ochsner, 2000).

First, in order to probe potential influences of *ADRA2B* on experienced arousal when viewing images, an ANCOVA was performed on arousal ratings for each Emotion Category with Emotion Condition (positive, negative, and neutral) as the within-subjects measure and genotype (*ADRA2B*) as the between-subjects measure. Unsurprisingly, there was a main effect of emotion, $F(2, 366) = 393.22$, $p < .001$, $\eta_\rho^2 = .68$, with negative and positive images rated as more arousing than neutral images, $p < .001$, and negative images rated as overall more arousing than positive images, $p < .001$. There was also a main effect of genotype, with deletion carriers rating images as overall more arousing than non-carriers, $F(1, 183) = 6.0$ $p < .001$, $\eta_\rho^2 = .03$. The interaction between genotype and Emotion Category was not significant, $F(2, 366) = 6.0$ $p = .10$.

To examine the relationship between *ADRA2B*, rated arousal, and emotional modulation of memory, an ANCOVA was performed on corrected memory accuracy (hits-false alarms) for each Emotion Category with Emotion Condition (positive, negative, and neutral) as the within-subjects measure and genotype (*ADRA2B*) as the between-subjects measure. Means for arousal and memory accuracy are presented in Table 1. Mean arousal ratings for each Emotion Category (negative, positive, and neutral) were included as separate covariates of interest. Because preliminary analyses revealed that physical abuse was associated with arousal ratings across all participants, $R = .18$, $p = .02$, physical abuse scores from the CTQ were also covaried. Results showed there was no main effect of Emotion Category, $F(2, 326) = 2.07$, $p = .13$, or *ADRA2B*, $F(1, 163) = .36$, $p = .55$, on memory accuracy. There was, however, a 3-way interaction between Emotion Category, *ADRA2B*, and arousal ratings for negative images, $F(2, 326) = 3.60$ $p = .03$, $\eta_\rho^2 = .02$. Specifically, arousal ratings for negative images at encoding influenced memory accuracy differently according to *ADRA2B* genotype. In contrast, 3-way interactions between Emotion Category, *ADRA2B*, and arousal ratings for positive, $F(2, 326) = 1.10$ $p = .34$, and neutral $F(2, 326) = 1.21$, $p = .30$, images were not significant. There was also an Emotion Category × Childhood Trauma interaction, $F(2, 326) = 3.1$, $p = .05$, $\eta_\rho^2 = .02$, indicating that a history of physical abuse also influenced emotional modulation of memory. Notably,

Table 1
Recognition memory and arousal rating means in *ADRA2B* deletion carriers and non-carriers.

	Negative			Neutral			Positive		
	Hits	FA	H-FA	Hits	FA	H-FA	Hits	FA	H-FA
Recognition memory accuracy									
No del	.84	.14	.70	.79	.10	.69	.79	.19	.59
Del	.84	.14	.71	.76	.05	.70	.82	.16	.65

	Negative	Neutral	Positive
Arousal ratings			
No del	5.65	2.12	4.43
Del	6.07	2.32	5.20

H = proportion hits, FA = proportion false alarms, and H-FA = hits-false alarms.

the interaction between genotype, Emotion Category, and Childhood Trauma was not significant, $F(4, 326) = 1.62$, $p = .17$.

Next, in order to investigate potential gene × gene interactions influencing emotional modulation of attention and memory, we included *COMT* (val carriers vs. met/met) and *5HTTLPR* (short allele carriers vs. long/long) genotypes as factors in the analysis. A mixed-model ANCOVA was performed on corrected memory accuracy for each Emotion Category with Emotion Condition (positive, negative, and neutral) as the within-subjects measure and genotype (*ADRA2B*, *COMT*, and *5HTTLPR*) as the between-subject measure. As preliminary correlation analyses revealed that physical abuse ratings from the CTQ, working memory, trait neuroticism, and sex were associated with memory performance in one or both groups, these variables were included as covariates. *KIBRA*, *BDNF* and *ApoE* genotypes, which are associated with individual differences in episodic memory, were also included as covariates in this larger analysis. Results revealed an effect of *k* estimate score on memory accuracy, $F(1, 148) = 7.00$, $p = .009$, such that those with higher *k*4 scores also showed overall better recollection. All other main effects were non-significant (see Table 2). There was again a 3-way interaction between Emotion Category, *ADRA2B*, and arousal ratings for negative images, $F(2, 298) = 5.60$, $p = .004$, $\eta_p^2 = .02$. There was also an Emotion Category × Childhood Trauma interaction, $F(2, 298) = 3.59$, $p = .03$, $\eta_p^2 = .03$. It is notable that the effects were larger when the full range of covariates was included.

This analysis also revealed a *ADRA2B* × *KIBRA* interaction influencing overall memory accuracy across all emotion categories, $F(1, 148) = 5.60$, $p = .02$, $\eta_p^2 = .04$, such that there was an overall better memory for deletion carriers ($n = 35$) than non-carriers ($n = 44$) with two C *KIBRA* alleles only. There was also a *KIBRA* × Emotion Category interaction, $F(2, 298) = 3.22$, $p = .04$, with carriers of the *KIBRA* T allele showing greater accuracy for neutral images, $p = .04$.

3.2. Examination of recollection

Because of the small number of images used in the study, we were not able to reliably employ conventional methods of estimating familiarity (d') and recollection (rho) (Yonelinas & Parks, 2007). Rather, in order to disembed influences specific to explicit recollection processes as measured by high confidence (Yonelinas, 2001; Yonelinas, Aly, Wang, & Koen, 2010), we performed the same inclusive ANCOVA described above using corrected accuracy only for trials where previously seen images were correctly rated with the highest confidence level of 6. Here, the *ADRA2B* × *KIBRA* interaction influencing overall memory accuracy was marginal, $F(1, 150) = 3.58$, $p = .06$. However, the Emotion Category × *ADRA2B*× Negative Arousal interaction remained robustly significant, $F(2, 300) = 5.05$, $p = .007$, $\eta_p^2 = .03$, suggesting that for deletion carriers, higher arousal ratings for negative images at encoding may be specifically associated with explicit recollective processes.

Table 2
All main effects and significant or trend level interactions revealed by a mixed-model ANCOVA performed on corrected memory accuracy with Emotion Condition (positive, negative, and neutral) as the within-subjects measure and genotype (*ADRA2B*, *COMT*, and *5HTTLPR*) as the between-subject measure. Childhood abuse ratings, working memory, trait neuroticism, and sex as well as *KIBRA*, *BDNF* and *APoE* are include as covariates.

Main effects		
	F	Sig
Between subject		
ADRA2B	2.57	.11
COMT	1.51	.22
5HTTLPR	.98	.32
KIBRA	.48	.49
BDNF	.14	.71
ApoE	1.34	.25
Sex	.04	.85
Neuroticism	1.65	.20
*k*4 (working memory)	7.00	.009
Physical abuse	.19	.67
Arousal rating negative	1.75	.19
Arousal rating positive	2.57	.11
Arousal rating neutral	.23	.64
Within subject		
Emotion Category	2.23	.11
Interactions (significant or trend level)		
Between subject		
ADRA2B × *KIBRA*	4.73	.03
Within subject		
Emotion category × *KIBRA*	3.22	.04
Emotion Category × neuroticism	2.53	.08
Emotion Category × physical abuse	4.65	.01
Emotion Category × sex	2.67	.07
Emotion Category × *arousal rating* neutral	2.77	.07
Emotion Category × ADRA2B × arousal rating negative	5.40	.005

3.3. Focused analyses

In order to probe the direction of the 3-way interaction between Emotion Category, *ADRA2B*, and arousal rating for negative images reported above, we divided participants into high, medium, and low arousal groups based on their mean arousal ratings for negative stimuli. An ANCOVA was performed on corrected memory accuracy (hits-false alarms) for negative images, with Arousal Group (low, medium, and high) as between-subject factors, and history of childhood abuse as a covariate of interest. There was no significant main effect of *ADRA2B*, $F(1, 166) = .06$, $p = .81$, or Arousal Group, $F(1, 166) = .004$, $p = .99$ on memory accuracy for negative images. There was, however, an Arousal Group × *ADRA2B* interaction, $F(2, 162) = 3.05$, $p = .05$, $\eta_p^2 = .03$. The interaction revealed opposing relations between arousal and memory for each group, such that memory improved for deletion carriers who rated images higher in arousal than those who rated them lower, and worsened with non-carriers who rated images as higher in arousal (Fig. 1). We next performed the same analysis with *COMT* and *5HTTLPR* as additional between-subject factors, and controlling for all covariates described above. This analysis again showed no main effects of *ADRA2B*, $p = .55$, or Arousal Group, $p = .10$ on memory accuracy. With full covariates there was an even stronger Arousal Group × *ADRA2B* interaction, $F(2, 139) = 4.55$, $p = .01$, $\eta_p^2 = .05$. *T*-tests revealed that deletion carriers who rated negative images as high in arousal remembered them more accurately than non-carriers who rated them as high arousal, $p = .04$.

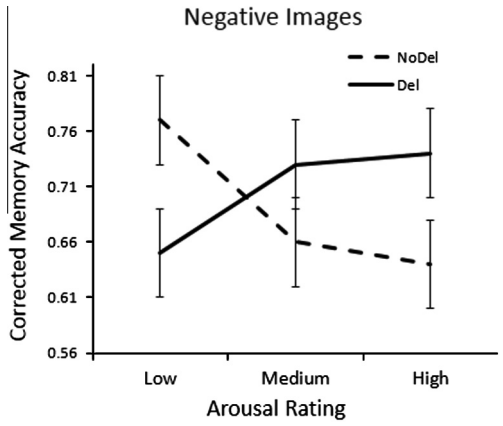

Fig. 1. Memory accuracy for negative images for participants grouped for high, medium, or low, arousal ratings, for *ADRA2B* deletion carriers and non-carriers. Deletion carriers who rated negative scenes as higher in arousal were more likely to remember them accurately. In contrast, non-carriers showed a negative relation between arousal and accuracy.

3.4. Regression analyses

In order to further probe the relation between Emotion Category, memory accuracy, and the continuous metrics of arousal rating at encoding, we next employed hierarchical regressions. In order to examine valenced relations between ratings of arousal and memory accuracy in each of the groups, we created valenced difference scores by subtracting arousal ratings for neutral images from arousal ratings for (1) negative images (negative arousal difference scores) and (2) positive images (positive arousal difference scores) and by subtracting corrected memory accuracy for neutral images from memory accuracy from (3) negative images (negative memory difference scores) and (4) positive images (positive memory difference scores).

Initial correlations revealed that negative arousal difference scores were correlated with negative memory difference scores for deletion carriers, $R = .22$, $p = .02$, but not for non-carriers, $R = -.07$, $p = .52$. Similarly, positive arousal difference scores were correlated with positive memory difference scores for deletion carriers, $R = .20$, $p = .04$, but not for non-carriers, $R = -.03$, $p = .79$. Four separate hierarchical linear regression analyses were employed to examine whether negative arousal difference scores predicted negative memory accuracy difference scores in (1) deletion carriers and (2) in non-carriers, and whether positive arousal difference scores predicted positive memory accuracy difference scores in (3) deletion carriers and (4) non-carriers respectively. For each of the four analyses, all covariates included in the inclusive ANCOVAs described above were entered into the regression at the first level and arousal difference scores were entered at the second level.

For negative images, after accounting for the influence of all control variables, difference scores in arousal ratings at encoding predicted difference scores in recognition memory, $R^2\Delta = .06$, $p = .03$. In contrast, there was no relation between difference scores in arousal at encoding and in recognition memory for non-carriers, $R^2\Delta = .01$, $p = .37$ (Fig 2a). For positive images, difference scores in arousal ratings at encoding predicted difference scores in recognition accuracy at trend level, $R^2\Delta = .03$, $p = .08$. Again, there was no relation between difference scores in arousal at encoding and recognition memory for non-carriers, $R^2\Delta = .00$, $p = .85$. Thus, for *ADRA2B* carriers only, there was a robust relation between what was perceived as more salient at encoding and what was subsequently recognized for negative relative to neutral images. The same pattern was observed to a lesser extent for positive images.

In order to further investigate the influence of childhood trauma on memory bias revealed by the Childhood Trauma × Emotion Category interaction reported above, we performed a separate hierarchical regression with all other covariates entered at the first level and physical abuse at the second on all participants regardless of *ADRA2B* genotype. Preliminary correlations revealed a history of physical abuse to be negatively correlated with memory accuracy for positive relative to neutral images, $R = -.20$, $p = .006$, but not with accuracy for negative relative to neutral images, $R = -.03$, $p = .70$. After accounting for the other variables, higher levels of childhood physical abuse were associated with poorer recognition accuracy for positive images, $R^2\Delta = .04$, $p = .006$.

3.5. Multilevel modeling

Emotional arousal has been found to enhance memory confidence more than it does memory accuracy (Phelps & Sharot, 2008). Although they did not differ from non-carriers in overall memory confidence, $t(182) = .65$, $p = .52$, we predicted that the

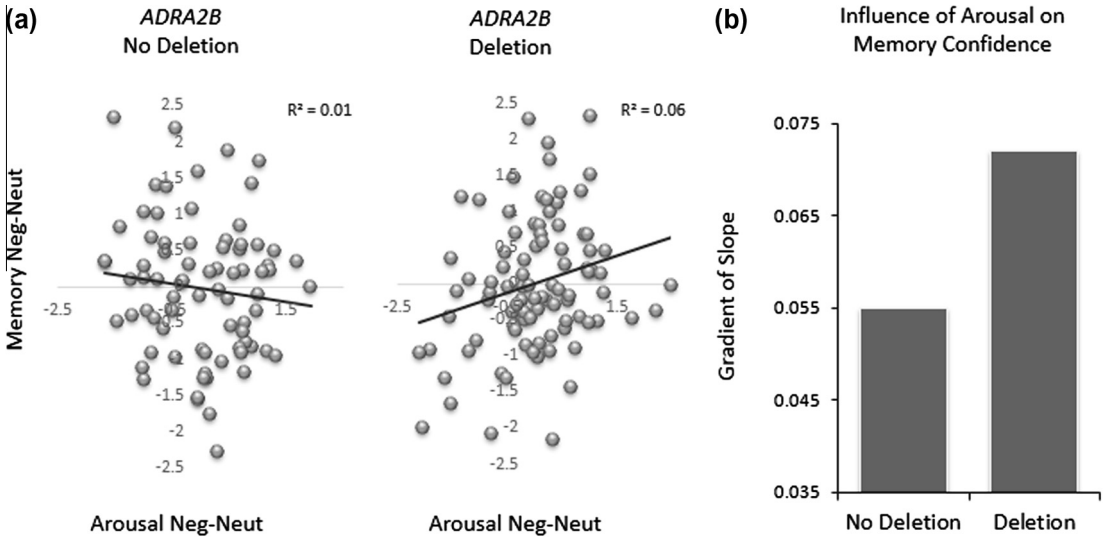

Fig. 2. (a) Standardized residual negative arousal difference scores (negative–neutral) predict standardized negative memory accuracy difference scores. (b) Gradient of slope values indicate the degree of increase in memory confidence with arousal across all trials (negative, positive and neutral) for *ADRA2B* deletion carriers and non-carriers. Multilevel modeling revealed that *ADRA2B* group moderated the influence of arousal rating on memory confidence for each image. The relation between arousal and memory was stronger in *ADRA2B* deletion carriers than in non-carriers.

association between arousal and confidence might be enhanced in deletion carriers across *all* categories of images. Moreover, the previous analyses examined the influence of genotype on the relation between each participant's mean arousal and recognition memory scores without taking into account within-subject variance. We next employed multilevel modeling to examine the influence of *ADRA2B* genotype on the degree to which arousal rating predicted memory confidence *within* each subject, trial by trial, for individual images originally viewed in the task. A 2-level model was used to account for within-subject variability by estimating a random intercept for each participant using the variance components covariance structure and the Satterthwaite method of estimating degrees of freedom (Satterthwaite, 1946). Results revealed a significant main effect of Arousal Rating on memory confidence, $b = 0.06$, $SE = 0.008$, $t(5370) = 7.05$, $p < .001$, with greater memory confidence for images experienced as more arousing. This was qualified by an *ADRA2B* × Arousal Rating interaction, indicating that *ADRA2B* variant moderated the relationship between rated arousal and memory confidence, $b = 0.02$, $SE = .008$, $t(5370) = 2.27$, $p = 0.02$. In order to examine the direction of the interaction, simple slopes were examined at one standard deviation above and below the means of both predictors (Aiken & West, 1991). This analysis revealed that, while arousal rating significantly predicted memory confidence for both groups, the relation was stronger in deletion carriers $t(5370) = 14.78$, $p < .001$, than in non-carriers, $t(5370) = 4.40$, $p < .001$ (Fig. 2b). Thus, this high-resolution trial by trial analysis revealed that, for *ADRA2B* deletion carriers, the association between arousal rating at encoding and memory confidence for previously viewed images was greater than in non-carriers.

4. Discussion

Here we showed an influence of *ADRA2B* on the degree to which affective experience at encoding predicted memory accuracy and confidence 1 week later. Our results suggest that carrying the *ADRA2B* deletion variant, which is associated with higher levels of extracellular NE, enhances the relationship between subjective ratings of emotional arousal and subsequent memory. Whereas previous studies have linked the deletion variant to emotional modulation of perception (Rasch et al., 2009; Todd et al., 2013) and memory (de Quervain et al., 2007) respectively, this study is the first to document a role for *ADRA2B* in the relationship between arousal at encoding and subsequent memory.

ADRA2B carriers and non-carriers showed opposing patterns of the influence of subjective arousal on memory accuracy for negative events, which were also rated the most arousing. Only deletion carriers showed a positive relationship between how arousing they found the negative images at encoding and memory accuracy for them 1 week later. Previous findings have suggested that deletion carriers are not only more vulnerable to intrusive memories following trauma than non-carriers (de Quervain et al., 2007), they also show greater perceptual encoding of negative images under conditions of high perceptual competition (Todd et al., in press), and greater amygdala activation when viewing negative images (Rasch et al., 2009). The present findings suggest that there is a link between arousal at encoding and recognition memory accuracy for deletion carriers for images viewed in the laboratory, but that non-carriers show no such relationship. These genetically influenced individual differences might account for null findings for effects of emotion on later memory accuracy reported in some studies (Sharot, Verfaellie et al., 2007).

Regression analyses revealed that, after controlling for variables influencing memory and its emotional enhancement, arousal rating predicted memory accuracy for negative relative to neutral images for deletion carriers but not for non-carriers. The same pattern held for positive relative to neutral images at the level of a trend. As positive images were rated by our participants as less arousing than negative images, the stronger pattern of results for negative images may reflect differences in subjectively experienced arousal. Our memory confidence findings support this interpretation. We further used multi-level modeling to examine the relation between arousal and memory confidence for each subject across all trials, regardless of valence. This analysis also revealed a stronger overall relationship for *ADRA2B* deletion carriers between the experienced arousal level of each image at encoding and memory confidence for the same image 1 week later. Thus, carrying the deletion variant not only predisposed participants to rate images of all valences as more arousing, it increased the likelihood that intensity of initial experience would predict higher levels of explicit episodic memory. Our findings suggest that the higher levels of NE related to activity at α2b receptors enhance encoding processes that are tied to later memory enhancement. That the deletion variant influences the relation between emotional arousal at encoding and memory further suggests that altered α2b activity may in turn influence post-encoding processes in a manner consistent with the modulation hypothesis (Cahill & Alkire, 2003; McGaugh, 2002).

The deletion variant is associated with impaired receptor regulation by G protein-coupled receptor kinases in inhibitory α2b adrenoceptors (Small et al., 2001). The resulting deficit in inhibitory activity in pre-synaptic α2b receptors may result in increased *tonic* levels of extracellular NE. Both ongoing tonic and stimulus-locked phasic activity in NE-producing neurons of the locus coeruleus (LC) play a key role in gating sensory responses to salient stimuli (Berridge & Waterhouse, 2003; Sara, 2009). The adaptive gain model (Aston-Jones & Cohen, 2005) suggests that tonic LC activity influences phasic activity, with higher levels of tonic activity being related to greater sensitivity to motivationally significant environmental stimuli. Such increased sensitivity to motivationally salient stimuli may be a function of reduced levels of negative feedback at α2b receptors in deletion carriers. Moreover, in the absence of negative feedback at α2b receptors, phasic responses to salient events can further lead to even higher levels of extracellular NE. Thus, whereas NE levels in non-carriers may be stabilized via negative feedback in response to both tonic and phasic activity, carriers may experience more volatile NE levels related to positive feedback to both types of activity. This is consistent with the findings of a recent study finding that amygdala activity was greater in deletion carriers in response to salient stimuli only after a sustained mood induction (Cousijn et al., 2010), suggesting *ADRA2B*-related differences in response to phasic activity are contingent on more sustained processes.

Higher levels of NE in response to affectively salient stimuli in deletion carriers may in turn have greater influence on emotional memory consolidation processes mediated by basolateral amygdala activity (Roozendaal & McGaugh, 2011). According to the modulation hypothesis, phasic arousal related to perceptual vividness interacts with more tonic arousal extending beyond initial encoding to further enhance memory consolidation (Cahill & Alkire, 2003). Our finding that carriers of the deletion variant showed a greater association between arousal at encoding and memory for emotionally salient images suggests that, for these individuals, it is precisely this NE-mediated relationship between encoding and post-encoding processes that is enhanced—at least for moderately arousing events [see also (Roozendaal, Castello, Vedana, Barsegyan, & McGaugh, 2008)]. Of course, noradrenergic influences on perception, encoding, and memory do not work in isolation, but interact with the influence of other neuromodulators (Sara, 2009; Sara & Bouret, 2012). Although we did not find any interactions with genes modulating serotonin or dopamine, the influence of NE at adrenoceptors found in terminals of serotonergic

and dopaminergic neurons (Sara & Bouret, 2012) may also play a role in the influence of *ADRA2B* on encoding and memory. This is supported by our finding of a larger effect size for the relation between encoding and retrieval when these other genes were considered as covariates.

Similar to previous studies (de Quervain et al., 2007), we found no difference between carriers and non-carriers in arousal ratings for emotional relative to neutral images. Yet we did find that deletion carriers rated images as more arousing overall across all categories of positive, negative and neutral images—an effect not reported in previous research. It is unclear whether the discrepancy is because the effect was not of interest and not examined or whether it was non-significant in previous research. A limitation of our own as well as de Quervain and colleagues' study is that arousal was measured through subjective ratings and not objective measures such as pupil size, heart rate, and skin conductance. Future research using objective physiological measures will be able to better assess the influence of *ADRA2B* on arousal and its relation to memory.

Although previous research found carriers of the *ADRA2B* deletion variant to have overall increased memory for emotional relative to neutral images (de Quervain et al., 2007), we failed to find an effect of *ADRA2B* deletion group on memory accuracy for emotionally arousing images. One explanation may be the difference in time lag between retrieval and encoding as well as the type of memory tested. Whereas de Quervain and colleagues employed free recall 10 min after encoding we measured recognition memory 1 week later. Like other studies that have failed to find this effect (Gibbs, Naudts, Azevedo, & David, 2010; Rasch et al., 2009), we may also have lacked sufficient power to detect the effect due to our smaller sample size.

Although *KIBRA* was included as a control variable rather than a polymorphism of interest, we did find an influence of *KIBRA* on memory accuracy for neutral images only. This finding is consistent with reports that carriers of the *KIBRA* T allele have better episodic memory (Milnik et al., 2012; Papassotiropoulos et al., 2006) and greater hippocampal volume (Palombo et al., 2013) than non-carriers in non-affective contexts. This result suggests that emotional salience may mitigate that advantage, although such an interpretation will need to be supported by future studies.

Epistasis, or interactions between genes, often qualify the influence of genotype on cognitive processes (de Quervain & Papassotiropoulos, 2006). Here, although we did not find any genes interacting with *ADRA2B* to influence emotional modulation of memory, there was an interaction between *ADRA2B* and *KIBRA* on overall memory accuracy, with better memory for deletion carriers than non-carriers in participants who were homozygous for the *KIBRA* C allele. Recent research has found that carriers of this SNP show reduced episodic memory performance in comparison to non-carriers (Milnik et al., 2012; Papassotiropoulos et al., 2006). Here *ADRA2B* enhanced episodic memory performance for participants with a genetic predisposition for worse overall memory performance. However, the small numbers of participants in each group qualify interpretation of this finding.

Although reports of higher levels of childhood physical abuse predicted poorer memory accuracy for positive images across all subjects, potentially due to memory suppression related to the images' sexual content/co-occurrence of sexual and physical abuse (Mullen, Martin, Anderson, Romans, & Herbison, 1993), we did not find an interaction between carrying the *ADRA2B* deletion variant and reports of childhood trauma. Studies investigating the role of *5HTTLPR* on behavioral outcomes (Canli & Lesch, 2007) as well as those looking at the role of genes influencing the hypothalamic–pituitary–adrenal (HPA) axis in PTSD (Klengel et al., 2013; Mehta & Binder, 2012) have reported key gene-environment interactions in which childhood trauma or social support have moderated the influence of genetic variation on outcome. Our findings suggest that the influence of *ADRA2B* on memory bias may be independent of childhood trauma; however, the range of experienced childhood trauma in an undergraduate sample may have been too limited, or this study may have lacked sufficient power, to detect an interaction. Designs using larger sample sizes, additional measures of lifetime trauma (e.g., number of traumatic events), or neuroimaging measures may be more sensitive to gene by environment interactions.

The role of *ADRA2B*-related differences in patterns of neural activation that link subjective emotional intensity at encoding and in memory is as yet unknown. We have recently demonstrated that the experience of emotionally enhanced perceptual vividness, mediated by the amygdala and high-level visual cortex, predicts enhanced memory vividness (Todd et al., 2012). Future research can investigate whether BOLD activation patterns associated with the link we identified between emotionally-enhanced perceptual vividness and memory is greater in *ADRA2B* deletion carriers than non-carriers. Given the association between *ADRA2B* and traumatic memory (de Quervain et al., 2007), another important area for future research is investigation of potential links between encoding and memory, *ADRA2B* genotype, and post-traumatic stress disorder.

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