Research Paper

Catechol-*O*-methyltransferase val158met genotype determines effect of reboxetine on emotional memory in healthy male volunteers

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Background: Catechol-*O*-methyltransferase (COMT) metabolizes catecholamines in the prefrontal cortex (PFC). A common polymorphism in the *COMT* gene (COMT val158met) has pleiotropic effects on cognitive and emotional processing. The met allele has been associated with enhanced cognitive processing but impaired emotional processing relative to the val allele. **Methods:** We genotyped healthy, white men in relation to the COMT val158met polymorphism. They were given a single 4 mg dose of the selective noradrenaline reuptake inhibitor (NRI) reboxetine or placebo in a randomized, double-blind between-subjects model and then completed an emotional memory task 2 hours later. **Results:** We included 75 men in the study; 41 received reboxetine and 34 received placebo. In the placebo group, met/met carriers did not demonstrate the usual memory advantage for emotional stimuli that was observed in val carriers. Reboxetine restored this emotional enhancement of memory in met/met carriers, but had no significant effect in val carriers. **Limitations:** We studied only men, thus limiting the generalizability of our findings. We also relied on self-reported responses to screening questions to establish healthy volunteer status, and in spite of the double-blind design, participants were significantly better than chance at identifying their intervention allocation. **Conclusion:** Emotional memory is impaired in healthy met homozygotes and selectively improved in this group by reboxetine. This has potential translational implications for the use of reboxetine, which is currently licensed as an antidepressant in several countries, and edivoxetine, a new selective NRI currently in development.

Introduction

The catechol-*O*-methyltransferase (COMT) enzyme is responsible for degradation of catecholamines, such as dopamine (DA) and noradrenaline. The substitution of methionine (met) for valine (val) at codon 158 in the *COMT* gene is associated with a 40% reduction in enzyme activity and higher levels of extracelluar DA.[1] This single nucleotide polymorphism has been most extensively studied in relation to cognitive function; several studies have linked the low-activity met allele to enhanced performance on prefrontal cortex (PFC) tasks compared with the high-activity val allele, albeit with some inconsistencies.[2]

In addition, there is evidence suggesting *COMT* involvement in emotional processing. Several studies have demonstrated increased limbic–prefrontal activation in response to negative emotional stimuli in healthy met carriers.[3–6] This has been taken to represent less efficient emotional processing in met, compared with val, allele carriers. Other studies have found the reverse pattern — increased limbic reactivity in response to emotional stimuli in val, compared with met carriers.[7–9] However, a meta-analysis of functional neuroimaging

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studies examining the impact of the COMT genotype on both cognitive processing and emotional processing tasks demonstrated strong opposing effects, with the former favouring met allele carriers and the latter favouring val carriers.[10]

Fewer studies have reported COMT effects on behavioural measures of emotional processing; however, these studies suggest impaired performance in met, compared with val carriers, consistent with the neuroimaging findings.[11–13] It has therefore been suggested that COMT modulation of DA in the PFC may lead to imbalances in the PFC–subcortical networks differentially recruited in cognitive and emotional tasks.[14] Both the imbalances and the theory have been linked to stability of cortical representation mediated by tonic dopaminergic activation centring on the frontal cortex. On the other hand, it has been suggested that cognitive flexibility is mediated via phasic arousal centring on subcortical regions, including the amygdala. Enhanced tonic dopaminergic neurotransmission associated with the met allele is considered to confer greater cognitive stability, consistent with enhanced performance on executive cognitive tasks, but with a reduction in the cognitive flexibility required for processing emotional stimuli. It has been suggested that this emotional/cognitive functional trade-off may be of evolutionary significance, playing a role in the maintenance the nearly equal frequency of both COMT alleles in the population — the "warriors versus worriers" model characterizing the val and met alleles, respectively.[15]

These findings suggest that impaired emotional processing may mediate the association between the COMT met allele and increased vulnerability to emotional disorders. Several studies have linked the met allele to an increased risk of anxiety and depressive disorders.[16,17] Additional mediating variables may include personality traits associated with emotional disorders. For example, a number of studies also suggest a positive correlation between the val allele and extraversion,[18,19] a personality trait associated with a reduced risk of anxiety and depressive disorders. Other studies,[20,21] including 2 meta-analyses,[22,23] suggest that these effects may also be sex-dependent. Given that COMT is linked to the neurobiology of anxiety and depressive disorders via its effects on catecholaminergic neurotransmission, it may play a role in modulating the effects of therapeutic drugs that act on these systems. Such gene × drug interactions have already been demonstrated in association with the effects of catecholaminergic agents on cognitive performance.[24–26] Here, we hypothesized that the COMT val158met genotype would also moderate the effect of such drugs on emotional processing. We therefore set out to examine the effects of the selective noradrenaline reuptake inhibitor (NRI) antidepressant reboxetine on emotional processing in healthy volunteers based on COMT genotype.

Methods

Participants

To avoid confounding of our results by sex effects in association with COMT and emotional processing, we limited our sample to men. We recruited healthy, white male volunteers aged 18–40 years from the staff and student communities at the Universities of Sussex and Brighton and from the Brighton and Sussex Medical School (BSMS). The study was approved by the BSMS Research Governance and Ethics Committee. Participants gave written informed consent and received financial compensation for their participation. Potential participants were screened and excluded on the basis of any self-reported history of heart, liver, kidney or prostate disease; psychiatric or neurologic disorder (depression, anxiety, psychosis, bipolar disorder or epilepsy); alcohol dependence; and regular prescribed or illicit drug use. Cigarette use was recorded, and smokers were asked not to smoke until after testing on the day of the experiment. Participants were asked to abstain from alcoholic beverages for 24 hours before the experiment and to avoid any beverages containing caffeine until after testing on the day of the experiment. We derived estimates of verbal IQ using the National Adult Reading Test (NART),[27] and we used the Eysenck Personality Questionnaire Revised (EPQ-R)[28] to assess participants on the personality dimensions of extraversion (EPQ-E) and neuroticism (EPQ-N).

Drug intervention

Participants received identical opaque capsules containing either 4 mg of reboxetine or sugar (placebo) in a double-blind, randomized, between-subjects model. Testing began 2 hours later, in keeping with the time to reach peak plasma concentration for reboxetine.

Genotyping

We obtained buccal swabs or saliva samples from participants. The DNA extraction was carried out by KBioscience using their internal GuSCN-based extraction protocol, and genotyping was carried out with their polymerase chain reaction (PCR) SNP genotyping system (KASPar®), using 1.5 uL DNA (about 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) for 36 cycles. Plates were read using a BMG PheraStar microtitre plate fluorescence reader. We used 2 forward primers (GAAGGTGACCAAGTTCATGCTGGCATGCACACCTTGTCCTTCAT, which detects the A allele, and GAAGGTCGGAGTCAACGGATTGCATGCACACCTTGTCTTCAC, which detects the G allele) and 1 reverse primer (CATCACCCAGCGGATGGTGGAT) for the COMT val158met polymorphism.

Measurements

We measured pulse rate (PR) and blood pressure (BP) before administering reboxetine or placebo (baseline) and approximately 2 hours post-treatment. The Positive And Negative Affect Schedule (PANAS) was administered at baseline and post-treatment to ascertain any effects of reboxetine on

subjective mood state. The PANAS comprises 2 mood scales, 1 measuring positive affect and 1 measuring negative affect. There are 20 items in total, each rated on a 5-point scale ranging from 1 (very slightly or not at all) to 5 (extremely). We assessed adverse effects of the intervention using a visual analogue Bodily Symptom Scale (BSS) comprising 9 symptoms (dry mouth, anxiety, sweating, palpitations, nausea, dizziness, irritability, tiredness, loss of concentration) at baseline and post-treatment. Participants were asked to place an X on a line to indicate the extent to which they experienced each symptom ranging from not at all to extremely severe. To assess the effectiveness of blinding, at the end of the experiment we asked participants to guess whether they had received reboxetine or placebo.

Emotional memory task

The emotional memory (EM) task was an incidental learning task administered 2 hours after reboxetine treatment. Two sets of pictures (A and B), each comprising 72 pictures rated for arousal and valence (24 positive, 24 negative and 24 neutral) were selected from the International Affective Picture System (IAPS) stimulus set. Positive and negative pictures were matched for arousal, and sets A and B were matched on content, valence and arousal based on standardized ratings. Positive and negative pictures differed significantly from neutral pictures on arousal ($p < 0.001$) but not from each other ($p = 0.10$). Participants were assigned to view either set A or B in an encoding phase. To minimize potential bias associated with any possible between-set differences, either set A or B was randomly assigned to each participant for encoding, with the unseen set serving as foils for a subsequent recognition memory test (described later in this paragraph). Within each set, pictures were presented in a random order. Each image was presented for 2.5 seconds, followed by a consolidation period of 10 seconds, during which participants rated each image on dimensions of valence and arousal using a 9-point Likert-type scale in line with the approach used in the normative ratings. Thirty minutes later, participants received a surprise recall memory test in which they were asked to spend 10 minutes providing a written description of as many pictures as they could remember. Descriptions were then independently rated for successful recall (yes or no) based on whether the picture could clearly be identified based on the description given. This was carried out by 2 raters (A.A.G. and C.E.B.), with an inter-rater reliability of 0.94. Recall was followed by a recognition memory test in which participants were presented with all pictures from both sets A and B (1 set previously seen and 1 unseen) in a random order. Participants were asked to indicate whether each picture had previously been seen during the encoding phase or not and to rate their confidence in their decision on a 9-point Likert scale.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 20. We analyzed categorical variables using χ^2 tests or logistic regression models where appropriate. Continuous variables were analyzed using analysis of variance (ANOVA) with COMT genotype (val/val, val/met and met/met) and intervention group (reboxetine, placebo) as independent variables using a full factorial model. Where repeated-measures were used to examine the effect of emotional category (i.e., neutral, positive, negative) as an additional within-subjects variable, the following a priori pairwise comparisons were entered as planned contrasts in SPSS: negative versus neutral, positive versus neutral and positive versus negative. We made post hoc comparisons using planned 2-tailed t tests where appropriate. We considered results to be significant at $p = 0.05$.

Results

Participant characteristics and genotyping

We recruited 94 men to participate in our study. Genotypes could not be established for 19 of them (13 from the placebo group and 6 from the reboxetine group) owing to inadequate samples or failure of genotyping. Our final sample comprised 75 participants: 34 in the placebo group and 41 in the reboxetine group. Participant characteristics and genotypes are summarized in Table 1. There were no significant differences in age or IQ between the participants included in the final analysis and those who were excluded owing to lack of genotyping data. The COMT

Table 1: Participant characteristics and genotypes

	Group; mean ± SD*					
	Placebo, $n = 34$			Reboxetine, $n = 41$		
Characteristic	Val/Val	Val/Met	Met/Met	Val/Val	Val/Met	Met/Met
COMT genotype, no. (%)	7 (9.3)	18 (24.0)	9 (12.0)	16 (21.3)	16 (21.3)	9 (12.0)
Smokers, no. (%)	2 (2.7)	5 (6.7)	2 (2.7)	1 (1.3)	8 (10.7)	1 (1.3)
Age, yr	21.9 ± 3.9	22.1 ± 3.7	22.0 ± 3.2	22.2 ± 3.7	20.8 ± 2.6	22.2 ± 2.8
Full scale IQ	109 ± 7	113 ± 6	112 ± 7	110 ± 7	111± 7	114 ± 6
Personality						
EPQ-E	17.3 ± 3.5	15.1 ± 5.4	15.2 ± 6.4	15.3 ± 5.2	16.0 ± 4.9	9.6 ± 4.8
EPQ-N	12.4 ± 4.4	10.6 ± 5.3	12.0 ± 5.5	12.8 ± 3.7	13.3 ± 4.7	13.9 ± 6.3

COMT = catechol-*O*-methyltransferase; EPQ-E = Eysenck Personality Questionnaire–Extraversion; EPQ-N = Eysenck Personality Questionnaire–Neuroticism; SD = standard deviation.
*Unless otherwise indicated.

allele frequencies were in Hardy–Weinberg equilibrium ($\chi^2_1 = 13$, $p = 0.25$). The χ^2 testing confirmed independence of genotype and intervention group ($\chi^2_2 = 3.0$, $p = 0.22$). A 3 × 2 ANOVA with COMT genotype (val/val, val/met, met/met) and intervention group (reboxetine, placebo) as independent variables confirmed that there were no significant between-group differences or interactions with respect to age or IQ. There was a main effect of COMT genotype on extraversion scores ($F_{2, 69} = 3.1$, $p = 0.05$), with met homozygotes having significantly lower scores than val homozygotes ($p = 0.024$) or heterozygotes ($p = 0.041$). There was no main effect of COMT genotype on neuroticism scores, and there were no differences in either extraversion or neuroticism scores in relation to the intervention group. Data on smoking status was unavailable for 2 participants. Of the 75 participants included, 19 (25.3%) were smokers. These participants were evenly distributed across the groups, and a Fisher exact test confirmed that there was no significant association between smoking status and genotype or intervention group ($p = 0.52$). The number of cigarettes smoked per day was available for 17 of 19 participants (median 8, mode 10, range 1–25). Two participants smoked 20 or more cigarettes per day.

Cardiovascular measures, side effects and assessment of blinding

Table 2 shows baseline and post-treatment BSS, systolic/diastolic BP and PR by intervention group. A multivariate ANOVA using post-treatment BSS, systolic/diastolic BP and PR as dependent variables; intervention group (reboxetine, placebo) as the independent variable; and the baseline BSS, systolic/diastolic BP and PR as covariates demonstrated significant main effects of intervention group on post-treatment total BSS score ($F_{1, 69} = 4.9$, $p = 0.029$), systolic BP ($F_{1, 69} = 8.5$, $p = 0.005$) diastolic BP ($F_{1, 72} = 4.7$, $p = 0.034$) and PR ($F_{1, 72} = 12.6$, $p = 0.001$). Further multivariate analysis of BSS symptom domains revealed significant main effects for anxiety ($F_{1, 64} = 43$, $p = 0.043$) and nausea ($F_{1, 64} = 8.8$, $p = 0.004$). Twenty-three of 34 (67.6%) participants in the placebo group and 27 of 40 (67.5%) in the reboxetine group correctly guessed their group assignment. These data were missing for 1 participant in the reboxetine group. The χ^2 analysis indicated that actual group assignment and subjective assessment of group assignment were not independent ($\chi^2_1 = 9.1$, $p = 0.003$). Logistic regression analysis with participants' subjective assessment of their group assignment as the dependent variable and intervention group, total post-treatment BSS score, post-treatment systolic BP, diastolic BP and PR as independent predictors indicated that the full model was significant ($\chi^2_5 = 19.2$, $p = 0.002$); however, only intervention group ($p = 0.018$) and BSS scores ($p = 0.036$) emerged as significant predictors.

Mood profiles, valence and arousal ratings

Mean PANAS scores are shown in Table 2, and valence and arousal ratings are shown in Table 3. The effects of genotype and reboxetine on positive and negative PANAS scores were assessed in a 3 × 2 ANOVA with post-treatment positive and negative PANAS scores as the dependent variable, COMT genotype (i.e., val/val, val/met and met/met) and intervention group (i.e., reboxetine, placebo) as independent variables and baseline positive and negative PANAS scores as covariates. Baseline measures made a significant contribution to the model; however, there were no other main effects or interactions. In view of the significant association between COMT genotype and extraversion, EPQ-E scores were added as a covariate, but this neither made a significant contribution to the model nor resulted in any other main effects or interactions.

Table 2: Cardiovascular measures, side effects scores and mood profiles

	Group; mean ± SD					
	Placebo, *n* = 34			Reboxetine, *n* = 41		
Factor	Val/Val	Val/Met	Met/Met	Val/Val	Val/Met	Met/Met
Cardiovascular						
Systolic BP baseline	123.3 ± 14.1	116.8 ± 9.7	126.8 ± 10.9	120.8 ± 12.7	120.2 ± 9.0	126.2 ± 13.4
Systolic BP pretest	121.7 ± 13.8	117.2 ± 10.0	118.2 ± 10.9	121.1 ± 9.7	125.1 ± 11.5	133.4 ± 20.6
Diastolic BP baseline	65.7 ± 7.8	71.1 ± 7.7	69.2 ± 8.9	70.4 ± 11.4	72.9 ± 11.0	75.3 ± 10.7
Diastolic BP pretest	65.1 ± 7.5	70.9 ± 11.4	65.7 ± 5.6	74.0 ± 11.3	72.1 ± 9.2	78.4 ± 6.5
PR baseline	64.4 ± 10.7	73.0 ± 14.7	68.3 ± 11.7	70.1 ± 9.8	71.3 ± 11.6	74.3 ± 10.1
PR pretest	66.9 ± 14.5	70.2 ± 15.0	65.7 ± 12.7	77.4 ± 14.7	77.5 ± 12.3	89.4 ± 17.3
BSS						
Total score baseline	75.9 ± 68.6	122.6 ± 89.1	86.3 ± 61.6	119.1 ± 58.9	132.6 ± 87.9	139.9 ± 104.3
Total score pretest	78.6 ± 77.0	76.0 ± 50.5	83.4 ± 98.9	139.8 ± 95.5	129.6 ± 83.6	124.0 ± 137.1
PANAS						
Positive baseline	29.3 ± 5.8	25.2 ± 4.7	32.2 ± 7.2	26.4 ± 4.5	26.9 ± 5.4	28.7 ± 6.7
Positive pretest	31.0 ± 10.1	24.0 ± 5.2	29.2 ± 9.3	24.2 ± 6.1	28.1 ± 8.0	27.4 ± 9.8
Negative baseline	13.4 ± 5.3	12.0 ± 1.4	12.7 ± 2.3	12.6 ± 1.7	12.6 ± 1.9	15.8 ± 5.3
Negative pretest	12.6 ± 4.4	11.2 ± 1.2	11.0 ± 1.7	12.7 ± 4.2	12.1 ± 1.8	15.0 ± 5.4

BP = blood pressure; BSS = Bodily Symptom Scale; PANAS = Positive and Negative Affect Schedule; PR = pulse rate; SD = standard deviation.

We assessed the effect of genotype and reboxetine on ratings in a mixed 3 × 3 × 2 ANOVA with emotional category (i.e., neutral, positive, negative) as the within-subjects variable and COMT genotype (i.e., val/val, val/met and met/met) and intervention group (i.e., reboxetine, placebo) as the between-subjects variables. There was a significant main effect of emotional category on valence ratings ($F_{2, 138}$ = 547.4, $p < 0.001$) evident for neutral versus positive ($F_{1, 69}$ = 202.7, $p < 0.001$), neutral versus negative ($F_{1, 69}$ = 580.4, $p < 0.001$) and positive versus negative ($F_{1, 69}$ = 681.6, $p < 0.001$) pairwise comparisons. Similarly, there was a significant main effect of emotional category on arousal ratings ($F_{2, 138}$ = 116.5, $p < 0.001$) that was also evident for neutral versus positive ($F_{1, 69}$ = 156.3, $p < 0.001$), neutral versus negative ($F_{1, 69}$ = 181.7, $p < 0.001$) and positive versus negative ($F_{1, 69}$ = 14.8, $p < 0.001$) pairwise comparisons. There were no main effects or interactions in relation to COMT genotype or intervention group.

Emotional memory performance

Mean percentages of neutral, positive and negative pictures recalled are shown in Table 2. The effects of genotype and reboxetine on percentage recall were assessed in a mixed 3 × 3 × 2 ANOVA with emotional category (i.e., neutral, positive, negative) as the within-subjects variable and COMT genotype (i.e., val/val, val/met and met/met) and intervention group (i.e., reboxetine, placebo) as between-subjects variables. Given that there were main effects of COMT genotype on EPQ-E scores and intervention group on BSS score, diastolic BP and PR, we added these variables as covariates. Two participants from the placebo and reboxetine groups (4 in total) were excluded owing to failure to complete the recall task according to instructions. There was a main effect of emotional category ($F_{2, 122}$ = 6.72, $p = 0.002$), with pairwise comparisons revealing a significant advantage for recall of negative ($F_{1, 61}$ = 15.4, $p < 0.001$) but only a near significant trend advantage for positive ($F_{1, 61}$ = 3.4, $p = 0.07$) pictures relative to neutral ones. There was also a significant emotional category × genotype × intervention group interaction ($F_{4, 122}$ = 3.86, $p = 0.005$) for both positive ($F_{2, 61}$ = 5.35, $p = 0.007$) and negative ($F_{2, 61}$ = 6.58, $p = 0.003$) versus neutral pairwise comparisons, but not positive versus negative ones ($F_{2, 61}$ = 0.03, $p = 0.97$). We therefore combined negative and positive emotional pictures and calculated an EM index by subtracting the percentage of neutral pictures recalled from the percentage of emotional pictures recalled. We examined this index as the dependent variable in a 3 × 2 ANOVA with COMT genotype (i.e., val/val, val/met and met/met) and intervention group (i.e., reboxetine, placebo) as between-subjects variables and covariates. This revealed a significant interaction between COMT genotype and intervention group ($F_{2, 61}$ = 5.5, $p = 0.006$), which we followed up with post hoc independent t tests in met/met, val/met and val/val genotype groups comparing placebo and reboxetine conditions. In met homozygotes, the EM index was significantly greater under reboxetine than placebo (t_{15} = –3.33, $p = 0.005$); however, there was no significant difference in EM index under placebo versus reboxetine in val/met (t_{29} = 1.9, $p = 0.07$) or val/val (t_{21} = 0.22, $p = 0.77$) carriers. We therefore examined the EM index in val carriers and met homozygotes under placebo and reboxetine conditions and found that in the placebo group, it was significantly lower in met homozygotes than in val carriers (t_{30} = 2.53, $p = 0.017$), whereas the reverse was observed in the reboxetine group (t_{37} = –2.28, $p = 0.028$; Fig. 1). Since all groups performed the recognition memory task at ceiling, these data are not presented.

Discussion

There are 2 key novel findings from this study. First, with placebo, the enhancement of memory for emotional pictures observed in COMT val carriers was absent in met homozygotes, despite equivalent valence and arousal ratings. Second, COMT genotype interacted with a single 4 mg dose

Table 3: Picture valence and arousal ratings and percentage recall

	Group; mean ± SD					
	Placebo, *n* = 34			Reboxetine, *n* = 41		
Rating or recall	Val/Val	Val/Met	Met/Met	Val/Val	Val/Met	Met/Met
Valence rating						
Neutral	5.34 ± 0.46	5.17 ± 0.37	5.57 ± 0.44	5.40 ± 0.62	5.19 ± 0.57	5.21 ± 0.43
Positive	6.59 ± 0.49	6.23 ± 0.92	6.53 ± 0.84	6.56 ± 0.78	6.44 ± 0.78	6.92 ± 0.60
Negative	3.46 ± 0.47	2.91 ± 0.52	3.21 ± 0.39	3.03 ± 0.76	3.06 ± 0.93	3.70 ± 0.65
Arousal rating						
Neutral	3.24 ± 1.66	3.31 ± 1.16	4.30 ± 0.69	3.23 ± 1.32	3.86 ± 0.95	3.74 ± 1.25
Positive	4.77 ± 1.27	5.09 ± 1.61	5.69 ± 0.96	4.53 ±1.34	5.36 ± 1.30	4.87 ± 1.32
Negative	5.04 ± 1.82	5.20 ± 1.55	6.5 ± 0.75	5.23 ± 1.72	6.01 ± 1.15	5.48 ± 1.8
Percentage recall						
Neutral	29.7 ± 7.37	27.4 ± 11.5	35.9 ± 18.9	29.9 ± 15.3	28.0 ± 15.3	21.8 ± 8.0
Positive	32.7 ± 8.50	34.0 ± 12.9	29.2 ± 12.4	29.7 ± 16.9	29.7 ± 16.9	24.6 ± 10.6
Negative	47.6 ± 16.6	48.9 ± 11.6	39.1 ± 14.2	45.3 ± 16.4	41.4 ± 13.2	45.3 ± 13.7

SD = standard deviation.

of the selective NRI reboxetine to influence EM. Specifically, reboxetine enhanced EM in met homozygotes, but had no effect in val carriers. These findings indicate that EM is impaired in met homozygotes and normalized in this group by reboxetine.

Our findings are in keeping with those of several prior behavioural and functional neuroimaging studies that suggest that met carriers are impaired on emotional processing tasks compared with val carriers. However a number of other studies have found the reverse. These inconsistencies have been attributed to differences in stimuli (faces v. pictures) and population (sex effects and clinical v. healthy populations). Our findings are consistent with those of the 3 studies that used similar methodology — healthy male participants and pictures from the IAPS stimulus set[12,29,30] — although only 1 of these studies specifically reported EM measures.[12] Emotional memory refers to the enhanced conscious retrieval of emotionally arousing relative to nonarousing episodes, mediated by increased catecholaminergic transmission in subcortical brain regions, including the amygdala,[31–33] and depends on the arousal properties of the stimulus rather than valence per se.[34,35] Negative stimuli typically have greater arousal properties than positive stimuli,[36] as was also reflected by the fact that our participants rated negative pictures as significantly more arousing than positive ones in spite of careful matching on this dimension. This difference may explain the absence of a significant main effect of emotion on memory for positive pictures in our study.

There are at least 2 possible neurobiological explanations for the observed impairment in EM in the COMT met group. One possibility relates to the inverted U-shaped association between catecholamine levels and performance, under which optimal function does not result from maximal levels of catecholamines, but rather falls within a narrow range.[37] This explanation is supported by several studies demonstrating that pharmacological interventions that increase levels of extracellular catecholamines result in improved cognitive performance in val homozygotes and impairment in met homozygotes.[38–41] It is possible that the heightened noradrenergic neurotransmission associated with arousing stimuli shifts met homozygotes to a more disadvantageous functional position with respect to emotional processing. This would be consistent with the functional neuroimaging data reporting increased prefrontal/limbic activation in met relative to val carriers during emotional processing tasks. However, the fact that this impairment is reversed by reboxetine, a drug that increases subcortical noradrenaline levels suggests that an inverted U catecholaminergic model does not offer the best explanation for this phenomenon. Alternatively, impaired emotional processing in met individuals may be explained by a reduction in the arousal-mediated phasic dopaminergic response, consistent with the model proposed by Bilder and colleagues.[42] This is in keeping with evidence that the processing of emotionally salient information is supported by phasic firing of subcortical dopaminergic and noradrenergic neurons[43] and further supported by the fact that reboxetine increases burst firing of subcortical dopaminergic neurons.[44] It is therefore possible that reboxetine enhances the subcortical phasic response centred on the amygdala, thus improving flexibility of processing in met homozygotes, while leaving val carriers relatively unaffected. The fact that we did not find any evidence for diminished arousal in response to emotional pictures in met carriers suggests that the cause of impaired EM in this group lies on the neurobiological pathway between emotional arousal and its effects on memory. Furthermore, the absence of a main effect of reboxetine (or a reboxetine × genotype interaction effect) with respect to arousal, suggests that the effect of reboxetine on EM is unlikely to be mediated by arousal. Thus, reboxetine may have a direct effect on phasic firing of subcortical dopaminergic and noradrenergic neurons in met homozygotes that is independent of arousal.

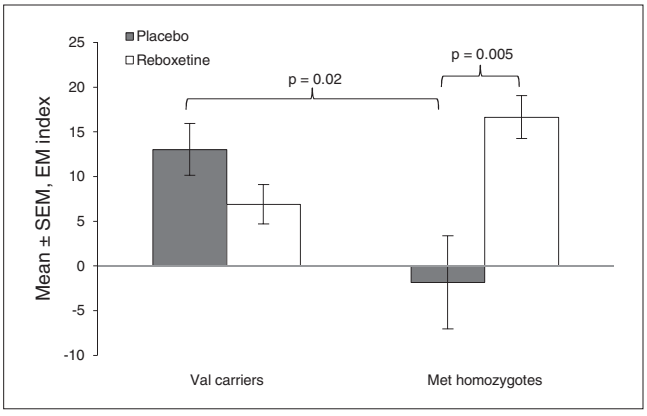

Fig. 1: Interactive behavioural effects of catechol-*O*-methyltransferase (COMT) genotype and reboxetine on emotional memory (EM) index. Under placebo, the EM index is significantly reduced in met homozygotes (n = 8) compared with val carriers (n = 24) and under reboxetine, it is significantly enhanced in met homozygotes (n = 9), but nonsignificantly attenuated in val carriers (n = 30). Bars reflect standard error of the mean (SEM).

We also did not find any main of reboxetine (or a reboxetine × emotion interaction effect) in relation to memory performance. This is perhaps at odds with what might be predicted from the extensive literature that suggests that memory for emotionally arousing positive and negative stimuli is modulated by adrenergic agents.[45,46] It is also inconsistent with several human behavioural pharmacology studies suggesting that a variety of serotonergic and noradrenergic antidepressants facilitate processing of positively valenced material and impair processing of negatively valenced material.[47] However only a handful of these studies have specifically investigated the effect of reboxetine on EM.[48–51] Contrary to their predictions, using a slide show with an emotionally arousing middle phase Papps and colleagues[48] found a dose-dependent impairment in memory with a single dose of reboxetine (4 mg or 8 mg) compared with placebo in healthy individuals, but no effect on EM. Harmer and colleagues[49,50] found that both single and repeated dosing with 4 mg of reboxetine preferentially enhanced memory for positive compared with negative personality traits, although no comparison with neutral words was made. Hurlemann and colleagues[51] found that 4 mg of reboxetine enhanced both retrograde amnesia and hyperamnesia associated with negatively and positively valenced arousing oddball

stimuli, respectively. Given the differing methodologies, it is unsurprising that these studies have been inconclusive; however, our findings suggest that COMT-dependent differences in emotional processing may contribute to these discrepancies.

Limitations

There are a number of limitations to our study that should be acknowledged. To minimize sex biases in our smaller total sample, we included only men, thus limiting the generalizability of our findings. We also relied on self-reported responses to screening questions to establish healthy volunteer status and did not use a diagnostic interview schedule to exclude men with psychiatric or neurologic disorders. Further, in spite of the double-blind design, participants were significantly better than chance at identifying their intervention allocation, ostensibly owing to side effects.

Conclusion

To our knowledge, this is the first demonstration of a COMT × drug interaction affecting emotional processing in healthy humans. This finding has potential translational implications for reboxetine and other selective NRI antidepressants, such as edivoxetine, which is currently in development. A recent study of reboxetine in depressed patients suggests that the therapeutic effects of selective NRIs may be linked to modulation of EM. Our study suggests that *COMT* gene variation may moderate these effects.[52] With emotional processing increasingly considered as a potential cognitive "biomarker" against which the therapeutic potential of novel drugs for anxiety/depressive disorders can be evaluated,[53] the influence of COMT genotype on emotional processing may be relevant to the personalization for antidepressant therapy.

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