

Improvement of Prepulse Inhibition and Executive Function by the COMT Inhibitor Tolcapone Depends on COMT Val158Met Polymorphism

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Recent evidence suggests that prepulse inhibition (PPI) levels relate to executive function possibly by a prefrontal cortex (PFC) dopamine (DA) link. We explored the effects of enhanced PFC DA signaling by the nonstimulant catechol-*O*-methyltransferase (COMT) inhibitor tolcapone, on PPI and working memory of subjects homozygous for the Val (low PFC DA) and the Met (high PFC DA) alleles of the COMT Val158Met polymorphism. Twelve Val/Val and eleven Met/Met healthy male subjects entered the study. Tolcapone 200 mg was administered in two weekly sessions, according to a balanced, crossover, double-blind, placebo-controlled design. PPI was assessed with 5 dB and 15 dB above background prepulses, at 30-, 60-, and 120 ms prepulse–pulse intervals. Subjects also underwent the n-back and the letter–number sequencing (LNS) tasks. PPI was lower in the Val/Val compared to the Met/Met group in the placebo condition. Tolcapone increased PPI significantly in the Val/Val group and tended to have the opposite effect in the Met/Met group. Baseline startle was not affected by tolcapone in the Val/Val group but it was slightly increased in the Met/Met group. Tolcapone improved performance in the n-back and LNS tasks only in the Val/Val group. Enhancement of PFC DA signaling with tolcapone improves both PPI and working memory in a COMT Val158Met genotype-specific manner. These results suggest that early information processing and working memory may both depend on PFC DA signaling, and that they may both relate to PFC DA levels according to an inverted U-shaped curve function.

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INTRODUCTION

The enzyme catechol-*O*-methyltransferase (COMT) is the main catabolic pathway by which dopamine (DA) is removed from the cortical synaptic cleft in humans (Karoum *et al*, 1994). Indeed, COMT is found in high concentrations in the cortex relative to subcortical regions (Matsumoto *et al*, 2003) consistent with the absence of functional DA transporters in cortical areas such as the prefrontal cortex (PFC) and hippocampus (Mazei *et al*, 2002). The Val158Met polymorphism in the *COMT* gene leads to an amino-acid substitution (valine (Val) to methionine (Met)) and results in the Met/Met variant showing 40% less enzymatic activity than the Val/Val (Chen *et al*, 2004). There is now abundant evidence (reviewed in Harrison and Weinberger, 2005; Tunbridge *et al*, 2006) that

Met158 allele loading is dose dependently associated with superior performance on a variety of cognitive tests assessing executive function, as well as prefrontal physiology as assessed by neuroimaging. The evidence suggests that PFC DA facilitates ‘focusing and stabilizing’ activity in PFC networks during executive cognition, ie enhances prefrontal physiologic ‘efficiency’ by reduction of prefrontal noise (Cools *et al*, 2002; Mattay *et al*, 2002, 2003).

Prepulse inhibition (PPI) is thought to reflect ‘sensorimotor gating’, a form of central nervous system inhibition wherein irrelevant sensory information is filtered out during the early stages of processing so that attention can be focused on more salient features of the environment (Braff *et al*, 1978). A large number of studies have shown that individuals with schizophrenia show reduced PPI (Braff *et al*, 2001, 2005; Swerdlow *et al*, 2006; Kumari *et al*, 2007). The sensory overload resulting from reduced sensorimotor gating is thought to give rise to cognitive fragmentation, attentional deficits, and some of the complex clinical symptoms associated with this disorder (Geyer *et al*, 1990). PPI in rodents is modulated by activity in a well-defined cortico-striato-pallido-pontine circuitry (Swerdlow *et al*, 1992, 2001), which has been confirmed by functional

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imaging studies in humans (Kumari *et al*, 2003, 2007; Postma *et al*, 2006; Campbell *et al*, 2007). PPI levels predict gray matter availability in frontal cortical areas in patients with schizophrenia (Kumari *et al*, 2008), which extends to the hippocampal, striatal, thalamic, and temporal regions in healthy subjects (Kumari *et al*, 2005). Consistent with these neuroimaging findings and the notion that sensorimotor gating is important in human cognition (Geyer *et al*, 1990), neuropsychological studies show that higher PPI levels predict superior performance on tasks that rely on the integrity and efficiency of PFC function (Bitsios and Giakoumaki, 2005; Bitsios *et al*, 2006; Giakoumaki *et al*, 2006; Csomor *et al*, 2008).

We have recently shown that COMT Val158 allele loading is associated with lower PPI levels in healthy men (Roussos *et al*, 2008a). We proposed that this may be due to low PFC DA transmission and increased prefrontal noise in Val-loading subjects and/or that the Val158 allele may indirectly increase striatal dopaminergic function, thus reducing PPI, likely as downstream manifestation of reduction in cortical information processing. In any case, PFC DA transmission seems to be an important neural mechanism that modulates human PPI (Roussos *et al*, 2008a). The aim of the present study was to better understand the relationship among COMT, PPI, and executive function. To this end, we set out to explore the effect of increased cortical DA signaling by tolcapone, on PPI and PFC-dependent tasks, in subjects with either Val/Val or Met/Met status.

Tolcapone is a nonstimulant drug, which penetrates the blood-brain barrier (Ceravolo *et al*, 2002) and potently inhibits brain COMT activity *in vivo* (Da Prada *et al*, 1991). COMT inhibition by tolcapone is thought to lead to relatively specific increases of PFC DA, as COMT has little impact on norepinephrine flux in PFC, possibly because of the abundance of functional norepinephrine transporters (Gogos *et al*, 1998; Tunbridge *et al*, 2004). Tolcapone improved executive function in healthy Val158 homozygotes who have lower PFC DA concentrations at baseline but worsened the performance of Met/Met individuals who have high PFC DA concentrations, and operate near or at ceiling levels at baseline (Apud *et al*, 2007). These effects are consistent with the increasingly accepted model of the inverted U-shaped relationship between PFC DA signaling and PFC function (Goldman-Rakic, 1998, Williams and Goldman-Rakic, 1995). On the basis of the assumption that PFC DA signaling is important for both PPI and PFC function, we predicted that tolcapone would improve PPI and executive function in Val/Val homozygotes; we also predicted that tolcapone would decrease or have no effect on PPI and cognitive function of Met158 homozygotes.

MATERIALS AND METHODS

Subjects

A total of 24 healthy male subjects were recruited from a cohort of 93 subjects who had participated in a study examining the effects of the COMT Val158Met polymorphism on PPI. Subjects were selected such as to form two equal homozygote groups (Val/Val, $n = 12$ and Met/Met, $n = 12$). The selection was random and based on subject availability. All subjects had previously undergone genotyping,

thorough psychiatric and medical assessment including drug screening and audiometry (Roussos *et al*, 2008a), but they had a new urine toxicology screening prior to testing and their IQ was also assessed with the Raven's progressive matrices (Raven *et al*, 1977). The study was approved by the ethics committee of the University of Crete. All participants gave written informed consent before screening.

Design and Drugs

All subjects participated in two weekly sessions associated with either single, acute oral tolcapone (200 mg) or placebo administration in identical capsules. Within each separate genotype group, subjects were allocated to sessions and treatments in a balanced, crossover, double-blind manner according to a Latin square design. After the baseline measurement of subjects' mood state with the Profile of Mood States (POMS) self-rated questionnaire (McNair and Lorr, 1981), the POMS was administered again 1.8 h posttreatment at the time of tolcapone's peak effect (Hardman *et al*, 2001) to assess drug-induced changes in mood or activation. This procedure was followed by PPI testing and neuropsychological assessment.

Measurement of the Startle Response

A commercially available electromyographic (EMG) startle system (EMG SR-LAB, San Diego Instruments, San Diego, CA, USA) was used to examine the eyeblink component of the acoustic startle response from the right orbicularis oculi muscle. Equipment descriptions, setup, and scoring criteria have been previously described in detail (Bitsios *et al*, 2005). We used a range of stimulus parameters designed to explore potential stimulus- or stimulus by genotype-dependent effects of the drug. Pulses consisted of 40 ms, 115 dB white noise bursts, and prepulses consisted of 20 ms, 75 and 85 dB white noise bursts over 70 dB background noise. Recording began with 3 min acclimation period when only the background noise was present. The recording period consisted of 12 pulse-alone trials, 36 prepulse-pulse trials and 6 no-stimulus (NOSTIM) trials for the assessment of drug effects on basal EMG activity. Three lead intervals (onset to onset) were used (30, 60, and 120 ms). For each interval, there were six trials with the 75 dB prepulse and six trials with the 85 dB prepulse. All trials were presented in pseudorandom order with the constraint that no two identical trials occurred in succession. The intertrial interval varied between 9 and 23 s (average 15 s). The entire test session lasted approximately 15 min. Before scoring and data analysis, all recordings were screened for spontaneous eyeblink activity. Trials were excluded (3% of trials across genotypes and treatment conditions) using published criteria (Braff *et al*, 1992). No subjects had more than three (out of six) trials per trial type discarded at any one session.

Neuropsychological Testing

Neuropsychological testing was carried out immediately after startle testing. The following tests were selected because they engage prefrontal cortical processes and have demonstrated sensitivity to COMT genotype: (1) n-back sequential letter task—the task consisted of four conditions

(0-, 1-, 2-, and 3-back) where subjects were asked to respond by a button-press when they saw a target letter (letter 'X' for 0-back and any letter that was identical to the one presented in the preceding 1, 2, or 3 trials, respectively). The outcome variables were the number of correct responses and reaction time. The n-back task is a working memory test allowing 'online' manipulation of information, demonstrated to engage a wide network of brain regions with dorsal PFC activation being the most consistent finding (Fletcher and Henson, 2001). (2) Letter-number sequencing (LNS; Wechsler, 1997)—subjects were asked to store and reorder (recite in numeric and alphabetical order) strings of intermingled letters and numbers with increasing difficulty. The outcome variable was the total number of correct strings. It is a test of working memory and overt manipulation of information, requiring subjects not only to store information but also to reorder it according to preset rules. Areas of activation include the orbital frontal lobe, dorsolateral PFC, and posterior parietal cortex (Haut *et al*, 2000).

Statistical Analysis

Demographic data (age, years of education, IQ) were compared between the groups using one-way analysis of variance (ANOVA). Pre-posttreatment changes in each POMS scale were calculated for the placebo and tolcapone treatment conditions and were compared using separate 2×2 (genotype \times treatment) ANOVAs. The mean background EMG activity from the six NOSTIM trials in each treatment condition was subjected to separate 2×2 (genotype \times treatment) ANOVAs. Startle data from the 12 pulse-alone trials were collapsed in four blocks of three trials each and the means of each block were subjected to a $2 \times 2 \times 4$ (genotype \times treatment \times block) ANOVA to examine genotype and treatment effects on startle amplitude and habituation. The maximal amplitudes of the raw EMG responses from each trial were averaged across all trials of the same type. Percentage PPI ($\%PPI = ((\text{Amplitude}_{\text{pulse-alone}} - \text{Amplitude}_{\text{prepulse-pulse}}) / \text{Amplitude}_{\text{pulse-alone}}) \times 100$) and peak latency data were analyzed with $2 \times 2 \times 2 \times 3$ (genotype \times treatment \times prepulse \times interval) ANOVAs. Performance variables from the neuropsychological tests were analyzed using four-way ANOVAs with genotype as the between- and treatment, difficulty level and order (drug then placebo or placebo then drug) as the within-subject factors. All repeated measures with more than two levels (or one degree of freedom) employed the Greenhouse–Geisser ϵ -correction. Uncorrected degrees of freedom are reported in this case, with the corrected p -values and the ϵ -value. Effect sizes (partial η^2) are also reported.

RESULTS

Demographic Variables

One Met/Met individual failed to complete the study and was therefore excluded from the analyses. The age, education in years, and IQ of the Val/Val group ($n = 12$) were (mean \pm SD) 26.6 ± 3.9 , 17.9 ± 2.8 , and 108.3 ± 9.1 , respectively and for the Met/Met group ($n = 11$) were 24.6 ± 2.8 , 16.8 ± 2.1 , and 116.4 ± 11.6 , respectively. ANOVA comparisons

revealed no differences between the two genotype groups (age: $F(1, 21) = 1.8$, $p > 0.2$; education: $F(1, 21) = 1.1$, $p > 0.3$; IQ: $F(1, 21) = 3.4$, $p > 0.08$). The smokers/nonsmokers ratio was 6/6 for the Val/Val and 2/9 for the Met/Met groups ($\chi^2 = 2.6$, $p > 0.1$).

Subjective Ratings

Figure 1 shows the post-pretreatment changes in the seven items of the POMS ratings for the two genotype groups and the two treatment conditions. Separate 2×2 (treatment \times genotype) ANOVAs of the pre-posttreatment changes in the POMS ratings did not reveal any significant main effect of treatment, genotype, or their interaction in any of the POMS items (all p -values > 0.18).

Basal EMG Activity and Startle Latency: Amplitude and Habituation

Table 1 shows the background EMG activity, and startle characteristics of the two genotype groups for the two treatment conditions. There was no main effect of genotype or treatment or significant interaction on background EMG activity and on startle onset and peak latencies (all p -values > 0.16). There were no effects of smoking status on these variables. A $2 \times 2 \times 4$ (treatment \times genotype \times block) ANOVA of startle in pulse-alone trials showed significant main effects of block indicating habituation ($F(3, 63) = 7.6$, $p < 0.001$, $\epsilon = 0.789$, linear trends: $F(1, 21) = 21.4$, $p < 0.001$), but not treatment ($F(1, 21) = 2.9$, $p > 0.1$) or genotype ($F(1, 21) = 3.7$, $p = 0.07$). The treatment by genotype interaction was significant ($F(1, 21) = 5.0$, $p < 0.037$). None of these effects was altered when smoking status entered as an additional grouping factor (smoking status main effect: $F < 1$; no interactions). Follow-up ANOVAs within each genotype group showed a trend level increase in startle by tolcapone in the case of the Met/Met (treatment main effect: $F(1, 10) = 3.9$, $p = 0.076$) but not the Val/Val group (treatment main effect: $F < 1$).

Prepulse Inhibition

Figure 2 shows that compared to placebo tolcapone had opposite effects on %PPI in the two genotype groups. An overall $2 \times 2 \times 2 \times 3$ (genotype \times treatment \times prepulse \times interval) ANOVA revealed a significant treatment \times genotype interaction ($F(1, 21) = 16.1$, $p < 0.001$, $\eta^2 = 0.434$), reflecting the opposite effects of tolcapone in the two genotype groups. There were also significant main effects of prepulse ($F(1, 21) = 64.1$, $p < 0.001$, $\eta^2 = 0.753$) and interval ($F(2, 42) = 40.6$, $p < 0.001$, $\eta^2 = 0.659$, $\epsilon = 0.721$) (all other p -values > 0.1). Because of trend genotype effects on baseline startle and IQ and treatment effects on baseline startle, we repeated the analysis with baseline startle and IQ as covariates. The ANCOVA showed that the critical treatment by genotype interaction remained significant ($F(1, 18) = 15.2$, $p < 0.001$, $\eta^2 = 0.457$). None of the effects above was altered when smoking status entered as an additional grouping factor (smoking status main effect: $F < 1$; no interactions). The significant treatment \times genotype interaction was followed up by $2 \times 2 \times 3$ (treatment by prepulse by interval) ANOVAs within each genotype group; these

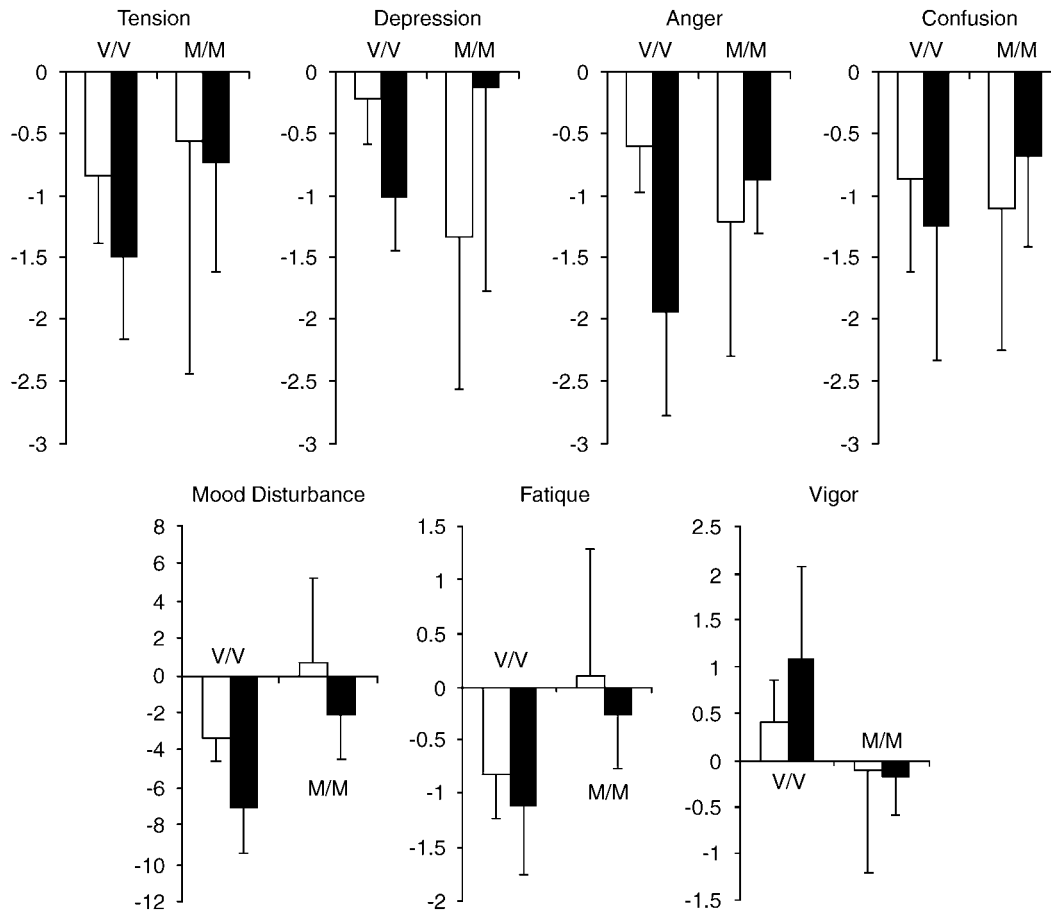


Figure 1 Post-pretreatment changes in ratings of the Profile of Mood States (POMS) items for the two genotype groups under the two treatment conditions. Bars represent SEM.

Table 1 Startle Characteristics (mean \pm SD) for the Two Genotype Groups Under the Two Treatment Conditions

	Val/Val		Met/Met	
	Placebo	Tolcapone	Placebo	Tolcapone
Background EMG activity (μ V)	11.9 \pm 7.8	11.5 \pm 2.8	12.9 \pm 3.2	11.4 \pm 2.4
Mean pulse-alone startle (μ V)	248.3 \pm 151	239.6 \pm 155	355.2 \pm 219	422.6 \pm 219
Startle onset latency (ms)	44.4 \pm 4.3	45.6 \pm 6.7	41.8 \pm 6.1	42.1 \pm 4.8
Startle peak latency (ms)	62.6 \pm 3.1	62.4 \pm 2.5	61.9 \pm 3.4	62.9 \pm 3.0

Abbreviation: EMG, electromyographic.

revealed that tolcapone significantly increased PPI in the Val/Val group (treatment main effect: $F(1, 11) = 14.1$, $p < 0.003$). In the Met/Met group tolcapone reduced PPI at trend level ($F(1, 10) = 3.7$, $p = 0.082$).

PPI levels were greater in the placebo treatment condition for the Met/Met compared to the Val/Val group as evidenced by a $2 \times 2 \times 3$ (genotype \times prepulse \times interval) ANOVA for the placebo data only (Figure 2). This analysis revealed main effects of prepulse ($F(1, 21) = 74.2$, $p < 0.001$, $\eta^2 = 0.779$), interval ($F(2, 42) = 23.0$, $p < 0.001$, $\varepsilon = 0.8$, $\eta^2 = 0.522$), and genotype ($F(1, 21) = 6.2$, $p < 0.02$, $\eta^2 = 0.229$). There were no differences in startle amplitude in

the placebo condition between the two genotype groups ($F(1, 21) = 1.9$, $p > 0.18$).

Prepulse Latency Facilitation

Figure 3 shows the peak latency data of the two genotype groups for the two treatments. The overall $2 \times 2 \times 3$ (treatment \times prepulse \times interval) ANOVA of the peak latency data revealed significant main effects of prepulse ($F(1, 21) = 45.5$, $p < 0.001$, $\eta^2 = 0.684$) and interval ($F(2, 42) = 11.8$, $p < 0.001$, $\varepsilon = 0.699$, $\eta^2 = 0.359$) but not of treatment or genotype ($F_s < 1$). There was a significant

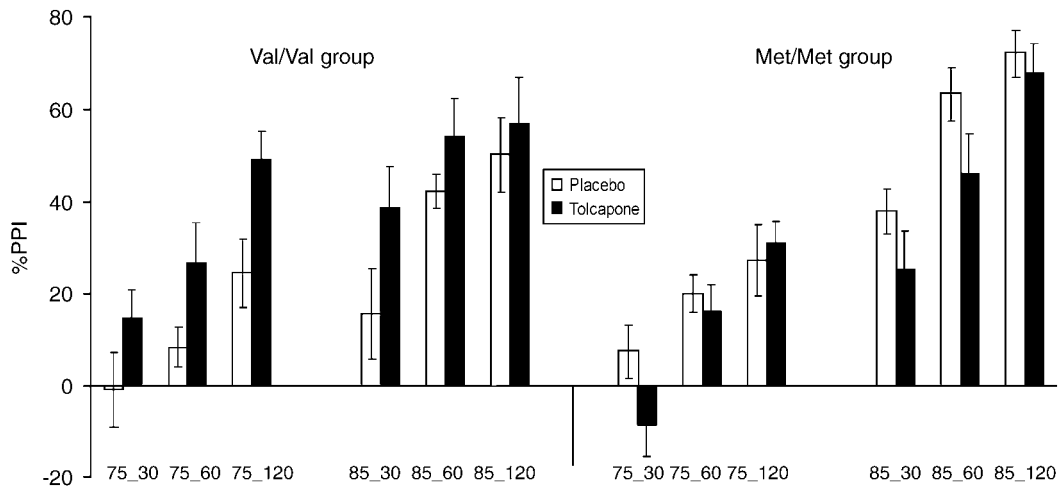


Figure 2 Percent prepulse inhibition (%PPI) for the two genotype groups under the two treatment conditions. Bars represent SEM.

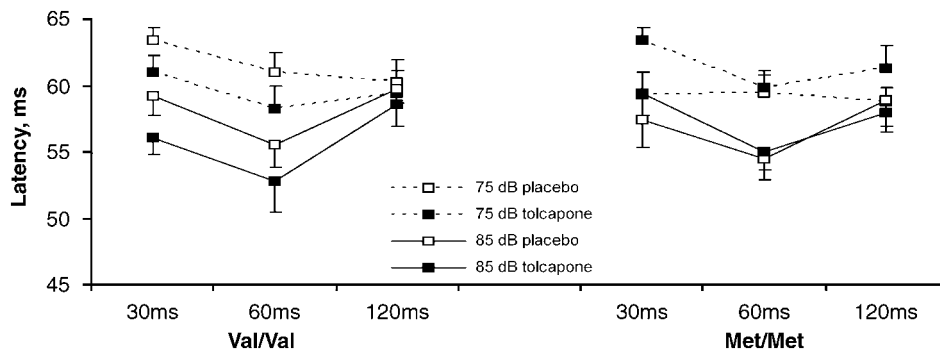


Figure 3 Peak latencies in prepulse-pulse trials for the two genotype groups under the two treatment conditions. Bars represent SEM.

treatment \times genotype interaction ($F(1,21) = 6.7$, $p < 0.02$, $\eta^2 = 0.242$). Follow-up of this interaction with separate ANOVAs within each genotype group showed a significant treatment main effect in the case of the Val/Val ($F(1,11) = 5.9$, $p < 0.033$) but not the Met/Met group ($F(1,10) = 1.8$, $p > 0.2$).

Neuropsychological Tests

N-back. Reaction times: Figure 4 (top) shows the reaction times for both groups under the two treatment conditions. The overall $2 \times 2 \times 2 \times 3$ (genotype \times treatment \times order \times difficulty) ANOVA revealed significant main effect of treatment ($F(1,19) = 7.5$, $p < 0.013$, $\eta^2 = 0.284$) and difficulty level ($F(2,38) = 5.2$, $p < 0.017$, $\epsilon = 0.78$, $\eta^2 = 0.216$) and a significant treatment \times genotype ($F(1,19) = 5.2$, $p < 0.034$, $\eta^2 = 0.216$) interaction but not genotype or order ($F_s < 1$) main effects. Because of trend genotype effects on IQ, we repeated the analysis with IQ as the covariate. Following this ANCOVA, the critical treatment by genotype interaction was significant only at trend level ($F(1,18) = 3.8$, $p = 0.06$, $\eta^2 = 0.175$). The treatment \times genotype interaction was followed up with ANOVAs within each separate genotype group. In the Val/Val group, there were significant treatment ($F(1,10) = 10.6$, $p < 0.009$) and difficulty ($F(2,20,10) = 4.96$, $p < 0.042$) main effects and a treatment \times difficulty interaction ($F(1,10) = 3.9$, $p < 0.04$), indicating significant improvement

in performance with tolcapone, especially at the more demanding 2- and 3-back levels of difficulty. In contrast, there were no significant main effects or interactions in the case of the Met/Met group.

Correct responses: the overall ANOVA revealed only an expected significant main effect of difficulty level ($F(2,42) = 7.2$, $\epsilon = 0.626$, $p < 0.008$) (all other $p > 0.16$; Figure 4, middle).

Letter-number sequencing. Figure 4 (bottom) shows the correct responses for both groups under the two treatment conditions. The overall $2 \times 2 \times 2 \times 7$ (genotype \times treatment \times order \times difficulty) ANOVA revealed significant main effects of treatment ($F(1,19) = 7.1$, $p < 0.016$, $\eta^2 = 0.271$) and difficulty level ($F(6,114) = 178.9$, $\epsilon = 0.4$, $p < 0.000$, $\eta^2 = 0.904$) and significant treatment \times genotype ($F(1,19) = 4.4$, $p < 0.05$, $\eta^2 = 0.189$) and treatment \times order ($F(1,19) = 7.1$, $p < 0.016$, $\eta^2 = 0.271$) interactions but not genotype ($F = 1.15$) or order ($F < 1$) main effects. The critical treatment by genotype interaction was significant only at trend level ($F(1,18) = 3.9$, $p = 0.06$, $\eta^2 = 0.178$) when IQ was included as a covariate. The treatment \times genotype interaction was followed up with ANOVAs within each separate genotype group. These ANOVAs indicated a significant effect of treatment in the Val/Val ($F(1,10) = 8.5$, $p < 0.015$) but not in the Met/Met group ($F < 1$; Figure 4, bottom).

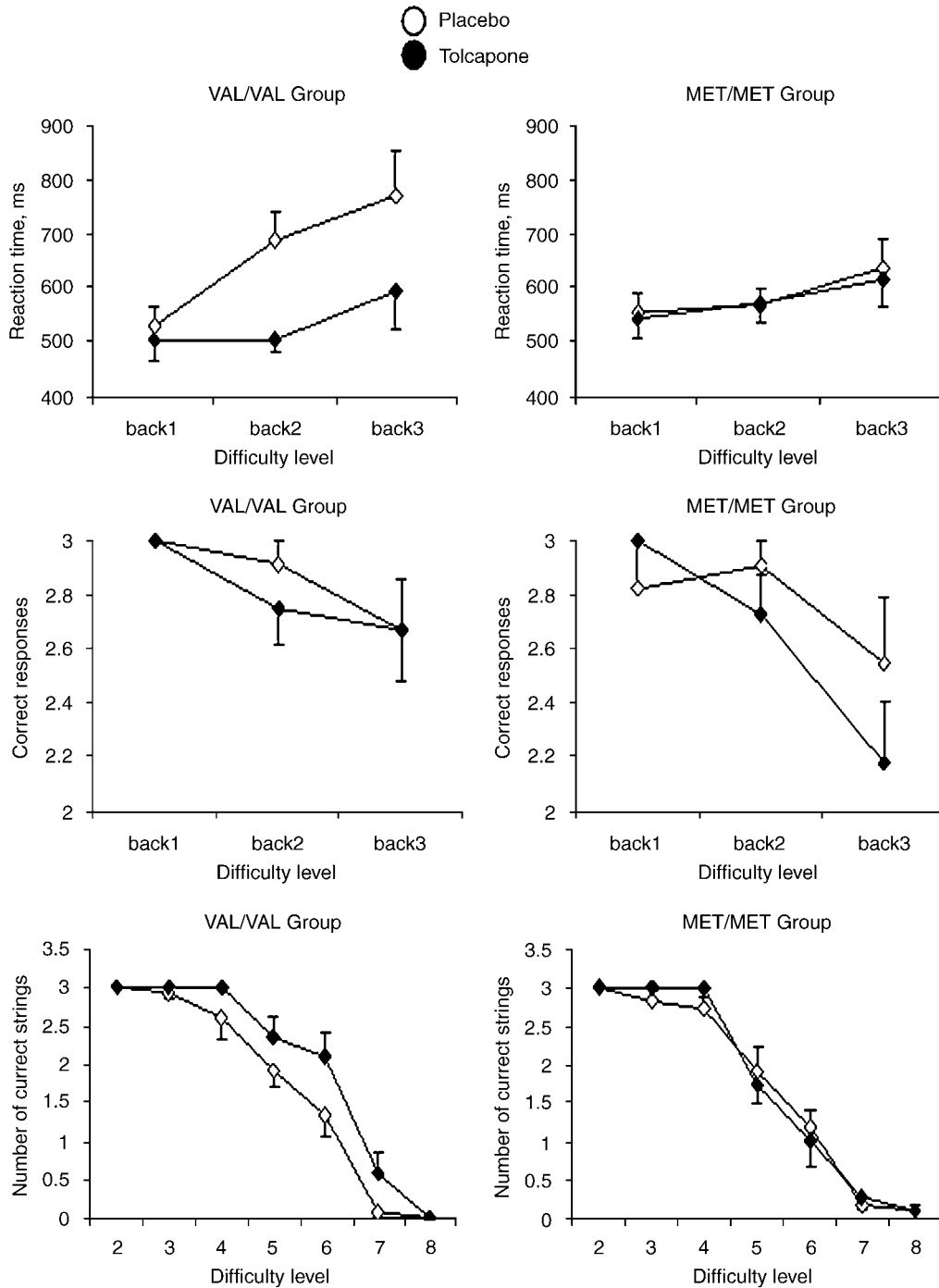


Figure 4 Reaction time (top) and correct responses (middle) for the n-back task and correct responses for the letter–number sequencing (LNS, bottom) for the two genotype groups under the two treatment conditions. Bars represent SEM.

As a further exploration of the relationship between the tolcapone effects on PPI and cognition, we also constructed a series of multiple regressions to assess whether variance in tolcapone-induced startle and PPI changes independently contributed to variance in tolcapone-induced effects on cognition. Placebo–tolcapone difference scores (Δ) for n-back total reaction time and LNS total correct strings served as the dependent variables. Tolcapone-induced changes in %PPI (Δ PPI) at each trial type served as the independent

variables. These regressions revealed that in the Val/Val group, Δ PPI at 85 dB per 60 ms trials significantly ($F(1, 10) = 8.4, p < 0.016$) explained 45.6% of the variance in Δ LNS (total correct strings), whereas 53.6% of the variance in Δ n-back (total reaction time) was explained significantly ($F(3, 8) = 6.5, p < 0.02$) by Δ PPI at 85 dB per 60 ms, 85 dB per 30 ms, and 75 dB per 30 ms. Table 2 shows the Pearson's correlations between Δ scores in both working memory tests and Δ PPI and Δ pulse-alone in the entire sample.

Table 2 Correlation Matrix Between Placebo-Tolcapone Difference (Δ) Scores of both Working Memory Tasks and Δ PPI at Six Trial Types, as well as Δ startle Amplitude in Pulse-Alone Trials

	75_30	75_60	75_120	85_30	85_60	85_120	Pulse-alone
LNS	0.244	0.546**	0.227	0.501**	0.584**	0.382*	-0.076
nBackRT	-0.283	-0.354*	-0.359*	-0.219	-0.384*	0.061	0.248

Abbreviations: LNS, letter-number sequencing (total correct strings); nBackRT, nBack total reaction time.

Values represent Pearson's correlation coefficients; * $p < 0.05$; ** $p < 0.007$ (p correction for accumulation of α error (0.05:7) = 0.00714).

DISCUSSION

The present study provides first evidence of parallel improvement of working memory and PPI at short and long intervals specific to normal COMT Val158 homozygote subjects, after PFC DA increases by the COMT inhibitor tolcapone. More specifically, we found that tolcapone significantly increased PPI in Val158 homozygote subjects who have lower PFC DA levels and lower PPI than Met/Met subjects (Roussos *et al*, 2008a). We also found that tolcapone tended to have the opposite effect in Met/Met individuals. Similar to PPI, latency facilitation was also affected by tolcapone in a genotype-specific manner, only the Val/Val subjects reducing their time to peak with tolcapone. Comparison of the two groups for PPI in the placebo condition replicated the genotype differences in PPI (Roussos *et al*, 2008a) extending them to short, 30 ms intervals. These results confirm the importance of baseline PPI levels for the effect of dopaminergic drugs, which has been previously highlighted by different research groups (Swerdlow *et al*, 2003; Bitsios *et al*, 2005; Csomor *et al*, 2008) and strengthen our formulation of an interaction between PFC DA levels and PPI, according to an inverted U-shaped curve (Bitsios *et al*, 2005). These results also strengthen our previous suggestion that the PFC influences PPI levels, and by inference the early stages of attentional processing (Giakoumaki *et al*, 2006; Bitsios *et al*, 2006; Roussos *et al*, 2008a).

In perfect symmetry with our PPI findings, tolcapone also improved performance in two working memory tests only in Val158 but not in Met158 homozygotes. In the LNS where the sequencing of letters and numbers proceeds in an alternating fashion, we found that Val158 homozygotes had significantly more accurate responses following tolcapone administration. Replicating previous results (Apud *et al*, 2007), we also found that after tolcapone administration, the Val158 but not Met158 homozygotes were faster to respond correctly in the n-back task, especially with the hardest 2- and 3-back high-load versions, in which updating of the working memory buffer is near continuous. These results extend recent findings showing that DA agonists such as amphetamine (Mattay *et al*, 2003) or relatively specific increases in PFC DA signaling by tolcapone (Apud *et al*, 2007) can lead to improved working memory performance in Val homozygotes who have suboptimal PFC DA levels; in contrast, the performance of Met homozygotes who have high PFC DA levels and stand near or at the top of the

inverted U-shaped curve remains the same or may even deteriorate.

The similar pattern of tolcapone effects on PPI and working memory suggests (1) that PPI and working memory are closely linked and (2) the operation of a common underlying mechanism. The robust treatment by genotype effect observed in both PPI and working memory is consistent with relatively lower PFC DA signaling in Val/Val subjects and presumed benefit of enhanced PFC DA in this context (Weinberger *et al*, 2001; Egan *et al*, 2001; Mattay *et al*, 2003; Winterer and Goldman, 2003; Winterer *et al*, 2006). Notably, the improvement of PPI by tolcapone in the Val/Val group, especially at short intervals, was found to account for a substantial part of the variance in tolcapone-induced performance improvements in both working memory tests.

These observations aside, and despite empirical evidence that suggests that PPI may be critical for human cognition (Geyer *et al*, 1990), the present findings may reflect a common underlying circuit rather than a causal link between PPI and cognition. Although there is evidence for a close link between PFC DA activity and PPI in rodents (Bubser and Koch, 1994; Ellenbroek *et al*, 1996; Zavitsanou *et al*, 1999; Broersen *et al*, 1999; Lacroix *et al*, 2000) and the importance of PFC for PPI modulation in humans is rapidly accumulating (see 'Introduction'), PPI is regulated by a complex cortico-striato-pallido-pontine circuit (Swerdlow *et al*, 1992, 2001), in which the PFC is only one critical node. For instance, COMT is also expressed in the hippocampus (Matsumoto *et al*, 2003), which is also involved in PPI modulation (Swerdlow *et al*, 2001) and it is not known how COMT inhibition by tolcapone within the hippocampus may have influenced our results. Moreover, although the COMT Val158Met polymorphism determines basal PFC DA neurotransmission levels, it may also regulate striatal DA activity. Indeed, higher COMT activity, as conferred by the Val158 allele, is associated with elevated midbrain DA synthesis (Meyer-Lindenberg *et al*, 2005) and higher tyrosine-hydroxylase expression in neurons projecting to the striatum (Akil *et al*, 2003). This suggests that besides a direct reduction in cortical information processing resulting in less efficient executive cognition (eg working memory) the Val158 allele may indirectly increase striatal dopaminergic function, thus reducing PPI. On the other hand, the available evidence from the COMT literature (eg from COMT knockout mice) (Gogos *et al*, 1998; Huotari *et al*, 2002) argues for a definite role of the PFC vs striatum, favoring an impact particularly on cortical DA signaling and larger cortical than striatal effects in studies using COMT inhibitors. In the Val158 homozygotes, the tolcapone-induced improvement of PPI at long (ie 120 ms), more 'frontally mediated' intervals (Filion *et al*, 1993), is consistent with the known reduction of COMT activity by the drug, predominantly in the PFC, which presumably would lead to a boost of PFC DA and PFC function. However, the improvement of PPI at short 'preattentive' (ie 30 ms) intervals cannot be easily attributed to such a direct PFC effect of the drug, as PPI at these short intervals is thought to be automatic and not a valid marker for PFC function (Schell *et al*, 2000). If, as mentioned above, high COMT activity as conferred by the Val158 is indeed associated with indirect increase in striatal dopaminergic

function (Akil *et al*, 2003; Meyer-Lindenberg *et al*, 2005), then it is an intriguing possibility that reduction of COMT activity by tolcapone leads to reduction in striatal dopaminergic function, which may underlie the observed improvement in short lead PPI in Val158 homozygotes.

A more elaborate mechanism is drawn from the model put forward by Grace (1993) and Bilder *et al* (2004). This model posits that low tonic PFC DA levels (Val/Val subjects) may cause high phasic dopaminergic responses in the nucleus accumbens (NAC) and equally, high tonic PFC DA levels (Met/Met subjects) may cause low phasic DA responses in the NAC (Grace, 1993; Bilder *et al*, 2004). Low phasic (eg in response to a prepulse) DA levels within the NAC of Met/Met subjects would result in greater activity in the startle inhibiting pedunculopontine tegmental nucleus (Swerdlow *et al*, 2001) and thus greater PPI levels. The opposite would be true for the Val/Val subjects. By tonically boosting PFC DA levels, tolcapone would improve both cognition and PPI at all intervals in Val/Val subjects. Although admittedly speculative, we believe that at this moment, this view best explains all the available evidence, as it maintains tolcapone's prominent locus of action within the PFC, although it allows for meaningful interactions between the PFC and mesolimbic systems known to regulate PPI. Future research ought to examine DA release in the striatum during passive PPI paradigms at baseline and following tolcapone administration in Val158 and Met158 homozygotes. There have to be some common processes and neural regions involved in short and long lead PPI, as PPI at various short and long intervals correlates highly positively (Kumari *et al*, 2005, a, 2008). Certainly, more research is required on the effects of tolcapone on cognition and PPI with a greater range of intervals in passive and attentional paradigms and with other COMT polymorphisms.

Importantly, our findings were obtained from a homogeneous cohort of healthy male subjects and cannot be attributed to differences in gender, age, education, or startle characteristics. The magnitudes of the effects of tolcapone on working memory performance were relatively small and remained significant at trend level after covarying for the relatively large IQ genotype differences observed in this study. It is important to emphasize that our subjects were normal individuals without obvious deficits on these tasks and a 'ceiling effect' on performance is therefore built into our study, making the positive effects more remarkable. Also, our findings cannot be attributed to tolcapone effects on mood and activation, as there were no significant drug effects in any of the POMS measures. Tolcapone's beneficial effects on PPI and working memory in Val158 homozygotes were not accompanied by changes in activation and mood, suggesting that tolcapone was devoid of gross effects on the mesolimbic and mesostriatal dopaminergic systems in this group. This is consistent with evidence showing that COMT does not significantly affect extracellular DA levels in the rat striatum (Gogos *et al*, 1998; Li *et al*, 1998; Mazei *et al*, 2002; Tunbridge *et al*, 2004) and suggests that tolcapone's beneficial effects on PPI and cognition would be expected to occur in the absence of psychostimulant effects and abuse potential. The COMT enzyme of Val158 homozygotes may have more capacity to bind tolcapone because of its greater stability (Chen *et al*, 2004). Thus, it could be argued that the observed treatment \times genotype interactions were merely a

reflection of greater sensitivity to tolcapone of the Val/Val individuals. Although this possibility cannot be totally excluded with regard to the effect of tolcapone on working memory, it is unlikely that it can account for our PPI findings, as tolcapone improved PPI in the Val/Val group and affected the Met/Met group in the opposite way. Although the latter effect failed to reach significance, it is at odds with the above interpretation. It is possible that with a larger sample of Met/Met subjects a significant tolcapone-induced PPI disruption could be detected in this group. More importantly, we obtained evidence for significant tolcapone bioactivity in the Met/Met group as documented in startle increases by the drug in Met158 but not in Val158 homozygotes.

The increase in startle by tolcapone in the Met158 but not Val158 homozygotes was unexpected and we do not have a definite explanation for it. Activation of the central noradrenergic and/or dopaminergic systems in rodents and humans is known to increase the startle reflex (Davis *et al*, 1979; Davis, 1985; Morgan *et al*, 1993). However, a putative effect of tolcapone on noradrenergic and/or dopaminergic neurotransmission within brainstem circuits mediating the startle reflex cannot easily explain the selective startle increase by the drug in the Met/Met group only. Startle reflex increases during negative mood (see Lang and Davis, 2006 for review), and Met homozygotes have reduced resilience against such negative mood states (Smolka *et al*, 2005; Drabant *et al*, 2006; Weiss *et al*, 2007). It is therefore possible that the startle increase by tolcapone in the Met/Met group is related to tolcapone-induced dysphoric mood in Met158 homozygotes. Although this is not supported by the subjective data, it is possible that startle, an automatic reflex response, is a more accurate and sensitive measure of dysphoric mood, independent of the slower, language-based appraisal processes (Lang *et al*, 2000). Certainly, more research is required on the interaction between tolcapone and COMT genotypes on emotional arousal and affective processing, using objective and specific paradigms such as the startle modulation by affective pictures (Lang *et al*, 1999).

PPI is a widely used surrogate measure of psychosis in animal models (Swerdlow *et al*, 1994). It is also considered a candidate endophenotype for schizophrenia (Braff and Light, 2005; Calkins *et al*, 2007) because of its high heritability (Anokhin *et al*, 2003; Greenwood *et al*, 2007) and the presence of PPI deficits in the unaffected first-degree relatives of probands (Cadenhead *et al*, 2000; Kumari *et al*, 2005b). However, the genetic architecture of the PPI endophenotype is in its infancy. Two recent studies show two DA gene-specific influences on PPI levels that may explain observed individual differences (Roussos *et al*, 2008a, b). This is the first study on the enhancement of PPI and executive cognition by the nonstimulant tolcapone. Through specific manipulation of PFC DA, tolcapone offers a novel approach of 'targeted' pharmacology for the improvement of cognitive function and PPI, presumably by increasing DA-mediated prefrontal signal-to-noise ratio (Apud and Weinberger, 2007). The present study suggests that this novel pharmacological strategy may also be genotype targeted, as these effects were modified by COMT genotype. Our findings may have important implications for the treatment of disorders characterized by PFC

dysfunction with deficient executive cognition and PPI such as schizophrenia.

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DISCLOSURE/CONFLICT OF INTEREST

All authors have no conflict of interest or any involvement, financial, or otherwise, that might have biased the present work.

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