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SHORT COMMUNICATION

Deletion variant of α2b-adrenergic receptor gene moderates the effect of COMT val^{158}met polymorphism on episodic memory performance

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Abstract

The COMT *val*^{158} variant has been associated with impaired cognitive function compared to the *met*^{158} variant yet gene–gene interactions are not well described. In this study we demonstrate an interaction between this COMT polymorphism and a deletion variant of ADRA2B, the gene encoding the α2b-adrenergic receptor on episodic memory performance. Specifically, carriage of the ADRA2B deletion abolished the relative memory impairment in homozygous COMT *val*^{158} carriers compared to *met*^{158} carriers.

1. Introduction

Animal studies suggest that memory formation is dependent on noradrenergic modulation of the process of long-term potentiation (LTP) in the hippocampus (Straube and Frey, 2003). Other work also implicates the dopamine system of the prefrontal cortex in modulating memory storage (Williams and Goldman-Rakic, 1995). Enhancement of memory for emotionally arousing events in animals and humans has been linked to an increase in central noradrenergic transmission, mediated via the amygdala and its projections to the hippocampus and other brain regions, such as the dopamine system of the prefrontal cortex (Roozendaal et al., 2009). Amygdala lesions in animals have been demonstrated to result in an attenuated stress-induced increase in dopamine turnover in the prefrontal cortex (Davis et al., 1994). This suggests that the effect of emotional arousal on memory may depend in part, on noradrenergic amygdala-influenced effects on the dopamine-related activity of the prefrontal cortex. This is supported by functional neuroimaging data highlighting the importance of interaction between these brain regions during emotional processing (Keightley et al., 2003). More recently, the function of both of these regions has been related to genetic variation (Smolka et al., 2005).

A deletion variant of the ADRA2B gene results in reduced functionality of the α2b-adrenergic autoreceptor and presumed potentiation of central noradrenergic transmission. This variant has been associated with enhanced emotional memory in humans (de Quervain et al., 2007). A G to A missense variant of the COMT gene (*met*^{158}) results in

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reduced functionality the catechol-O-methyl transferase enzyme responsible for the degradation of dopamine in the prefrontal cortex and presumed higher extracellular dopamine levels (Chen et al., 2004). This variant has been associated with enhanced episodic memory as well as exaggerated amygdala and prefrontal cortical responses to emotional stimuli relative to the *val*^{158} allele (de Frias et al., 2004; Smolka et al., 2005). However, no studies have so far investigated the effects of interaction between these gene systems on memory formation.

In this study we set out to determine whether the ADRA2B and COMT genotypes would interact to modulate emotional and non emotional memories. We predicted that episodic memory performance would be better in COMT *met*^{158} carriers and this variant would produce additive effects in combination with the ADRA2B deletion variant to produce greater emotional enhancement of memory.

2. Experimental procedures

Memory testing and genotyping in relation to the ADRA2B deletion and COMT val^{158}met polymorphisms were carried out in 97 Caucasian healthy male volunteers aged 18–35 years (mean = 24.1, SD = 4.8). The study was approved by the King's College London Research Ethics Committee and all participants gave written informed consent. During the encoding phase participants viewed 92 pictures from the International Affective Picture System (IAPS) (Lang et al., 1998). Half of them were negative-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). The pictures were presented on a laptop computer for 3 s with a 4 second inter-stimulus interval (ISI), during which a fixation cross was present on the screen. The order of presentation was randomized across participants. Estimates of verbal IQ were derived from the National Adult Reading Test (NART). 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. After each picture, participants made an "old"/"new" judgment and rated the arousal and valence of each picture using a 9-point scale. The hit rate (HR) and false alarm rate (FAR) were calculated for each participant and memory accuracy was assessed by the calculation of the discrimination index (P_r) based on a two-high-threshold theory (Snodgrass and Corwin, 1988).

DNA extraction from buccal swabs was carried out by KBiosciences using their internal GuSCN-based extraction protocol and genotyping was carried out using their PCR SNP genotyping system (KASPar®). 1.5 μl DNA (at ~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:GAAGGTGACCAAGTTCATGCTCCTCCTCCTCCTCCTCTTCA (detects 'Short' allele) and
pF2:GAAGGTCGGAGTCAACGGATTCCTCCTCCTCCTCCTCTTCC (detects 'Long' allele)
pR:GAAGGAGGGTGTTTGTGGGGCAT and COMT:
pF1:GAAGGTGACCAAGTTCATGCTGGCATGCACACCTTGTCCTTCAT (detects 'A' allele)
pF2:GAAGGTCGGAGTCAACGGATTGCATGCACACCTTGTCCTTCAC (detects 'G' allele)
pR:CATCACCCAGCGGATGGTGGAT

3. Results

Of the 97 participants, 9 were homozygous carriers of the ADRA2B deletion, 48 heterozygotes and 41 did not carry the deletion. Due to the small number of homozygous carriers, they were combined with the heterozygotes. Thirty-five participants were homozygous for the *met*^{158} allele of the COMT gene, 25 were homozygous for the *val*^{158} allele and 37 were heterozygous. These frequencies did not deviate from Hardy–Weinberg equilibrium. Repeated measures analysis of variance revealed that memory accuracy as measured by P_r was significantly greater for negative-arousing pictures than neutral pictures [$F = 29.0$, degrees of freedom = 1, error degrees of freedom = 91, $p < 0.001$]. However there was no effect of ADRA2B or COMT genotype on emotional memory as assessed by the absence of both 2-way and 3-way arousal × genotype interactions. However, there was a highly significant interaction between ADRA2B and COMT genotype [$F(2, 91) = 6.7$, $p = 0.002$] accompanied by a trend towards a significant main effect of COMT on overall memory performance [$F(2, 91) = 2.7$, $p = 0.07$] (Fig. 1). Mean memory performance measures (hit rate, false alarm rate and P_r) for aversive and neutral stimuli by genotype are given in Table 1. There were no group differences in age or IQ.

4. Discussion

In line with previous studies, our results are indicative of episodic memory impairment in carriers of the COMT *val*^{158} allele relative to the *met*^{158} allele. However, we demonstrate for the first time that this disadvantage is abolished by possession of the ADRA2B deletion variant. This is the first demonstration of an effect of ADRA2B genotype on episodic memory performance and its interaction with COMT. This suggests that genes that do not exert direct effects on cognition might do so indirectly via gene–gene interactions. Our hypotheses relating to the effects on emotional enhancement of memory were not confirmed.

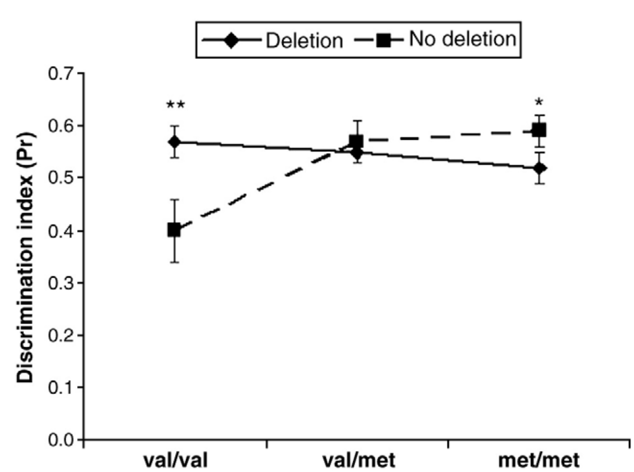

Figure 1 Discrimination index (P_r) for all items. There was no difference in memory performance between COMT genotypes in those with the ADRA2B deletion. However, in the absence of the deletion memory performance of homozygous COMT *val*^{158} carriers were significantly worse than carriers of the *metl*^{158} allele. $^{**}p < 0.01$, $^{*}p < 0.05$.

Table 1 Mean memory performance measures (hit rate, false alarm rate and P_r) for aversive and neutral stimuli by genotype.

Performance measure	ADRA2B	COMT	Stimulus	Mean	SD
Hit rate	No deletion	*val*/*val*	Aversive	.70	.23
			Neutral	.55	.21
		val/*met*	Aversive	.80	.12
			Neutral	.69	.12
		met/*met*	Aversive	.82	.08
			Neutral	.69	.12
	Deletion	*val*/*val*	Aversive	.81	.10
			Neutral	.69	.14
		val/*met*	Aversive	.80	.11
			Neutral	.63	.14
		met/*met*	Aversive	.76	.13
			Neutral	.62	.14
False alarm rate	No deletion	*val*/*val*	Aversive	.25	.13
			Neutral	.21	.13
		val/*met*	Aversive	.22	.15
			Neutral	.15	.14
		met/*met*	Aversive	.18	.07
			Neutral	.13	.07
	Deletion	*val*/*val*	Aversive	.21	.13
			Neutral	.14	.08
		val/*met*	Aversive	.19	.10
			Neutral	.11	.07
		met/*met*	Aversive	.19	.08
			Neutral	.15	.10
Discrimination index (P_r)	No deletion	*val*/*val*	Aversive	.46	.16
			Neutral	.35	.20
		val/*met*	Aversive	.58	.19
			Neutral	.53	.16
		met/*met*	Aversive	.64	.11
			Neutral	.56	.15
	Deletion	*val*/*val*	Aversive	.60	.16
			Neutral	.55	.12
		val/*met*	Aversive	.61	.11
			Neutral	.52	.11
		met/*met*	Aversive	.57	.14
			Neutral	.46	.16

The enhanced cognitive performance associated with COMT *met*^{158} allele carrier status has been attributed to enhanced dopaminergic, rather than noradrenergic transmission in the prefrontal cortex (Tunbridge et al., 2006). However, prior studies described above have indicated that noradrenergic transmission in other brain regions may play a role in modulating this effect. Our findings suggest that enhanced noradrenergic transmission as a result of reduced function of the α2b-adrenergic autoreceptor may compensate for the reduction in dopamine-related activity of the prefrontal cortex associated with the higher activity COMT *met*^{158} allele. However, the neuroanatomical substrate for this effect remains unclear.

We also demonstrated a reduction in memory performance in ADRA2B deletion carriers relative to non deletion carriers in COMT *met*158 allele heterozygotes. This may be related to the observed inverted-U-shaped relationship between catecholamine levels and prefrontal cortical function (Meyer-Lindenberg et al., 2005). Given that *met*/*met* individuals are hypothesised to have near-optimal central catecholamine function, increased noradrenergic transmission via the ADRA2B deletion may result in a relative impairment in memory performance.

One limitation of this study is the relatively small sample size that may have contributed to our failure to demonstrate arousal × genotype effects. This failure may also be related to the use of recognition memory testing as opposed to recall. Although emotional arousal may lead to enhanced recall of information, it may not always lead to increased accuracy on recognition memory testing (Windmann and Kutas, 2001). This has been attributed to an emotion-induced sense of familiarity, leading to a more liberal response bias, i.e. an increased tendency to classify stimuli as previously seen, irrespective of whether they have been or not (Dougal and Rotello, 2007). Under such circumstances, the response bias criterion may provide a better marker of emotional modulation of memory.

Recent pharmacogenetic approaches to therapeutic drug development for neuropsychiatric disorders have begun to examine the interaction between genetic variation and cognitive response. For example, pre-clinical studies in healthy volunteers indicate that the COMT inhibitor tolcapone interacts with COMT genotype in producing effects on cognition, such that *val*/*val* genotypes exhibit improvement and *met*/*met* genotypes worsen (Apud et al., 2006). This is consistent with our findings which may have implications for future neuropharmacological attempts to enhance cognition via the noradrenergic system.

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Contributors

A.A.G. designed the study, analysed the data and wrote the manuscript. A.S.D and K.H.N. edited the manuscript and R.T.A collected the data and edited the manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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