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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)