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ORIGINAL ARTICLE

Prepulse inhibition of the startle reflex depends on the catechol *O*-methyltransferase Val158Met gene polymorphism

P. Roussos[1], S. G. Giakoumaki[1,2], M. Rogdaki[1], S. Pavlakis[1,3], S. Frangou[1] and P. Bitsios[1,2]*

[1] *Department of Psychiatry and Behavioural Sciences, University of Crete, Heraklion, Greece*
[2] *Section of Neurobiology of Psychosis, Institute of Psychiatry, London, UK*
[3] *Royal Free and University College Medical School, Department of Clinical Sciences, University College London, UK*

Background. Recent evidence suggests that dopamine (DA) agonist-induced disruption of prepulse inhibition (PPI) depends on basal PPI values, in a manner that suggests an inverted U-shaped relationship between PPI and prefrontal DA levels. This is the first study to examine possible genetic determinants of PPI and the catechol *O*-methyltransferase (*COMT*) Val158Met polymorphism, the main catabolic pathway of released DA in the prefrontal cortex (PFC).

Method. PPI was measured in 93 healthy males presented with 75-dB and 85-dB prepulses at 60-ms and 120-ms prepulse–pulse intervals. Subjects were grouped according to their *COMT* status into a Val/Val, a Val/Met and a Met/Met group.

Results. ANOVAs showed that at all prepulse and interval conditions, Val/Val individuals had the lowest PPI, Met/Met the highest, and Val/Met were intermediate.

Conclusions. These results suggest that PPI is regulated by DA neurotransmission in the PFC and its levels depend on the *COMT* Val158Met gene polymorphism. These findings enhance the value of the PPI paradigm in examining individual variability of early information processing in healthy subjects and psychiatric disorders associated with changes in PFC DA activity and attentional deficits such as schizophrenia.

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Introduction

Prepulse inhibition (PPI) is a measure of inhibitory control of information processing in which a weak sensory stimulus (the prepulse) inhibits the startle response to a subsequent sudden intense stimulus (pulse). PPI is thought to reflect 'sensorimotor gating', a form of central nervous system inhibition wherein distracting 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; Braff & Geyer, 1990).

PPI is a widely used surrogate measure of psychosis in animal models. It is also considered a candidate endophenotype for schizophrenia (Braff & Light, 2005; Calkins *et al*. 2007) because of its high heritability (Anokhin *et al*. 2003) and the presence of PPI deficits in the unaffected first-degree relatives of probands (Cadenhead *et al*. 2000; Kumari *et al*. 2005). However, the genetic architecture of the PPI endophenotype is in its infancy. To date, only one study has reported PPI deficits in both schizophrenia and healthy control populations with a missense mutation on rs3924999 of the neuregulin 1 gene, one of the leading candidate genes in schizophrenia (Hong *et al*. 2007).

Animal studies show that PPI involves a widely distributed cortico-striato-pallido-pontine network (Swerdlow *et al*. 1991, 2001*a*) potently regulated by dopaminergic neurotransmission (Swerdlow *et al*. 1992; Koch & Schnitzler, 1997; Geyer *et al*. 2001). Dopamine (DA) agonists disrupt PPI in rats (Mansbach *et al*. 1988; Swerdlow *et al*. 1998, 2001*b*, 2002, 2003) and this DA-stimulated loss of PPI has been proposed as an animal model with face, predictive and construct validity for the loss of sensorimotor gating in schizophrenia (Swerdlow *et al*. 1994). There is now abundant evidence (for reviews, see Harrison & Weinberger, 2005; Tunbridge *et al*. 2006) that COMT impacts critically on dopaminergic transmission. A polymorphism in the *COMT* gene, leading to an amino

* Address for correspondence: Dr P. Bitsios, Department of Psychiatry and Behavioural Sciences, Faculty of Medicine, PO Box 2208, University of Crete, Heraklion 71003, Crete, Greece.
(Email: pbitsios@med.uoc.gr)

acid substitution [valine (Val) to methionine (Met)], results in the Met/Met variant showing 40% less enzymatic activity than the Val/Val (Chen *et al*. 2004). This *COMT* polymorphism determines basal cortical DA neurotransmission levels that, in turn, 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). This suggests that the Val158 allele may indirectly increase striatal dopaminergic function, thus reducing PPI. The *COMT* Val158Met polymorphism has been associated with auditory information gating deficits (Lu *et al*. 2007), and this is the first study to test the effects of this polymorphism on PPI in healthy male subjects.

Method

Subjects

One hundred and fifteen subjects were recruited from a pooled volunteer list of university students. We restricted the sample to men to avoid PPI variability related to gender (Swerdlow *et al*. 1993; Aasen *et al*. 2005) and menstrual cycle (Swerdlow *et al*. 1997) and to avoid the regulatory effect on the expressed activity of the COMT enzyme by the circulatory oestrogens in women (Salama *et al*. 2006). Inclusion criteria included right-handedness, absence of personal history of head trauma, medical and neurological conditions, or use of prescribed and recreational drugs; absence of personal or family (up to second-degree relatives) history of DSM-IV Axis I disorders and hearing threshold greater than 40 dB at 1 kHz. All subjects underwent psychiatric assessment using the Mini-International Neuropsychiatric Interview (Sheehan *et al*. 1998) and physical assessment including a urine toxicology screening and audiometry using a Kamplex AC30 Clinical Audiometer (PC Werth Ltd, London, UK). Eight subjects were excluded because of a family history of psychiatric illness, 10 subjects were startle non-responders (mean startle amplitude $<10\,\mu$V) and four had a positive drug screen. Ninety-three Greek/Caucasian healthy males aged 18–35 years (mean $\pm$ S.D., 26.2 ± 4.0) entered and completed the study. The study was approved by the Ethics Committee of the University of Crete. All participants gave written informed consent before screening. Participants were seen and assessed on a single occasion.

Genotyping

Genomic DNA was extracted from venous blood samples. The *COMT* Val158Met genotype was determined by restriction fragment length polymorphism (RFLP) after polymerase chain reaction (PCR) amplification and digestion with *Nla*III, similarly to a previously described methodology (Lachman *et al*. 1996).

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 and set-up have been described previously in detail (Bitsios *et al*. 2005). Pulses consisted of 40-ms, 115-dB white noise bursts, and prepulses consisted of 20-ms, 75-dB and 85-dB white noise bursts over 70-dB background noise. Recording began with 3 min of acclimation when only background noise was present. The recording period comprised 12 pulse-alone trials and 24 prepulse–pulse trials. Two lead intervals (onset to onset) were used (60 ms, 120 ms). For each interval, there were six trials with the 75-dB prepulse and six with the 85-dB prepulse. All trials were presented in pseudo-random order with the constraint that no two identical trials occurred in succession. The intertrial interval varied between 9 s and 23 s (average 15 s). The entire test session lasted approximately 15 min. No specific instructions were given to the subjects with regards to the prepulses (passive PPI paradigm).

The EMG data were at first inspected on a trial-to-trial basis (to exclude erroneous trials for a particular subject) and then scored by the system's analytic programme for response amplitude and latencies. Trials were rejected ($<5\%$) if excessive EMG activity (>20 digital units) was observed during the first 20 ms of recording or when onset latencies (defined by a shift of 20 digital units from the baseline value, occurring within 20–85 ms after the onset of the pulse stimulus) and peak latencies differed by more than 95 ms (Braff *et al*. 1992, 1999). The maximum absolute amplitude of the raw EMG data occurring in the 20–150-ms time window of the non-rejected trials was scored offline and stored for averaging and data analysis.

Statistical analysis

$$\text{Percentage PPI} = 100 \times \frac{\text{amplitude}_{\text{pulse-alone}} - \text{amplitude}_{\text{prepulse–pulse}}}{\text{amplitude}_{\text{pulse-alone}}}$$

was calculated for each trial type. Kolmogorov–Smirnov tests showed normal distributions of startle and PPI data. Separate mixed model ANOVAs with genotype as the grouping factor and prepulse and interval as the within-subject factors were used to analyse %PPI and latency data. Partial η^2 values are reported.

Table 1. *Demographic and startle characteristics for each genotype group and the entire sample* (*mean ± standard deviation*)

	Val/Val ($n=30$)	Val/Met ($n=48$)	Met/Met ($n=15$)	F/χ^2	p	Entire sample
Age (years)[a]	25.9 ± 3.9	26.4 ± 4.2	26.3 ± 3.8	<1	>0.8	26.2 ± 4.0
Education (years)[a]	16.8 ± 2.2	17.3 ± 2.7	16.6 ± 2.2	<1	>0.6	17.0 ± 2.5
Smokers/non-smokers[b]	12/18	23/25	5/10	1.1	>0.5	40/53
Smokers (cigarettes/day)	19.5 ± 6.9	16.9 ± 6.6	12.2 ± 7.2	2.0	>0.1	17.1 ± 6.9
Baseline startle (μV)	274.9 ± 246	349.6 ± 189	405.6 ± 292	2.1	>0.1	332.6 ± 228
Onset latency (ms)	45.4 ± 7.6	43.3 ± 8.2	42.7 ± 4.4	<1	>0.3	43.9 ± 7.5
Peak latency (ms)	60.6 ± 4.5	59.6 ± 4.0	59.9 ± 3.5	<1	>0.6	59.9 ± 4.1

[a] For this measure, the overall distribution of the score differed from normality and the equivalent non-parametric Kruskal–Wallis procedure was applied.

[b] χ^2 comparison.

Table 2. *Test for significant differences in allele frequencies for each locus when dividing samples by COMT Val158Met*

Locus	Chromosome	χ^2 (df = 1)	p
BDNF rs6265	11p13	0.47	0.49
DRD2A1 rs1800497	11q23	0.52	0.47
DAT1 rs28363170	5p15	0.1	0.75
DRD1 rs4532	5q35	0.77	0.38
ZDHHC8 rs175174	22q11	0.24	0.62

COMT, catechol *O*-methyltransferase; BDNF rs6265, brain-derived neurotrophic factor Val66Met polymorphism; DRD2A1 rs1800497, dopamine receptor D_2 *Taq*IA restriction fragment length polymorphism; DAT1 rs28363170, a 40-bp tandem repeat polymorphism in the 3′ region of the SLC6A3 gene; DRD1 rs4532, dopamine receptor D_1 A-48G polymorphism in the 5′ untranslated region of the DRD1 gene; ZDHHC8 rs175174, zinc finger DHHC domain-containing protein 8 A/G polymorphism; df, degrees of freedom.

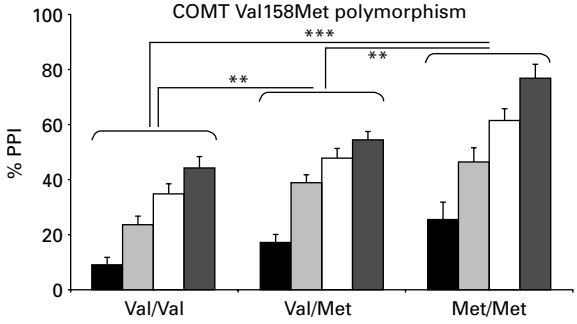

Fig. 1. Group means and standard error of the mean (S.E.M.) for percentage prepulse inhibition (%PPI) for the three genotype groups with 75-dB and 85-dB prepulses, at 60-ms and 120-ms prepulse–pulse intervals. ■, 75 dB, 60 ms; ▨, 75 dB, 120 ms; □, 85 dB, 60 ms; ▩, 85 dB, 120 ms (** $p<0.01$; *** $p<0.001$).

Table 3. *Onset and peak latency data* (*mean ± standard deviation*) *at each trial type for the three genotype groups*

		Val/Val	Val/Met	Met/Met
Onset	pp75_60	43.5 ± 7.6	39.1 ± 6.3	40.6 ± 5.9
	pp75_120	45.0 ± 7.2	43.6 ± 7.2	45.8 ± 5.7
	pp85_60	41.3 ± 8.1	40.0 ± 9.7	43.6 ± 6.6
	pp85_120	45.9 ± 8.4	43.1 ± 10.6	48.2 ± 5.8
Peak	pp75_60	58.4 ± 4.4	57.1 ± 5.2	56.6 ± 4.7
	pp75_120	60.0 ± 5.4	60.0 ± 3.1	61.2 ± 3.5
	pp85_60	54.1 ± 6.1	54.8 ± 5.2	54.5 ± 5.5
	pp85_120	58.4 ± 4.6	58.3 ± 4.8	58.2 ± 4.8

Results

Thirty subjects were homozygous for Val/Val, 48 were heterozygous for Val/Met, and 15 were homozygous for Met/Met, a distribution consistent with Hardy–Weinberg expectations ($\chi^2=0.33$, df = 2, $p=0.85$). There were no differences in demographic and startle variables between the three genotype groups (Table 1) and polynomial contrasts failed to show a significant linear trend in baseline startle amplitude from the Val/Val to the Met/Met group. As an additional control to rule out gross stratification effects, genotyping was also performed for five unrelated gene polymorphisms. A contingency table approach (Raymond & Rousset, 1995; Roussos *et al.* in press) was used to test for differences in the allelic distributions of these additional markers for COMT Val/Val and Met/Met subjects. This analysis revealed no significant differences at $p<0.05$ in allele frequencies for each locus (Table 2). This finding makes genetic inhomogeneity of the tested population unlikely. Figure 1 shows the

Table 4. *%PPI (mean ± S.D.) at all trial types, when the sample was regrouped for BDNF (M/M n = 2, V/M n = 34, V/V n = 57), DRD2A1 (A1/A1 n = 3, A1/A2 n = 19, A2/A2 n = 71), DAT1 (9/9 n = 11, 9/10 n = 37, 10/10 n = 45), DRD1 (A/A n = 47, A/G n = 41, G/G n = 5), and ZDHHC8 (A/A n = 6, A/G n = 73, G/G n = 14) gene polymorphisms*

	BDNF	DRD2	DAT1	DRD1	ZDHHC8
75_60	M/M: 9.5 ± 23.3	A1/A1: 16.5 ± 10.4	9/9: 19.4 ± 15.8	A/A: 16.1 ± 19.6	A/A: 17.4 ± 10.1
	V/M: 17.2 ± 16.2	A1/A2: 18.4 ± 16.8	9/10: 15.6 ± 21.0	A/G: 13.6 ± 19.2	A/G: 16.9 ± 20.3
	V/V: 15.2 ± 21.4	A2/A2: 15.0 ± 20.5	10/10: 15.0 ± 19.4	G/G: 31.2 ± 17.4	G/G: 7.8 ± 17.3
75_120	M/M: 55.0 ± 3.5	A1/A1: 29.5 ± 16.0	9/9: 39.8 ± 21.7	A/A: 34.0 ± 20.0	A/A: 25.2 ± 19.5
	V/M: 35.2 ± 16.6	A1/A2: 30.3 ± 21.4	9/10: 35.6 ± 20.5	A/G: 35.7 ± 21.7	A/G: 36.2 ± 20.4
	V/V: 34.5 ± 22.8	A2/A2: 36.8 ± 20.6	10/10: 33.7 ± 20.8	G/G: 42.2 ± 20.0	G/G: 34.9 ± 23.4
85_60	M/M: 51.0 ± 9.9	A1/A1: 49.7 ± 8.3	9/9: 42.3 ± 15.7	A/A: 43.6 ± 24.8	A/A: 43.1 ± 19.6
	V/M: 45.8 ± 22.8	A1/A2: 47.7 ± 24.7	9/10: 46.7 ± 24.8	A/G: 48.5 ± 22.3	A/G: 47.0 ± 22.3
	V/V: 45.7 ± 24.0	A2/A2: 45.2 ± 23.4	10/10: 46.0 ± 23.8	G/G: 45.9 ± 14.2	G/G: 41.4 ± 31.0
85_120	M/M: 66.5 ± 31.8	A1/A1: 38.0 ± 5.8	9/9: 64.5 ± 22.5	A/A: 52.7 ± 26.3	A/A: 51.8 ± 27.0
	V/M: 53.9 ± 26.2	A1/A2: 50.1 ± 22.6	9/10: 56.5 ± 26.5	A/G: 55.4 ± 24.9	A/G: 53.2 ± 25.6
	V/V: 54.3 ± 25.2	A2/A2: 56.3 ± 26.4	10/10: 50.3 ± 24.8	G/G: 62.8 ± 24.3	G/G: 59.2 ± 23.2

PPI, Prepulse inhibition; S.D., standard deviation.

%PPI of the three genotype groups. The ANOVA revealed significant main effects of genotype [$F(2, 90) = 14.95$, $p < 0.001$, $\eta^2 = 0.25$], prepulse intensity [$F(1, 90) = 143.1$, $p < 0.001$, $\eta^2 = 0.61$] and interval [$F(1, 90) = 38.1$, $p < 0.001$, $\eta^2 = 0.30$] but no interactions (F's < 2.1, $p > 0.1$). These effects remained significant (all p values < 0.001) after covarying for both baseline startle and smoking status. *Post-hoc* Bonferroni comparisons revealed that PPI of the Met/Met group was greater than PPI of the Val/Met ($p < 0.01$) and the Val/Val group ($p < 0.001$); PPI of the Val/Met group was also greater than PPI of the Val/Val group ($p < 0.003$). There were no significant correlations between baseline startle and PPI for the entire sample or within the separate groups (all p values > 0.1). ANOVAs of the latency data (Table 3) revealed prepulse and interval but not genotype main effects or interactions (F values < 2.8, $p > 0.08$). ANOVAs with identical factorial design showed that none of the polymorphisms shown in Table 2 had a significant effect on PPI in our sample, as evidenced by lack of significant genotype main effects or interactions involving genotype (all F values < 1). Table 4 shows the %PPI in each genotype group for these polymorphisms and their distribution in our sample.

Discussion

We found that in healthy males *COMT* polymorphism is associated with PPI levels. Specifically, we observed a linear relationship between PPI levels and Val allele load; Val homozygotes had the lowest PPI, Met homozygotes the highest, and heterozygotes were intermediate for both prepulse intensities and both lead interval conditions. Importantly, our findings were obtained from a homogeneous cohort of healthy male subjects and cannot be attributed to differences in demographic characteristics or genetic inhomogeneity because the genotype groups did not differ in that respect (Tables 1 and 2). Our observations resonate closely with results from recent functional magnetic resonance imaging (fMRI) literature showing that, relative to Met-loading subjects, Val homozygotes underperform in prefrontal cortex (PFC)-related tasks and/or have prefrontal hyperactivation (Egan *et al*. 2001; Bilder *et al*. 2002; Malhotra *et al*. 2002; Mattay *et al*. 2003; Bertolino *et al*. 2004; Winterer *et al*. 2006). The lower PPI levels in our Val loading subjects are also suggestive of less efficient information processing and increased prefrontal neuronal 'noise' in individuals with the *COMT* Val allele (Egan *et al*. 2001; Winterer & Goldman, 2003; Winterer *et al*. 2006).

PPI in rodents is modulated by activity in cortico-striato-pallido-pontine circuitry (Swerdlow *et al*. 1991, 2001*a*) of which the PFC is a crucial node (Koch & Bubser, 1994; Swerdlow *et al*. 1995; Ellenbroek *et al*. 1996; Broersen *et al*. 1999; Japha & Koch, 1999; Zavitsanou *et al*. 1999; Lacroix *et al*. 2000; Yee, 2000). Our observations suggest that PFC DA transmission may be an important neural mechanism that modulates PPI in humans. The findings of the present study extend recent reports from our laboratory (Bitsios *et al*. 2006; Giakoumaki *et al*. 2006) and others (Csomor *et al*. 2008) showing (*a*) an association between PPI levels and performance on PFC-related tasks of working memory and planning, and (*b*) changes in PPI levels following administration of DA agonists or antagonists depending on basal PPI (Swerdlow *et al*. 2003; Bitsios *et al*. 2005; Csomor *et al*. 2008). Graham (1975) proposed that PPI reflects

automatic pre-attentive processes but recent evidence suggests that, even at this early stage of information processing, PPI is associated with cognitive processes controlled in a 'top-down' fashion by the PFC (Hazlett *et al*. 2001). This is supported by functional imaging studies in healthy individuals showing increased frontal and parietal cortical activation in attentionally modulated (Hazlett *et al*. 1998) and passive PPI paradigms (Kumari *et al*. 2003, 2007; Postma *et al*. 2006; Campbell *et al*. 2007). Animal studies also support a close link between PPI and PFC DA activity. Reductions in DA activity in the PFC after local injection of selective D2 or D1 antagonists or 6-hydroxydopamine lesions result in significant PPI reduction (Bubser & Koch, 1994; Ellenbroek *et al*. 1996; Zavitsanou *et al*. 1999). Conversely, increased PFC DA activity after local apomorphine infusions also disrupts PPI (Broersen *et al*. 1999; Lacroix *et al*. 2000).

Our results also strengthen the model of an interaction between prefrontal DA levels and PPI according to an inverted U-shaped curve (Bitsios *et al*. 2005). Our findings support our previous suggestion that the PFC influences PPI levels and, by inference, the early stages of attentional processing (Bitsios *et al*. 2006; Giakoumaki *et al*. 2006). The COMT is also expressed in other brain regions involved in PPI modulation, particularly the hippocampus (Swerdlow *et al*. 2001*a*; Matsumoto *et al*. 2003), which may have influenced our results. By extending the influence of the *COMT* genotype on PPI in healthy subjects, the present study contributes to the understanding of the genetic architecture of the PPI endophenotype.

Gender differences in the effects of *COMT* polymorphism on human PPI are possible because no effect of *COMT* polymorphism on PPI was found in a recent study with 96 German females (Montag *et al*. 2008). Unfortunately, however, that study is not directly comparable to the present one because of the different stimulus parameters used in startle elicitation. We used standard stimulation with a 40-ms, 115-dB pulse with nearly instantaneous rise time (<1 ms) and two 20-ms prepulses, 5-dB and 15-dB above background, whereas Montag *et al*. (2008) used a weaker pulse (106-dB, 35-ms, 5-ms rise time) and one prepulse, 19 dB above background. For a given prepulse, PPI increases with weaker pulses (Csomor *et al*. 2006), and therefore it is conceivable that small between-group PPI differences may be overriden by a ceiling effect when weak pulses are used. More importantly, prepulses closer to background noise, such as those used in the present study, increase the susceptibility of PPI to modulation by manipulations of dopaminergic transmission, for example PPI disruption by the DA agonist apomorphine (Davis *et al*. 1990) or attention (Gewirtz & Davis, 1995).

To our knowledge, this is the first demonstration in humans of a DA gene-specific influence on PPI levels that may explain observed individual differences. Future studies examining the effect of the *COMT* Val158Met polymorphism on pharmacological manipulations of the PPI following administration of DA agonists or *COMT* inhibitors, or the effects on PPI of other *COMT* polymorphisms that convey differences in enzyme activity (Diatchenko *et al*. 2005; Nackley *et al*. 2006; Roussos *et al*. in press), could further enhance our understanding of the relationship between *COMT*, PPI and cognition.

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Declaration of Interest

None.

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