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Influence of COMT val158met and ADRA2B deletion polymorphisms on recollection and familiarity components of human emotional memory

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Abstract

Emotional enhancement of memory is a widely accepted phenomenon that, in addition to its adaptive role, may play a role in the evolution of psychiatric disorders. Hence a comprehensive understanding of its neurobiological basis is imperative. Whilst the pharmacological and neural mechanisms are well known, the contribution of genetic variation is not. Research suggests that two qualitatively different processes (recollection and familiarity) contribute to recognition memory. In this study, we examined the relative contribution of two common genetic polymorphisms, the deletion variant of the ADRA2B gene that codes the α2b adrenergic receptor and the val158met polymorphism of the COMT gene that codes the catechol-O-methyltransferase enzyme, to emotional enhancement of these two memory processes in 97 healthy male volunteers. There was a significant interaction between COMT genotype and emotional arousal in relation to recollection, but not familiarity, with the former being significantly elevated for emotionally arousing versus neutral pictures in carriers of the val158 allele compared with met158 carriers. There were no main effects or interactions in relation to ADRA2B genotype.

Keywords

ADRA2B, catecholamines, *COMT*, emotional memory, episodic memory, genetics, noradrenaline

Introduction

It is well established that memory is enhanced for emotional compared with neutral events and experiences (Brown and Kulik, 1977). Whilst this phenomenon, termed 'emotional memory', has long been held to confer an evolutionary advantage related to the enhanced retention of information relevant to survival, there is increasing evidence that it may also contribute to psychopathological processes. For example, the intrusive reliving of traumatic memories associated with post-traumatic stress disorder (PTSD) is considered to be a maladaptive consequence of emotional memory processes (Elzinga and Bremner, 2002; Labar and Cabeza, 2006). Such processes are also hypothesized to contribute to abnormal belief formation in psychotic disorders (Fotopoulou, 2010; Gibbs and David, 2003). Thus, understanding the mechanisms of emotional memory formation and maintenance has become an increasingly important domain of cognitive neuroscience research.

Emotional memory has been investigated experimentally using a variety of stimuli including words (Kleinsmith and Kaplan, 1963), pictures (Bradley et al., 1992) and stories (Cahill and McGaugh, 1995), although the extent to which these laboratory paradigms accurately reflect real-life emotional memories has been questioned (Todd et al., 2011). Nevertheless, a wealth of research using these paradigms has elucidated many of the neurobiological mechanisms underlying emotional enhancement of memory. For example, initial lesion studies in humans demonstrated that the amygdala is a key neural substrate for emotional enhancement of memory (Adolphs et al., 1997; Cahill et al., 1995) and this has been confirmed in multiple subsequent functional neuroimaging studies (Cahill et al., 1996; Canli et al., 1999, 2000; Hamann et al., 1999). Pharmacological challenge studies with beta blockers and dopamine antagonists in healthy human volunteers have demonstrated the crucial role of the

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catecholamine neurotransmitters noradrenaline and dopamine (Cahill et al., 1994; Gibbs et al., 2007; van Stegeren et al., 1998, 2002) and multiple functional magnetic resonance imaging (fMRI) studies have confirmed the role of noradrenergic transmission in amygdala-mediated consolidation of emotional memories (van Stegeren, 2008; van Stegeren et al., 2005). Although similar pharmacological fMRI studies have not yet been conducted in relation to the effects of dopamine on emotional memory, there is evidence that dopamine is involved in modulating the human amygdala response (Takahashi et al., 2005, 2010; Tessitore et al., 2002), and its contribution to emotional memory has been established in a plethora of animal studies (Greba et al., 2001; Guarraci et al., 1999, 2000; LaLumiere et al., 2004).

However, the contribution of genetic variation to human emotional memory has only recently begun to be investigated. As yet, little is known about the factors underlying individual differences in emotional memory that might contribute to individual vulnerability or resilience to psychological disorders such as PTSD (Todd and Anderson, 2009). Consistent with existing literature, it has been hypothesized that genes contributing to noradrenergic and dopaminergic neurotransmission (*ADRA2B* and *COMT*) are likely to contribute to individual differences in emotional enhancement of memory (Todd et al., 2011). For instance, a polymorphic deletion in the ADRA2B gene has been linked to emotional memory. This deletion results in reduced agonist-promoted desensitization of the α2b adrenergic autoreceptor in vitro and is therefore presumed to contribute to potentiation of noradrenergic transmission (Small et al., 2001). Although this has not been directly demonstrated in vivo, indirect behavioral and neuroimaging data support this assumption. Two studies have demonstrated that recall of emotionally arousing, compared with neutral, images is enhanced in *ADRA2B* deletion carriers relative to non-carriers (de Quervain et al., 2007) and this is associated with increased amygdala activation during encoding (Rasch et al., 2009). The finding that the deletion variant was also associated with increased PTSD symptoms highlights the potential clinical relevance of genetically influenced emotional memory. However, two factors limit the conclusions that can be drawn about the role of *ADRA2B* in long-term emotional enhancement of memory from these two seminal studies. First, memory was tested after a very short (10-min) retention interval, and second, the observed genotype-related differences in amygdala activation during encoding were not associated with subsequent memory for the emotional stimuli. Thus, the contribution of *ADRA2B* to longer-term consolidation processes remains unclear. On the other hand, *COMT* has not been directly linked to emotional memory, although the relationship between the *COMT* polymorphism and dopamine levels has been demonstrated in vivo (Gogos et al., 1998). A common polymorphism (val158met) in this gene, the substitution of methionine (met) for valine (val) results in a functional reduction in the activity of the enzyme, catechol-O-methyltransferase (COMT), responsible for the degradation of dopamine in the prefrontal cortex. The met allele is associated with 40% less COMT activity (Chen et al., 2004), resulting in higher levels of dopamine in the prefrontal cortex. However, the behavioral effects of this polymorphism are complicated by increasing evidence of pleiotropy: the process by which a single gene exerts multiple behavioral effects (Mier et al., 2009). For example, initial studies suggested that the met allele is associated with enhanced prefrontal cognitive function, particularly executive function (Bertolino et al., 2006; Egan et al., 2001), but also episodic memory (de Frias et al., 2004). However, other evidence suggests that the COMT val158met polymorphism may also play a role in individual responses to emotional stimuli. A number of more recent studies suggest that the met allele is also associated with an increased neural response to aversive, relative to neutral and positive, stimuli, specifically involving the amygdala and prefrontal cortex (Drabant et al., 2006; Herrmann et al., 2009; Smolka et al., 2005, 2007). Thus, although there is no behavioral or neuroimaging evidence directly linking the COMT val158met polymorphism to emotional memory, its role in the reactivity of brain regions crucial to the emotional enhancement of memory is indicative.

It has therefore been suggested that both *ADRA2B* and *COMT* are likely to play a role in individual variation in emotional memory, with *ADRA2B* contributing to emotional enhancement of consolidation processes by influencing the amygdala and hippocampus, whilst *COMT*'s role may be more likely to relate to prefrontal regulation of amygdala responses to emotional (aversive) stimuli (Todd et al., 2011). This is consistent with the 'modulation hypothesis' suggesting that emotional enhancement of memory occurs via interaction between prefrontal–amygdala–hippocampal networks. This is supported by existing fMRI data demonstrating that subsequent memory effects for emotionally arousing stimuli can be predicted by correlated activation between these regions during encoding (Dolcos et al., 2004; Kilpatrick and Cahill, 2003; Richardson et al., 2004). Few studies have as yet attempted to investigate potential interactive (epistatic) effects of these genes on emotional memory. We recently began to address this gap by investigating epistasis between the ADRA2B deletion and COMT val158met polymorphisms on emotional memory in healthy human volunteers. We found a significant interaction between the two polymorphisms in relation to overall episodic memory performance. Specifically, ADRA2B deletion carriers who were homozygous for the COMT val allele showed better memory for both neutral and aversive stimuli than non-carriers, suggesting that possession of the deletion variant may moderate the cognitive impairments associated with the COMT val allele (Gibbs et al., 2010b). We hypothesized that this is related to the putative inverted 'U' that has been proposed to model the effects of catecholamine levels on prefrontal cognitive function (Meyer-Lindenberg et al., 2005) (see Figure 1).

Ostensibly, by increasing prefrontal noradrenaline levels, the ADRA2B deletion variant shifts high-activity COMT val/val individuals to more optimal catecholamine levels and consequently, improved cognitive performance. However, unlike de Quervain et al. (2007) we did not find an effect of either gene on emotional enhancement of memory per se. This may have been due to reduced power in our smaller sample which would be consistent with the absence of behavioral differences in their fMRI study, presumed to be due to the smaller sample size (Rasch et al., 2009).

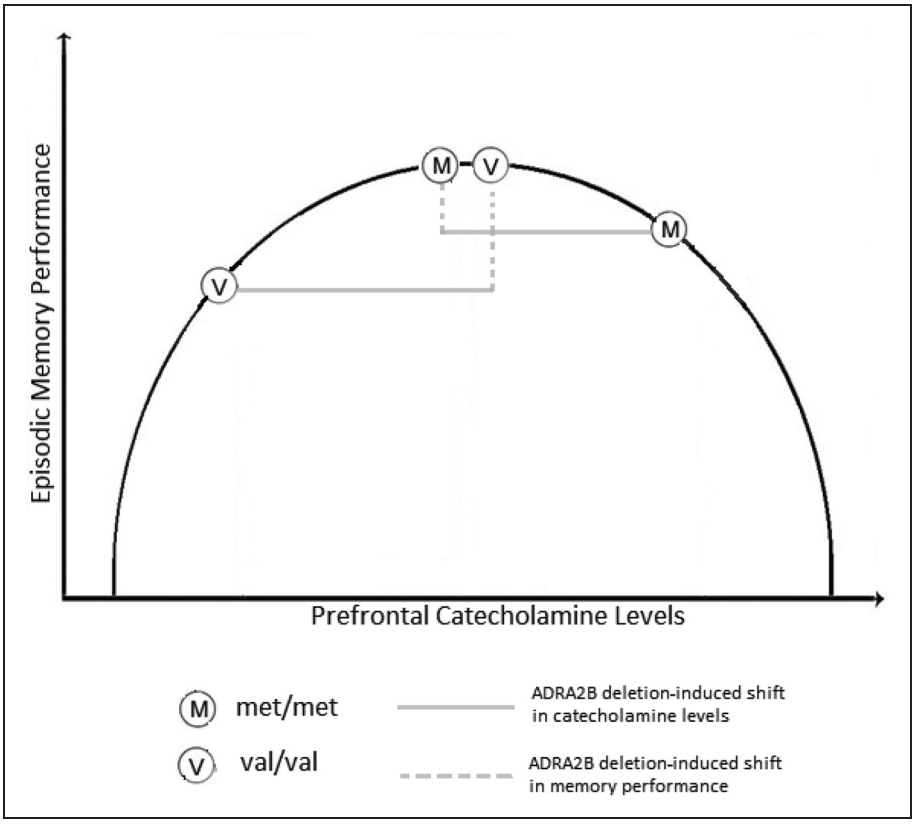

Figure 1 Inverted 'U'-shaped model of episodic memory performance against catecholamine levels as influenced by genotype. A putative inverted 'U' models the effects of COMT and ADRA2B genotypes on episodic memory performance and catecholamine levels in the prefrontal cortex (PFC). By presumably boosting noradrenergic catecholamine transmission, the deletion variant of ADRA2B shifts COMT val/val individuals – who normally have greater COMT activity, less dopaminergic catecholamine transmission, and relatively poorer episodic memory – to the right, and more optimal performance. The ADRA2B deletion variant also shifts met/met individuals, who are presumed to have optimal prefrontal function, to the right, but to less efficient performance.

However, the discrepancy may have been due to methodological differences. For example, in order to explore the contribution of genetic variation to longer-term consolidation processes, we examined memory after a delay of 1 week, rather than the 10-min interval used by de Quervain et al. We also used an 'old–new' recognition memory test, as opposed to free recall, in order to examine other processes that may be influenced by emotional arousal, such as memory confidence. In such *one-interval* designs, measures of accuracy or *discrimination* (d') may be derived from *single-process* memory models based on signal detection theory (SDT) (Green and Swets, 1966). In these models d' is considered to relate to a single process of memory strength, or familiarity, from which confidence judgements arise directly (Egan, 1958). However, *dual-process signal detection* (DPSD) models have increasingly been used to account for data indicating that two distinct processes may contribute to recognition memory: recollection and familiarity (Yonelinas, 2002). The latter is considered to be a quantitative, memory-strength-based process, associated with a 'sense of having previously seen'. By contrast, recollection is presumed to be a qualitative threshold process, associated with high levels of contextual detail and high-confidence judgements, and is considered most closely related to recall performance (Mandler, 1980). It is possible that differential effects of genotypes on emotional enhancement of these two different memory processes may account for the difference between our findings and those of de Quervain et al. (2007). Therefore, in the present study, we used a DPSD approach to investigate the relative contribution of variation in the ADRA2B and COMT genotypes (including possible interactions) to the recollection and familiarity components of emotional memory.

Materials and methods

Participants

For this study, 107 healthy white British male volunteers, aged 18–40 years (mean age = 24.1, SD = 4.8) were recruited through an advertisement and received financial compensation for their participation. Potential participants were screened for psychiatric or neurological disorder by means of a checklist questionnaire. Exclusion criteria were (i) any current or past history of psychiatric illness, (ii) any significant history of substance misuse, including nicotine, and (iii) taking regular medication. Estimates of verbal IQ were derived from the National Adult Reading Test (NART) (Nelson, 1982). The study was approved by the King's

College London Research Ethics Committee and all participants gave written informed consent.

Genetic testing

This was carried out as previously reported (Gibbs et al., 2010b). Specifically, DNA extraction from buccal swabs was carried out by KBioscience using their internal GuSCN-based extraction protocol, and genotyping was carried out using their PCR SNP genotyping system (KASPar®), using 1.5 μL DNA (at approximately 10 ng/μL) per well, dried down before PCR onto KBioscience 384-well plates, 4 μL PCR volume (using 2 × KASPar genotyping system reagent) at 94°C for 15 min (94°C for 10 s, 57°C for 60 s) × 36 cycles. Plates were read using a BMG PheraStar microtitre plate fluorescence reader. Two forward primers and one reverse primer were used as follows for ADRA2B: pF1:GAAGGTGACCAAGTTC ATGCTCCTCCTCCTCCTCCTCTTCA (detects 'Short' allele) and pF2:GAAGGTCGGAGTCAACGGATTCCTCC TCCTCCTCCTCTTCC (detects 'Long' allele), and pR:GA AGGAGGGTGTTTGTGGGGCAT; and for COMT, pF1: GAAGGTGACCAAGTTCATGCTGGCATGCACACCTT GTCCTTCAT (detects 'A' allele), pF2:GAAGGTCGGAGT CAACGGATTGCATGCACACCTTGTCCTTCAC (detects 'G' allele), pR:CATCACCCAGCGGATGGTGGAT.

Emotional memory task

We used an emotional memory task similar to that previously used by ourselves and others (de Quervain et al., 2007; Gibbs et al., 2007, 2010b; Rasch et al., 2009). During the encoding phase participants viewed 92 pictures from the International Affective Picture System (IAPS) stimulus set (Lang et al., 1998). Half were aversive-arousing (mean valence = 2.6, SD = 0.9 and mean arousal = 6.1, SD = 0.6) and half were neutral (mean valence = 5.1, SD = 0.6 and mean arousal = 3.3, SD = 0.8). Evidence suggests that the effects of emotional arousal on memory are larger and more consistently observed for aversive compared with positive emotional stimuli (de Quervain et al., 2007; Kensinger and Corkin, 2004; Rasch et al., 2009). In addition, the evidence to date suggests that *COMT* is associated with altered processing of aversive but not positive stimuli. Hence we chose to use only aversive emotional stimuli, given that we were interested in the effects of arousal, rather than valence per se. The pictures were presented on a laptop computer for 3 s with a 4-s inter-stimulus interval (ISI), during which a fixation cross was present on the screen. The order of presentation was randomized across participants. Participants were instructed to observe the picture while it was being presented and make a binary judgement as to whether they considered the image emotionally arousing or non-arousing by pressing one of two laptop keys. Delayed memory was tested 1 week later when participants returned for an unexpected recognition memory test in which they viewed all of the 92 previously seen pictures and 92 foils matched for content, valence and arousal. Participants were required to judge whether each picture was 'old' (previously seen) or 'new' (not previously seen) and then rate their confidence in this judgement using a scale ranging from 'uncertain' to 'very certain'. In order to reduce the likelihood of participants making only high-confidence or low-confidence judgements, they were advised to make use of the entire scale. Participants were also asked to rate each picture for arousal and valence on scales ranging from 'calm' to 'aroused' and 'unpleasant' to 'pleasant', respectively, in line with previous approaches (Lang et al., 1988).

Statistical analysis

Hit rates (proportion of previously seen items correctly identified as 'old') and false alarm rates (proportion of foils incorrectly identified as 'old') for each stimulus category were calculated for each participant. Estimates of recollection (R) and familiarity (d') for each participant were derived from receiver operating characteristic (ROC) curves generated by plotting performance (hit rate vs. false alarm rate) as a function of response confidence. This was carried out using a Microsoft Excel solver that used model dual-process equations to reduce the sum of squared errors between the predicted and observed data (Yonelinas et al., 1998). The number of items in each confidence category was examined to ensure that participants had followed the instructions to utilize the entire confidence scale. This was necessary as evidence suggests that failure to use the entire scale leads to ROC points that are closely clustered together, making it difficult to accurately assess the function.

Results

Genotypes

Of the 107 participants, ADRA2B genotypes were missing for two participants, 11 were homozygous carriers of the ADRA2B deletion, 48 were heterozygotes and 46 were non-carriers. These frequencies did not deviate from Hardy–Weinberg equilibrium ($X^2 = 0.09$, $p = 0.77$). Due to the small number of homozygous carriers, they were combined with the heterozygotes, giving two genotype groups of deletion carriers (del) and non-carriers (no del) as previously done by de Quervain et al 2007. The COMT genotype was missing for one participant. Some 36 participants were homozygous for the met158 allele, 27 were homozygous for the val158 allele and 43 were heterozygous, consistent with Hardy–Weinberg equilibrium ($X^2 = 3.54$, $p = 0.06$). Seven participants failed to attend for recognition memory testing and were excluded from further analysis. Genotype frequencies of participants included in the analysis are given in Table 1. Demographic characteristics (age and IQ) are given in Table 2. IQ data were missing for two participants. Differences in demographic variables between genotype

Table 1 Genotype frequencies

Genotype ADRA2B [1]		*COMT* [2]			*Total*
		val/val	val/met	met/met	
del	del/del	1	3	4	8
	del/no del	16	17	15	48
no del	no del/no del	8	17	16	41
	Total	25	37	35	97

[1] $X^2 = 1.38$, $p = 0.24$; [2] $X^2 = 5.08$, $p = 0.02$.

groups were assessed in a multivariate analysis of variance (ANOVA) with age and IQ as dependent variables and ADRA2B (del, no del) and COMT (val/val, val/met, met/met) genotypes as between-subjects factors. There were no significant main effects of genotype and no interactions.

Arousal and valence ratings

There were no differences between genetic variants in arousing versus non-arousing judgements made at encoding for COMT ($X^2 = 1.7$, $p = 0.42$) or ADRA2B ($X^2 = 1.9$, $p = 0.16$). The ratings made at recognition memory testing were significantly correlated with the standardized ratings for valence ($r = 0.72$, $p < 0.0001$) and arousal ($r = 0.63$, $p < 0.0001$). These ratings were entered into separate repeated measures ANOVA with emotional category (aversive, neutral) and stimulus category (encoding, foil) as the within-subject factors and ADRA2B (del, no del) and COMT (val/val, val/met, met/met) genotypes as between-subjects factors. There was a main effect of emotional category on both arousal [$F(1, 91) = 424.96$, $p < 0.001$] and valence [$F(1, 91) = 897.6$, $p < 0.001$] with emotional pictures being rated as significantly more arousing [mean(SD) = 6.53(1.08) vs. 4.03(1.04)] and more unpleasant [mean(SD) = 3.01(0.94) vs. 5.53(0.64)] than neutral. There were no main effects of genotype or stimulus category and no interactions.

Emotional memory

R and d' were entered into separate repeated-measures ANOVA with emotional category (aversive, neutral) as the within-subject factor and ADRA2B (del, no del) and COMT (val/val, val/met, met/met) genotypes as between-subjects factors. This revealed a significant emotion × COMT interaction [$F(2, 90) = 3.4$, $p = 0.04$] on recollection that accounted for 7% of the variance in the model, see Figure 2. There were no

Table 2. Socio-demographic characteristics for COMT and ADRA2B genotypes

	COMT						*ADRA2B*				
	val/val	val/met	met/met	*F*	*df*	*p*	del	no del	*F*	*df*	*p*
Age [yrs, mean (SD)]	24.7 (5.0)	24.1 (5.0)	23.8 (4.6)	0.89	2, 90	0.12	24.8 (5.1)	23.2 (4.3)	3.04	1, 90	0.08
IQ [mean (SD)]	106.4 (7.5)	105.0 (5.6)	106.2 (5.4)	0.50	2, 90	0.63	106.7 (5.7)	104.7 (6.4)	3.43	1, 90	0.07

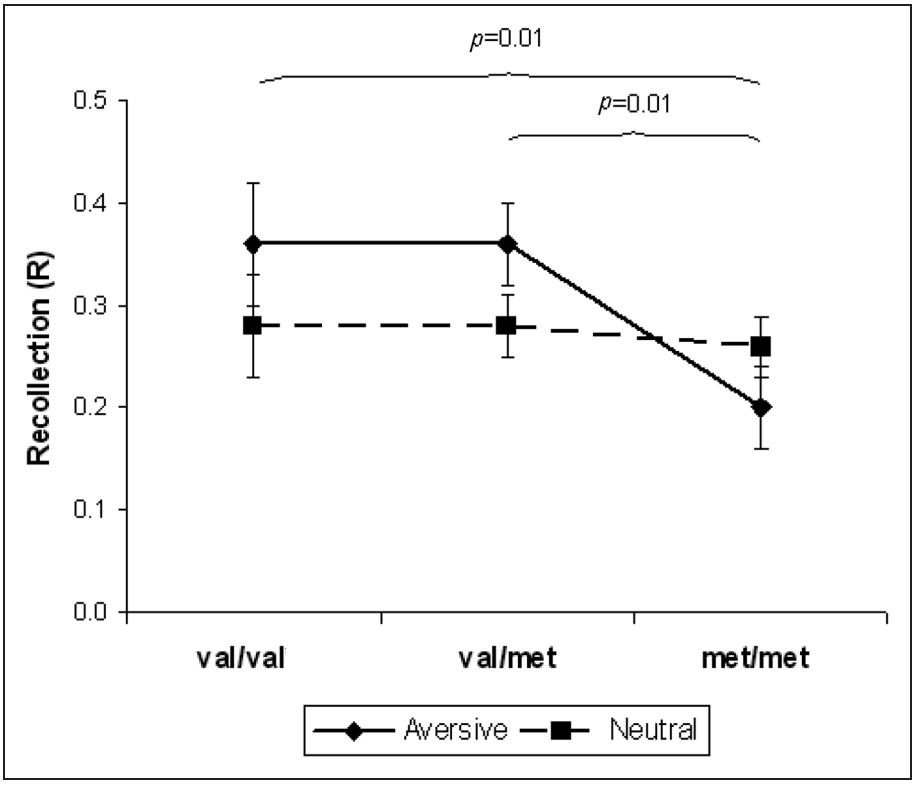

Figure 2 Recollection estimates in COMT genotypes for aversive and neutral stimuli. There was a significant interaction between COMT genotype and stimulus valence on recollection. Recollection estimates were significantly lower in COMT met/met genotypes compared with val/val and val/met for aversive, but not neutral stimuli.

other main effects or interactions. Post-hoc independent *t*-tests indicated that recollection estimates were significantly greater in COMT val/val [$t(57) = 2.52$, $p = 0.01$] and val/met [$t(70) = 2.60$, $p = 0.01$] individuals compared with met/met for aversive, but not neutral stimuli. ANOVA did not reveal any main effects or interactions in relation to familiarity. Mean hit/false alarm rates, confidence ratings, recollection/familiarity estimates are given in Tables 3, 4, and 5, respectively. The average ROC curves for the aversive and neutral conditions for the COMT val/val and met/met genotypes are presented in Figure 3a–d.

We have previously reported analyses of the standard SDT parameters sensitivity (d') and response bias (C), in

Table 3. Mean (SD) hit rate and false alarm rate for aversive and neutral stimuli for COMT and ADRA2B genotypes

			Hit Rate		*False Alarm Rate*	
COMT	*ADRA2B*	N	Aversive	Neutral	Aversive	Neutral
val/val	no del	8	0.70(0.23)	0.55(0.21)	0.25(0.13)	0.21(0.13)
	del	17	0.81(0.10)	0.69(0.14)	0.21(0.13)	0.14(0.08)
Total		25	0.77(0.16)	0.65(0.17)	0.22(0.13)	0.16(0.10)
val/met	no del	17	0.80(0.12)	0.69(0.12)	0.22(0.15)	0.15(0.14)
	del	20	0.80(0.11)	0.63(0.14)	0.19(0.10)	0.11(0.07)
Total		37	0.80(0.11)	0.66(0.13)	0.20(0.13)	0.13(0.11)
met/met	no del	16	0.82(0.02)	0.69(0.12)	0.18(0.07)	0.13(0.07)
	del	19	0.76(0.13)	0.62(0.14)	0.19(0.08)	0.15(0.10)
Total		35	0.79(0.11)	0.65(0.14)	0.18(0.08)	0.14(0.08)

Table 4. Mean (SD) confidence ratings for hits and false alarms for aversive and neutral stimuli for COMT and ADRA2B genotypes

			Hits		*False Alarms*	
COMT	*ADRA2B*	N	Aversive	Neutral	Aversive	Neutral
val/val	no del	8	7.33(1.10)	6.93(1.22)	6.25(1.48)	5.40(1.80)
	del	17	7.76(0.72)	6.28(1.56)	6.28(1.56)	4.86(1.33)
Total		25	7.62(0.86)	7.13(0.92)	6.27(1.40)	5.03(1.48)
val/met	no del	17	7.72(0.53)	7.28(0.82)	6.01(1.43)	5.18(1.35)
	del	20	7.52(0.61)	7.20(0.82)	5.73(1.30)	5.23(1.38)
Total		37	7.61(0.58)	7.23(0.81)	5.86(1.53)	5.21(1.35)
met/met	no del	16	7.87(0.66)	7.49(0.64)	6.43(0.90)	5.59(1.21)
	del	19	7.41(0.87)	6.73(1.19)	5.75(1.40)	4.31(1.66)
Total		35	7.62(0.80)	7.08(1.04)	6.06(1.23)	4.90(1.59)

Table 5. Mean (SD) recollection and familiarity estimates for aversive and neutral stimuli for COMT and ADRA2B genotypes

			Recollection		*Familiarity*	
COMT	*ADRA2B*	N	Aversive	Neutral	Aversive	Neutral
val/val	no del	7	0.29(0.32)	0.15(0.14)	1.33(0.96)	0.76(0.46)
	del	17	0.41(0.28)	0.35(0.25)	1.31(0.71)	1.08(0.53)
Total		24	0.38(0.29)	0.29(0.24)	1.32(0.77)	0.99(0.52)
val/met	no del	17	0.35(0.30)	0.30(0.20)	1.17(0.81)	1.10(0.53)
	del	20	0.37(0.25)	0.26(0.18)	1.30(0.68)	1.30(0.52)
Total		37	0.36(0.27)	0.28(0.19)	1.24(0.74)	1.21(0.53)
met/met	no del	16	0.22(0.30)	0.25(0.19)	1.59(0.55)	1.33(0.59)
	del	19	0.18(0.23)	0.27(0.16)	1.33(0.70)	1.07(0.41)
Total		35	0.20(0.26)	0.26(0.17)	1.45(0.64)	1.19(0.51)

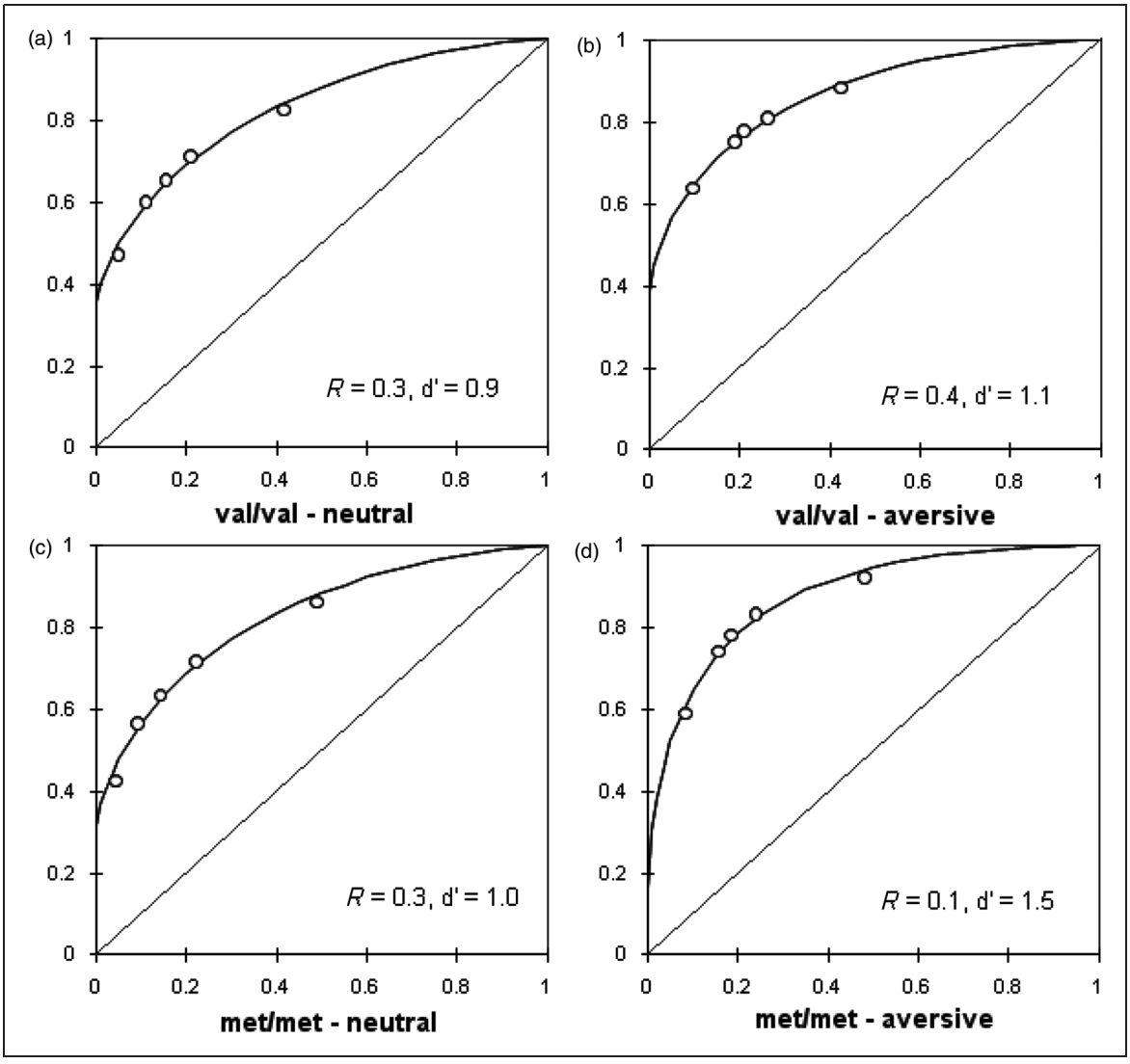

Figure 3 ROC curves for COMT val/val and met/met genotypes for aversive and neutral conditions plotted in probability space. The *x*-axis represents the proportion of new pictures incorrectly identified as 'old'. The *y*-axis represents the proportion of old pictures correctly identified. The diagonal represents chance discrimination. Functions a–c are curvilinear and asymmetrical along the diagonal, suggesting contributions of both recollection and familiarity to the recognition memory process (Yonelinas et al, 1998). Function b is skewed relative to a, suggesting a greater contribution of recollection for the aversive pictures, compared with neutral pictures in the val/val genotypes. Function d appears symmetrical along the diagonal, rather than skewed relative to c, suggesting that recollection made a limited contribution to the discrimination of aversive pictures, compared with neutral pictures in the met/met genotypes.

which we found no effect of *COMT* on emotional enhancement of memory (Gibbs et al., 2010b). However in the present analysis, we additionally examined d' based on hit rate and false alarm rate parameters derived only from responses in the highest confidence category. This produced a significant interaction between *COMT* and *ADRA2B* on overall memory performance, as previously reported, but no other significant main effects or interactions. However, in the model including only high-confidence responses, the interaction between COMT genotype and arousal explained a greater proportion of the variance (3%) than the model including all responses (1%).

Discussion

The aim of this study was to explore the contribution of genetic variation to the recollection and familiarity components of emotional enhancement of memory, and to the best of our knowledge, this is the first study to do so. Given that previous studies have indicated that the catecholamine neurotransmitters dopamine and noradrenaline play a key role in emotional processing, we examined the influence of two functional polymorphisms involved in catecholamine signalling (COMT val158met and the ADRA2B deletion polymorphism) on a DPSD model of emotional memory.

We found a significant interaction effect between COMT val158met genotype and emotional arousal on the recollection component of recognition memory. Specifically, long-term recollection for emotionally arousing, but not neutral, stimuli was impaired in met/met individuals, compared with val/val and val/met individuals. Although this interaction explained only a small proportion of the variance in the model, the observed increases in effect size when using DPSD measures versus standard SDT measures based on high-confidence responses versus standard SDT measures based on all responses further supports the validity of the DPSD approach in this case. No prior studies have directly investigated the potential link between the COMT val158met polymorphism and emotional memory. The present findings, along with our previous report, constitute the first published attempts to do so. Our present data suggest *COMT* moderation of high-confidence recollective emotional memory processes, but not low-confidence familiarity-based ones. This may be attributable to one of two possibilities: (i) a specific effect of COMT genotype on recollection, but not familiarity; or (ii) greater power to detect effects on recollection, given that emotional arousal is known to boost recollection to a greater degree than familiarity (Gibbs et al., 2010a; Ochsner, 2000; Sharot et al., 2007). The increasing effect sizes when moving from analysis of decisions made with any level of confidence levels to high-confidence decisions to recollection support the latter scenario. This suggests that future studies aiming to investigate effects of COMT genotype on emotional modulation of recognition memory may maximize detection of statistically significant results by limiting analyses to responses made with the highest degree of confidence, or adopting a DPSD approach.

Prior to this, no studies had specifically examined the role of *COMT* in declarative emotional memory. In the absence of an existing body of behavioral emotional memory literature, it is difficult to interpret our findings in the context of specific differential effects of the val versus met alleles. Previous studies investigating links between *COMT* and emotional processing have focussed on neural (as opposed to behavioral) effects and found that carriers of the met allele showed greater prefrontal cortical and amygdala activation in response to aversive scenes compared with carriers of the val allele (Domschke et al., 2008; Drabant et al., 2006; Smolka et al., 2005; Yacubian et al., 2007). It has therefore been suggested that the effect of *COMT* on emotional memory might relate to prefrontal regulation of amygdala reactivity to aversive events, in turn influencing consolidation of such events (Todd et al., 2011). This would be in keeping with the established role of the amygdala in modulating emotional memory (Cahill et al., 1996; Canli et al., 1999, 2000). However, these studies clearly document positive correlations between amygdala activation and emotional enhancement of memory, suggesting that the increased amygdala activation observed in met carriers would predict enhanced, rather than impaired, recollection for aversive stimuli as we observed. However, the relationship between the magnitude of brain activation as detected by functional neuroimaging and task performance remains complex and poorly understood. For example, some brain regions such as the prefrontal cortex appear to demonstrate a distinctive 'inverted U' or 'capacity-constrained' pattern of brain activation in relation to performance, such that the two are positively correlated up to the point that a capacity is reached, after which performance typically declines, and is uncoupled from brain activation (Callicott et al., 1999). Whilst this principle has not been specifically investigated in relation to the amygdala and other limbic structures involved in emotional memory, a similar pattern may also be applicable. For example, above a certain threshold, amygdala activation may cease to enhance memory performance and begin to result in impairment. This would explain our present findings and would be consistent with other work supporting an inverted U-shaped relationship between corticosteroids and cognition, including episodic memory performance (Lupien and McEwen, 1997; Roozendaal, 2000; Wolkowitz et al., 1990). However, functional neuroimaging studies examining the relationship between COMT genotypes and brain activation associated with successful encoding of emotional stimuli will be necessary to clarify the neural basis of these genotype effects on emotional memory.

Three prior studies have investigated *ADRA2B* influences on emotional memory. In a large single-gene study, de Quervain et al (2007) examined 435 Swiss participants and found that carriers of the deletion variant showed significantly greater recall memory for emotional (positive and negative) versus neutral pictures compared with non-carriers. In a further study to examine the relationship between genotype-dependent differences in brain activation and emotional memory, they collected fMRI from 57 participants using the same emotional memory task (Rasch et al., 2009). Deletion carriers demonstrated significantly increased amygdala activation in response to emotionally arousing pictures compared with non-carriers, although no behavioral differences in emotional memory were observed. This was considered due to low statistical power (32%) to detect the effect size of 0.4 in this much smaller sample. In an independent study examining both COMT and ADRA2B genotype influences on emotional memory in 97 British participants using aversive emotional pictures, we did not find any *ADRA2B*-related differences in emotional memory for aversive compared with neutral pictures based on standard SDT parameters (Gibbs et al., 2010b). In the present analysis of these data using a DPSD approach, we also did not find any main effect of the ADRA2B genotype on emotional enhancement of recollection or familiarity processes. In both cases this may be due to insufficient statistical power (60%) based on the effect size reported in the Swiss study. However, other methodological differences may also be relevant. Firstly, we used a 1-week interval between encoding and memory testing as opposed to their short 10-min retention interval. It is possible that the genotype-dependent differences observed by de Quervain and colleagues relate to encoding processes, such as attention and perception, influencing short-term memory, as opposed to the consolidation processes contributing to long-term memory. This would be consistent with their fMRI findings where ADRA2B genotype-dependent differences in amygdala activation were observed during encoding but did not influence subsequent memory. However, given that memory was tested at a single time point in both studies, it remains unclear whether the effects are due to encoding

or consolidation processes, or both. Further studies will be necessary to clarify the effects of *ADRA2B* on the affective modulation of attention/perception during encoding and the effects of post-encoding arousal (Todd et al., 2011). Although no genotype effects on emotional memory were found in our prior study, we did observe a significant interaction between *COMT* and *ADRA2B* on recognition memory for both aversive and neutral pictures, such that possession of the ADRA2B deletion appeared to ameliorate the impairment associated with the COMT val allele (Gibbs et al., 2010b). Yet no such interaction was observed in relation to recollection and familiarity in the present analysis. This may be because the epistatic effects of the two genes on overall recognition memory may influence both recollection and familiarity, and examining these processes separately may have resulted in a loss of power. Further studies are warranted using larger samples.

In addition to issues that may have arisen due to low statistical power, there are a number of limitations to our study. The COMT genotypes included in the final analysis deviated from Hardy–Weinberg equilibrium, raising the possibility of genotyping error or a selection bias limiting the generalizability of our findings. However, we consider this unlikely given that both genotypes were in Hardy–Weinberg equilibrium in the full sample of recruited individuals, although we acknowledge that the X^2 analysis for *COMT* was suggestive of trend-level statistical significance. In addition, we used an all-male group in order to avoid confounding the established gender differences in emotional memory and its neural correlates (Cahill, 2006) as well as sexually dimorphic effects of *COMT* (Chen et al., 2004; Gogos et al., 1998; Harrison and Tunbridge, 2007). Therefore, the extent to which the present findings are applicable to women remains unclear and will warrant further investigation in larger mixed-gender samples to allow adequate control for possible gender effects. Furthermore, we used only aversive emotionally arousing pictures. This is justified by the accumulating evidence that *COMT* preferentially influences processing of aversive as opposed to positive emotional stimuli (Herrmann et al., 2009; Montag et al., 2008; Smolka et al., 2007) and the fact that emotional enhancement of memory is arousal dependent, rather than valence dependent (Kensinger and Corkin, 2004). Nevertheless, the inclusion of only aversive emotional stimuli means that implications of our findings for positive emotional experiences are unclear. Finally, we examined only two genes amongst a number of variants that may contribute to emotional memory and its components (Todd et al., 2011). It is increasingly understood that epistatic effects are likely to be at least as important in modulating behavioral phenotypes, if not more so, than single-gene effects (Elvevåg and Weinberger, 2009). In fact, it has been suggested that one of the reasons that studies of single polymorphisms replicate poorly across independent samples is because epistasis is more important (Moore and Williams, 2002). In spite of this, gene–gene interactions have rarely been explored in behavioral genetics studies. This is because the phenomenon of biological epistasis is poorly understood, its analysis is more complex and as the number of genes involved increases, exponentially larger sample sizes are needed to estimate interaction effects (Moore, 2008). Indeed, the small number for each genotype combination in our present study may have limited power to detect such an effect.

In summary, the present study provides preliminary behavioral evidence concerning the effect of the COMT val158met polymorphism on the recollection component of emotional memory. As such, it contributes to an important emerging area of cognitive neuroscience research: the role of genetic variation in emotional enhancement of memory. It also begins to disentangle the effects in relation to two different forms of episodic memory: recollection and familiarity. However, it is acknowledged that the findings reported are preliminary and future studies are needed to independently replicate and extend this work.

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Conflict of interest

The authors declare that there is no conflict of interest.

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