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Genetic Variants in the Catechol-*o*-Methyltransferase Gene Are Associated With Impulsivity and Executive Function: Relevance for Major Depression

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The catechol-*o*-methyltransferase (COMT) gene has been extensively investigated in depression with somewhat contradictory results but the role of impulsivity, as a possible intermediate phenotype in this disorder, has not been considered yet. In our study, four tagging SNPs in the COMT gene (rs933271, rs740603, rs4680, rs4646316) were genotyped in two independent population cohorts: Manchester (n = 1267) and Budapest (n = 942). First, we investigated the association between COMT genotypes, impulsivity, neuroticism and depression using haplotype trend regression, and constructed a model using structural equation modeling to investigate the interaction between these factors. Secondly, we tested the effect of executive function on this model in a smaller interviewed sample (n = 207). Our results demonstrated that COMT haplotypes were significantly associated with impulsivity in the combined cohort, showing the same direction of effects in both populations. The COMT effect on depressive symptoms (in subjects without history of depression) and on executive function (interviewed sample) showed the opposite pattern to impulsivity. Structural equation models demonstrated that COMT and impulsivity acted, both together (through neuroticism) and independently, to increase the risk

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of depression. In addition, better executive function also operated as a risk factor for depression, possibly though reduced ability to flexibly disengage negative emotions. In conclusion, variations in the COMT gene exert complex effects on susceptibility to depression involving various intermediate phenotypes, such as impulsivity and executive function. These findings emphasise that modeling of disease pathways at phenotypic level are valuable for identifying genetic risk factors.

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Key words: COMT; depression; haplotype; intermediate phenotype; cognition; modelling

INTRODUCTION

Impulsivity is a complex and multidimensional personality trait that is characterized by a tendency to behave without considering the consequences, leading to unduly risky and often inappropriate actions, and thus sometimes resulting in undesirable outcomes [Peluso et al., 2007]. There is also significant evidence that impulsive behavior has a strong, heritable component; indeed, a recent metanalysis of 41 studies found that approximately half of the variance in impulsivity was explained by genetic influences [Bezdjian et al., 2011]. Although, impulsivity is not defined as a separate diagnostic category in DSM-IV, it is a crucial characteristic of several neuropsychiatric disorders and can therefore represent an intermediate phenotype to identify genetic risk factors for these conditions [Schumann et al., 2010]. Impulsivity is thought to be a core feature of bipolar disorder, especially motor impulsivity in mania [Swann et al., 2008; Strakowski et al., 2010]. In unipolar depression it is mainly considered in the context of suicidality [Mann, 1999; Pezawas et al., 2002; Peluso et al., 2007], however, recent studies indicate that impulsivity may also be an important risk factor for major depression [e.g., Cataldo et al., 2005; Grano et al., 2007].

Whiteside and Lynam [2001] investigated the construct of impulsivity and identified four main factors: urgency, lack of premeditation, sensation seeking and lack of perseverance. They compared these with the five-factor model of personality measured by the Revised NEO Personality Inventory (NEO-PI-R), which uses five domains (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness) and within each domain six facets. In this model, impulsivity is one facet of neuroticism and was most closely associated with the urgency factor. The main feature of urgency is the inability to withhold regrettable actions that increases the probability of dysfunctional behavior during negative affect, such as depression [Whiteside and Lynam, 2001]. It has been also suggested that the depressive state is closely related to lack of premeditation (or non-planning) [Swann et al., 2008] and this factor is strongly loaded in Eysenck's Impulsivity scale [Eysenck and Eysenck, 1978; Whiteside and Lynam, 2001].

Different aspects of impulsivity can be measured by computerised tasks such as the delay discounting task or the STOP task. Delay discounting task measures the preference for a reward as a function of the increasing delivery time and correlates highly with the Eysenck's impulsivity scale [Kirby and Finch, 2010]. The performance on the STOP signal task (characterized by the ability to inhibit a pre-potent action if a stop signal occurred) is closely related to motor impulsivity, and is dependent on the intact functionality of the right inferior frontal cortex [Aron et al., 2003]. In a broader sense, behavioral inhibition is one element of executive function, which is the main organiser of future directed behavior and is controlled by the prefrontal cortex [Bickel et al., 2012; Niendam et al., 2012]. In this way, impaired behavioral inhibition (increased impulsivity) will result in poorer executive function; thus impulsivity and executive function is inversely correlated [Bickel et al., 2012]. Another important component of executive function is planning (also implicated in impulsivity) that can be specifically tested with tasks, such as the Stocking of Cambridge task, which activates the dorsolateral prefrontal cortex [Cazalis et al., 2003]. Poor executive function is typically seen in depressive relapse and is associated with the dysfunction of the frontosubcortical network, including the prefrontal cortex (PFC) [Biringer et al., 2005; Clark et al., 2009].

The neurobiological mechanism that leads to increased impulsivity and thus vulnerability to depression may involve both serotonergic and dopaminergic neurotransmission. Based on animal and human pharmacological studies, decreased serotonin neurotransmission impairs behavioral inhibition [Pattij and Vanderschuren, 2008]. Our previous studies demonstrated significant effects of serotonin on impulsive aggression [Deakin, 2003], risk taking behavior [Juhasz et al., 2010] and self-reported impulsivity [Benko et al., 2009]; all are different aspects of impulsive behavior that may contribute to a depressive phenotype. Increased dopamine signaling, for example, by administration of psychostimulant drugs, has a dual effect on impulsivity; namely, enhancing impulsive actions through the nucleus accumbens, while improving delay discounting via the PFC [Pattij and Vanderschuren, 2008]. Genetic association studies have found significant effect of dopaminergic genes on delay discounting [Boettiger et al., 2007; Paloyelis et al., 2010]. In the present study, we investigated the dopamine system via the catechol-*o*-methyltransferase (COMT) gene that has been implicated in impulsivity in relation to ADHD [Halleland et al., 2009], and intensively investigated in depression with contradictory results [Opmeer et al., 2010]. Executive function has also been consistently associated with functional variants in the COMT gene [Egan et al., 2001; Nolan et al., 2004; Meyer-Lindenberg et al., 2006; Roussos et al., 2008].

COMT is responsible for eliminating dopamine from the synaptic cleft in the prefrontal cortex (PFC) due to the lack of dopamine transporter in this region [Chen et al., 2004]. The common functional polymorphism of COMT gene, the $Val^{158}/^{108}Met$ has been shown to affect enzyme activity and consequently intrasynaptic dopamine content. The Val allele is associated with 40% higher enzymatic activity in the human brain compared to the Met allele, leading to more efficient elimination of dopamine from the synaptic cleft, hence possession of the Val/Val genotype is associated with a lower level of synaptic dopamine in the PFC [Chen et al., 2004; Meyer-Lindenberg et al., 2005], and in turn more active striatal dopamine neurotransmission [Bilder et al., 2004; Meyer-Lindenberg et al., 2005; Tunbridge et al., 2006]. However, the COMT gene is complex and there is accumulating evidence showing that individual alleles have nonlinear effects on enzyme activity and their precise effect depends on other

genetic and environmental components [Akil et al., 2003; Bray et al., 2003; Chen et al., 2004; Craddock et al., 2006; Meyer-Lindenberg and Weinberger, 2006; Meyer-Lindenberg et al., 2006; Ursini et al., 2011]. Variations in the promoter two regions, which controls the transcription of the membrane bound, brain dominant form of COMT, and other synonymous and non-synonymous polymorphisms throughout the gene have functional effects on enzyme activity [Chen et al., 2004; Nackley et al., 2006]. Thus, it is necessary to investigate several polymorphisms in the COMT gene, for example, through haplotype tagging.

COMT activity related changes in dopaminergic neurotransmission are critical for modulating cognitive functions subserved by the PFC, such as working memory, executive functions [Sawaguchi, 2000; Tunbridge et al., 2006], cognitive flexibility [Nolan et al., 2004] and behavioral inhibition [Congdon and Canli, 2008] that have all been associated with impulsivity in previous studies [Peters and Buchel, 2011]. The COMT $Val^{158}/^{108}Met$ polymorphism was found to be associated with performance on delay discounting or immediate reward bias tasks in two studies, although both studies were small ($n = 19$ and $n = 68$, respectively) and had contradictory results: the risk variant was the Val/Val genotype in the immediate reward bias [Boettiger et al., 2007] but the Met/Met genotype in the delay discounting task [Paloyelis et al., 2010]. Despite the accumulating evidence that COMT may be associated with impulsivity, direct measures have not been investigated in large population cohort studies until now.

By contrast, there is extensive research concerning the association of COMT and a range of neuropsychiatric disorders such as ADHD, obsessive-compulsive disorder, addiction, antisocial behavior, aggression, suicidal behavior, anxiety, schizophrenia, and affective disorders [Schumann et al., 2010], although with conflicting results [Serretti et al., 2006; Wray et al., 2008; Zalsman et al., 2008]. Thus, an investigation of an intermediate phenotype, such as impulsivity or executive function, is of potential importance in understanding the relationship between COMT variants and neuropsychiatric disorders.

Our aim was to investigate the association between impulsivity and the COMT gene in two independent large population cohorts in order to determine the role of these factors in depression. In addition, we investigated the association of COMT with executive function and behavioral inhibition in a smaller interviewed cohort. We hypothesized that the less active COMT haplotype would decrease impulsivity and improve task performance regarding executive function and behavioral inhibition, and their complex interplay would modulate the degree of depression. Namely, impulsivity would be risk factor for depression while better executive function would be protective.

METHODS

Subjects

Subjects aged 18–60 years were recruited for the NewMood study (New Molecules in Mood Disorders, Sixth Framework Program of the EU, LSHM-CT-2004-503474) in Greater Manchester, UK (http://www.medicine.manchester.ac.uk/mentalhealth/newmood/) and a replication sample in Budapest, Hungary.

Details of recruitment strategies and responses have been published previously [Juhasz et al., 2009a]. In short, all subjects answered the NewMood questionnaire pack, English or Hungarian version as appropriate, and provided DNA by using a genetic saliva sampling kit. From the present study, we excluded those reporting manic or hypomanic episodes, psychotic symptoms, obsessive–compulsive disorder and those of non-Caucasian origin, but we did not exclude those with a self-reported history of depression or any other anxiety disorder, or substance misuse.

In Manchester, at a second level of NewMood, a subset of the population sample ($n = 145$) and new recruits ($n = 119$) were invited for a face-to-face diagnostic interview and computerized task session (interviewed Manchester cohort, L2). We used the same exclusion and inclusion criteria as above but we also excluded from the analysis subjects who had current major depressive disorder or anxiety disorder to exclude state effect on task performance, so the final sample consisted of $n = 207$ subjects. In the interviewed population, 17 remitted depressed subjects were medicated (2 SNRI, 11 SSRI and 4 TCA). However, as the task performance was not significantly different in the medicated and un-medicated subjects we have not excluded them from the genetic analysis.

The design of the study can be seen in the Supplementary Fig. S1. The studies were approved by the local Ethics Committees and were carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent before participating in the study.

Questionnaires and Tasks

The NewMood booklet included questions covering background information (age, ethnicity, and family circumstances), personal and family psychiatric history and questionnaires covering current mood and anxiety, personality, life events and childhood trauma. To minimize the time to complete the booklet, brief standard and validated questionnaires were used. Description of questionnaires has been published previously [Juhasz et al., 2009a,b, 2010, 2011; Mekli et al., 2010].

In NewMood to measure personality we used scales based on the five-factor personality model, because a previous metaanalysis suggested stronger genetic influence on these parameters than on the three-factor model [Sen et al., 2004]. For brevity, neuroticism was assessed by the Big Five Inventory (BFI-44) neuroticism items [John, 1999]. As it does not cover impulsivity explicitly, we added and analysed impulsivity subscale data from the Eysenck's Impulsivity, Venturesomeness and Empathy Questionnaire [Eysenck and Eysenck, 1978]. Depressive symptoms were measured using the depression items, plus the additional items, from the Brief Symptom Inventory (BSI) [Derogatis and Melisaratos, 1983]. A continuous weighted score (sum of item scores divided by the number of items completed) was calculated for each variable mentioned above. Reported lifetime depression was derived from the background questionnaire [Juhasz et al., 2011].

Subjects at the second level of the study filled out an extended and more detailed five-factor personality questionnaire, namely the NEO PI-R [Costa and McCrae, 1992]. The neuroticism subscale

and the neuroticism subscale impulsivity facet scores were used for this study. To asses the participants' current and lifetime psychiatric disorders we used the Structured Clinical Interview for DSM-IV (SCID) [First et al., 2002]. Mood symptoms were determined by the BSI [Derogatis and Melisaratos, 1983], and also rated by trained investigators using the Montgomery Asberg Depression Rating Scale [Montgomery and Asberg, 1979].

To selectively investigate motor impulsivity and planning our subjects completed two computerized tasks. The frequently used and short Stop task measured the participants' ability to inhibit prepotent behavioral responses [Logan and Davis, 1984]. Detailed description of the task can be seen in the Supplementary Document. In short, subjects were instructed to perform a go task, pressing the spacebar when they see a picture of a plane. Occasionally, the go stimulus was followed by a stop signal (a bomb, 300 ms latency), in which case the subjects had to withhold the response. Stop signal reaction times (SSRT) were calculated [Eagle et al., 2008] and analyzed. In addition, we used the Stocking of Cambridge task, which is a spatial planning test (Cambridge Cognition Ltd, http://www.camcog.com) and gives a measure of frontal lobe executive function. The subjects were shown two displays of three coloured balls held in pockets or "stockings". The subjects had to move the balls in the lower display to match the pattern shown in the upper display. The initial thinking time of Stocking of Cambridge (SOC-ITT) and the percentage of correctly solved problems (SOC%) in the specified minimum number of moves was used for the analysis.

Genotyping

Buccal mucosa cells were collected using a cytology brush (Cytobrush plus C0012, Durbin PLC) and 15 ml plastic tube containing 2.0 ml of collection buffer. Genomic DNA was extracted according to a published protocol [Freeman et al., 2003]. The HaploView software package (http://www.broad.mit.edu/personal/jcbarret/haploview/) was employed to identify haplotype tag SNPs (htSNP), according to Gabriel et al.'s method [Barrett, 2002; Gabriel et al., 2002], based on the CEPH population data of the International HapMap Project (http://www.hapmap.org, Phase I. June 2005). The chosen SNPs were genotyped using the Sequenom® MassARRAY technology (Sequenom®, San Diego). The Iplex™ assay was followed according to manufacturers instructions (http://www.sequenom.com) using 25 ng of DNA. Genotyping was blinded with regard to phenotype. All laboratory work was performed under the ISO 9001:2000 quality management requirements.

Statistical Analysis

HelixTreeTM 6.4.3 (Golden Helix, Inc., Bozeman, MT, http://www.goldenhelix.com/) software was used to analyze genetic data (Hardy–Weinberg Equilibrium, linkage disequilibrium, allelic and haplotypic association). For haplotypic association analysis, we used haplotype trend regression. Only haplotypes with a frequency greater than 5% were used in the analysis. In all cases, data were adjusted for age and sex. We used a linear or logistic regression model in HelixTree to identify variance in the dependent variable explained by age and sex (the "reduced model"). We then used a variance ratio *F*-test to determine whether adding haplotype frequencies to the model (the "full model") explained significantly more variance than the reduced model. To remove the influence of multiple testing we used a permutation test, randomly grouping the sample 1,000×. We used the same method for allelic association. For the discovery-sample (Manchester) Bonferroni correction was used to correct for the number of tested phenotypes. For the replication samples (Budapest, Interviewed population) nominal $P < 0.05$ and concordant direction of effect was the criteria for significance.

Other statistical analysis was performed with SPSS 15.0 for Windows. All statistical testing used two-tailed $P < 0.05$ threshold. AMOS 7.0.0 software was used for structural equation modelling (SEM), which can be used to test the goodness of fit of a prehypothesised model that was built up based on expert knowledge. In the model, observed (measured) variables are depicted with rectangles while unobserved latent variables are depicted with ovals. To improve the model, modification indices were used (Byrne, 2001). We report three fit indices that describe the quality of the model: the minimum value of the discrepancy function between the sample covariance matrix and the estimated covariance matrix (CMIN) with df (CMIN/df ratio $\leq$2 values indicate acceptable models and CMIN/df ratio $\leq$1 values indicate good models), the comparative fit index (CFI; values $\geq$0.95 are considered good) and the root mean square error of approximation (RMSEA; good models have values of $\leq$0.05) [Byrne, 2001].

RESULTS

Detailed description of the study populations are shown in Table I. It has to be mentioned that the Manchester population were slightly older, reported significantly more lifetime psychiatric disorders and more impulsivity, neuroticism and depressive symptoms.

Genetic Markers

The selected four haplotype tagging SNPs (rs933271, rs740603, rs4680, and rs4646316, Fig. 1) correspond to the haplotype structure of the European population capturing the promoter one and two regions, the coding region and the 3′ end [Mukherjee et al., 2008] together with the most investigated functional variant of the COMT gene, the Val^{108}/^{158}Met polymorphism (rs4680). All SNPs are in modest LD and in Hardy–Weinberg equilibrium (Supplementary Table S1 and S2).

Association Results in the Population Cohorts

Haplotype tagging SNPs did not show significant allelic association with impulsivity, neuroticism, depressive symptoms or reported depression in the Manchester, Budapest or combined population cohorts (data not shown).

In the Manchester cohort, haplotype trend regression was significant for impulsivity ($p_{perm} = 0.003$) but not for the other phenotypes (neuroticism $p_{perm} = 0.142$; depressive symptoms $p_{perm} = 0.325$; self-reported depression $p_{perm} = 0.760$; Table II). The association between COMT gene and impulsivity remained

TABLE I. Details of the Three Investigated Populations

	Level 1		Level 2
	Manchester	Budapest	Interviewed population
Number	1,267	942	207
Female (%)	70	71	69
Male (%)	30	29	3
Age (mean ± SEM)*	34 ± 0.3	31 ± 0.3	32 ± 0.7
Impulsivity (mean ± SEM)*	0.37 ± 0.007[a]	0.30 ± 0.007[a]	17.17 ± 0.33[d]
Neuroticism (mean ± SEM)*	3.30 ± 0.025[b]	2.79 ± 0.026[b]	90.17 ± 1.87[e]
Depressive symptoms (mean ± SEM)*	1.00 ± 0.027[c]	0.52 ± 0.020[c]	2.44 ± 0.20[f]
Reported lifetime psychiatric disorder			
Depression* (%)	53	19	49[g]
Recurrent depression* (%)	41	13	35
Suicide attempt* (%)	15	4	11
Anxiety* (%)	28	18	17
Drug or alcohol problem* (%)	7	2	2
SOC% (mean ± SEM)			0.74 ± 0.01
SOC-ITT (ms,mean ± SEM)			5573.52 ± 317.26
SSRT (ms, mean ± SEM)			199.06 ± 10.29

BFI, Big Five Inventory; BSI, Brief Symptom Inventory; IVE, Eysenck's Impulsivity, Venturesomeness and Empathy Questionnaire; MADRS, Montgomery Asberg Depression Rating Scale; NEO-PI-R, NEO Personality Inventory Revised; SCID, Structured Clinical Interview for DSM-IV; SOC, Stocking of Cambridge task; SOC-ITT, initial thinking time of SOC; SOC%, percentage of correctly solved problems in the specified minimum number of moves in SOC; SSRT, Stop signal reaction times of the Stop task.
For comparison purposes, data of excluded subjects can be seen in Supplementary Table S7.
[a]IVE impulsivity subscale.
[b]BFI neuroticism subscale.
[c]BSI depression plus additive items score.
[d]NEO-PI-R neuroticism impulsivity facet.
[e]NEO-PI-R neuroticism subscale.
[f]MADRS.
[g]SCID.
*Significant difference between the Manchester and Budapest population at $P < 0.001$ level (univariate ANOVA for the continuous variables and Chi^2-test for the nominal variables).

significant even after Bonferroni correction for the four tested phenotypes ($P < 0.0125$). COMT haplotypes explained 1.29% variance in impulsivity and the T,G,$G^{(V)}$,C haplotype showed significant preventive effect ($P = 0.001$; Table III).

In the replication Budapest cohort, the haplotype trend regression was significant for impulsivity ($p_{perm} = 0.038$) supporting the finding in the Manchester cohort, although it did not survive correction for multiple testing. In addition, significant association was seen for depressive symptoms ($p_{perm} = 0.008$; Table II and Fig. 2), but not for neuroticism ($p_{perm} = 0.221$) or reported depression ($p_{perm} = 0.772$; Table II). COMT haplotypes explained 1.19% variance in impulsivity and C,G,$A^{(M)}$,C was a significant risk haplotype ($P = 0.002$; Table III). However, in depressive symptoms COMT haplotypes explained 1.64% variance with the T,G,$G^{(V)}$,C haplotype being the risk variant ($P = 0.001$), which is the opposite direction of effect compared to impulsivity (Table IV).

Figure 2 demonstrates that the haplotypes have similar direction of effects on impulsivity in both populations. Indeed, analysis of the combined sample shows significant haplotypic association between COMT and impulsivity ($p_{perm} = 0.006$). In the combined populations, COMT haplotypes were no longer associated with depressive symptoms ($p_{perm} = 0.647$), neuroticism ($p_{perm} = 0.867$) or reported depression ($p_{perm} = 0.848$; Table II).

FIG. 1. Schematic figure of the COMT gene and the genotyped SNPs according to the University of California at Santa Cruz Browser (http://genome.ucsc.edu/). black line: introns; white boxes: exons; gray boxes: promoters and 3′ end.

Impulsivity, COMT And Depression

Next, we investigated the relationship between impulsivity and depression related phenotypes. Subjects who reported lifetime history of depression scored significantly higher on impulsivity both in the Manchester ($F = 48.36$, df = 1,1264, $P < 0.001$; $n_{depr} = 674$, $n_{co} = 593$) and Budapest (**$F = 7.56$, df = 1,938, $P = 0.006$; $n_{depr} = 182$, $n_{co} = 760$) samples, and impulsivity showed positive correlation with neuroticism (Manchester: Pearson $R = 0.25$, $P < 0.001$; Budapest: Pearson $R = 0.30$, $P < 0.001$) and depressive

TABLE II. Global Haplotypic Association With the Different Phenotypes in the Population Cohorts

	Manchester				Budapest				Combined			
Full vs. reduced model	**F**	**df**	***P***	**p (perm)**	**F**	**df**	***P***	**p (perm)**	**F**	**df**	***P***	**p (perm)**
Impulsivity	3.416	7, 2	0.005	0.003*	2.275	7, 2	0.045	0.038	3.066	7, 2	0.009	0.006*
Neuroticism	1.670	7, 2	0.139	0.142	1.431	7, 2	0.210	0.221	0.390	7, 2	0.856	0.867
Depressive symptoms	1.178	7, 2	0.318	0.325	3.104	7, 2	0.009	0.008*	0.671	7, 2	0.646	0.647

	Manchester				Budapest				Combined			
Full vs. reduced model	**Chi square**	**df**	***P***	**p (perm)**	**Chi square**	**df**	***P***	**p (perm)**	**Chi square**	**df**	***P***	**p (perm)**
Rreported depression	2.489	7, 2	0.778	0.76	2.627	7, 2	0.757	0.772	2.091	7, 2	0.836	0.848

Age and sex were covariate in all calculations. Linear and logistic haplotype trend regression analysis as implemented in HelixTreeTM 6.4.3 (Golden Helix) software was used to calculate associations.
*P value, which survived Bonferroni correction for multiple testing.

symptoms (Manchester: Pearson R = 0.32, $P < 0.001$; Budapest: Pearson R = 0.23, $P < 0.001$). Correlation data for the different phenotypes in the different cohorts can be seen in Supplementary Table S3.

Based on these data, the genetic association results and the previous literature we developed a preliminary SEM model and tested it in the combined cohort. Complete data were available for n = 2,193 subjects. We hypothesized that impulsivity would increase neuroticism and, through this, depressive symptoms and reported depression. The basic model can be seen in Supplementary Figure S2A. Based on modification indices we added four paths to our original model: covariation between (step 1) reported depression and neuroticism, (step 2) depressive symptoms and impulsivity, (step 3) reported depression and impulsivity, and (step 4) reported depression and COMT. The model fit data for these models are reported in Supplementary Table S4A. The best-fit model (CMIN = 6.905, df = 7, CMIN/df = 0.986, CFI = 1.000, RMSEA < 0.001) can be seen in Figure 3. The model explained 35% of the variance (R^2) in depressive symptoms and 19% in reported depression. This model showed reasonable good fit when the two population cohorts were tested separately (Budapest: CMIN = 8.596, df = 7, CMIN/df = 1.228, CFI = 0.997, RMSEA = 0.016; Manchester: CMIN = 10.845, df = 7, CMIN/df = 1.549, CFI = 0.997, RMSEA = 0.021).

To further investigate, the possible intermediate phenotypes between COMT, impulsivity and depression we used a behavioral inhibition (Stop) task and an executive function (SOC) task to probe frontal lobe function in the second level of this study.

Association With Tasks

The only nominally significant allelic association can be seen between SOC% and rs933271 C allele ($p_{perm} = 0.036$). SOC% also shown significant association with the COMT gene in the haplotype trend regression ($p_{perm} = 0.028$, explained variance 5.98%; Table IV). Although this association did not survive Bonferroni correction and none of the haplotypes were significantly associated with SOC% alone, it is intriguing that the haplotypes that increased impulsivity in the Manchester and Budapest samples were associated with decreased performance on this task (Fig. 2).

TABLE III. Specific Haplotype Effects in the Haplotypic Association With Impulsivity in the Population Cohorts

Haplotype Regression	Manchester				Budapest				Combined			
Regressor	**Frequency (%)**	**B**	**t**	***P***	**Frequency (%)**	**B**	**t**	***P***	**Frequency (%)**	**B**	**t**	***P***
T,A,A$^{(M)}$,C	30.86	−0.044	−1.490	0.136	31.86	0.042	1.438	0.151	31.29	−0.005	−0.245	0.807
T,G,G$^{(V)}$,C	17.70	−0.127	−3.361	0.001	16.63	0.075	1.686	0.092	17.30	−0.042	−1.441	0.144
C,G,A$^{(M)}$,C	12.80	0.039	0.706	0.480	10.32	0.184	3.134	0.002	11.79	0.112	2.722	0.007
T,G,G$^{(V)}$,T	11.26	0.054	1.236	0.214	11.78	0.047	0.974	0.330	11.44	0.050	1.517	0.126
T,A,G$^{(V)}$,T	5.23	−0.054	−0.516	0.606	5.61	0.119	1.393	0.164	5.33	0.038	0.563	0.573
Rare	22.15				23.79				22.85			
	p (full vs. reduced model)			0.005				0.045				0.009
	p (permutated)			0.003				0.038				0.006

Age and sex were covariate in all calculations and the order of the htSNPs in the haplotypes corresponds to the SNP order in Figure 1.

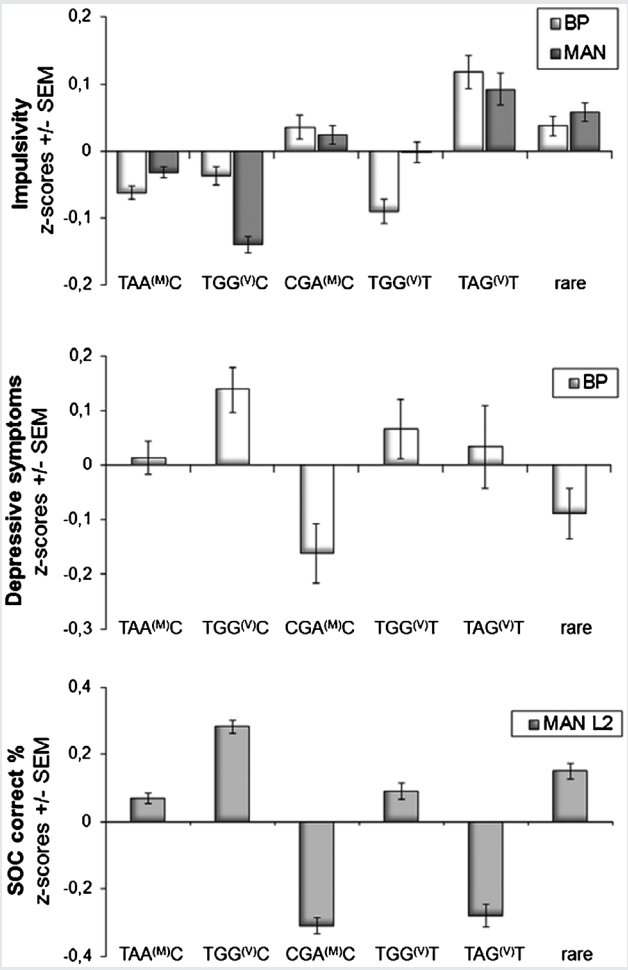

FIG. 2. Nominally significant haplotypic effect on impulsivity in both population cohorts (BP, MAN), on depressive symptoms (Brief Symptom Inventory) in the Budapest cohort, and on the SOC task in the interviewed Manchester cohort (MAN L2). For demonstration purposes, haplotypes have been assigned to participants where the expectation maximisation (EM) was greater than 70% (Manchester (MAN): n = 949; Budapest (BP): n = 640; Interviewed sample: n = 161). Next z-scores ± standard errors of mean (SEM) were calculated for each haplotype group. Age and sex were covariate in all calculations. The order of the htSNPs in the haplotypes corresponds to the SNP order in Figure 1. SOC, Stocking of Cambridge task; SOC correct %: percentage of correctly solved problems in the specified minimum number of moves in SOC

Our study did not support significant allelic or global haplotypic association between COMT gene and SOC-ITT ($p_{perm} = 0.197$) or SSRT ($p_{perm} = 0.754$; Table V).

Executive Function, Impulsivity and Depression

Finally, we investigated the relationship between task performance, impulsivity and depression. In the interviewed population remitted depressed subjects scored higher on the NEO-PI-R neuroticism impulsivity facet (**F = 7.25, df = 1,200, $P = 0.008$; $n_{depr} = 101$, $n_{co} = 106$) suggesting that increased impulsivity may be a trait marker for major depression. However, performance on the SOC and Stop tasks was independent of diagnosis (SOC-ITT: **F = 0.43, df = 1,188, $P = 0.51$; SOC%: F = 0.03, df = 1,188, $P = 0.87$; SSRT: %: F = 0.56, df = 1,173, $P = 0.45$) suggesting that these are not trait markers for major depression.

NEO-PI-R neuroticism impulsivity facet and Eysenck's Impulsivity scale show a significant correlation in those who provided both data (n = 113, Pearson R = 0.48, $P < 0.001$). In this subgroup, Eysenck's Impulsivity scale did not show significant correlation with SOC or Stop tasks performance. However, in a bigger sample, NEO-PI-R neuroticism impulsivity facet and SOC-ITT were significantly negatively correlated (n = 190, Pearson R = −0.22, $P = 0.003$), while the SOC% and SSRT were not correlated significantly with this measure of impulsivity. SOC-ITT was also correlated with SOC% (n = 192, Pearson R = 0.18, $P = 0.014$). Correlation data for the different phenotypes can be seen in Supplementary Table S5.

Based on these observations, we adapted the population cohort SEM model to investigate the relationship between executive function, impulsivity and depression. Complete data were available for n = 189 subjects. We hypothesised that impulsivity would increase neuroticism and, through this, the more objective interviewer rated depressive symptoms and lifetime depression diagnosis, similarly as in the population cohort model. Interviewer rated depressive symptoms and self reported depressive symptoms are directly related in our model. In addition, we hypothesised that executive function will be inversely related to impulsivity and both impulsivity and executive function are being influenced by the COMT gene (basic model, Supplementary Fig. S2B). We omitted SSRT because it did not show association with any other investigated phenotype. At the first step, we removed all co-variations that were non-significant. In the second step, co-variation between self-reported depressive symptoms and neuroticism, and self-reported depressive symptoms and SOC% were added based on modification indices. The model fit data for these models are reported in Supplementary Table S4B. In summary, in the best-fit model (CMIN = 21.433, df = 26, CMIN/df = 0.824, CFI = 1.000, RMSEA < 0.001; Fig. 4) impulsivity no longer co-varied with depressive symptoms and major depression diagnosis (MDD) but executive function (SOC correct %) positively correlated with self-reported depressive symptoms. The model explained 20% of the variance (R^2) in self-reported depressive symptoms, 29% in interviewer rated depressive symptoms and 16% in MDD diagnosis.

DISCUSSION

The main finding of our study is that haplotypic variants in the COMT gene are associated with impulsivity, measured by the Eysenck's impulsivity scale, in a combined European population cohort from Manchester and Budapest. The significance survived correction for multiple testing in the Manchester cohort, but not in the Budapest cohort, and this disparity could perhaps be explained by differences in the populations—the Manchester cohort had significantly more lifetime depression, psychiatric morbidity,

TABLE IV. Specific Haplotype Effects in the Haplotypic Association With Depressive Symptoms (BSI) in the Budapest Cohort, and on the SOC Task in the Interviewed Manchester Cohort

Haplotype regression	Depression score (BSI) Budapest				SOC correct (%) Interviewed sample			
Regressor	Frequency (%)	B	t	*P*	Frequency (%)	Beta	t	*P*
T.A.A$^{(M)}$.C	31.86	0.076	0.855	0.393	32.30	0.050	0.991	0.323
T.G.G$^{(V)}$.C	16.63	0.437	3.237	0.001	17.63	0.081	1.465	0.144
C.G.A$^{(M)}$.C	10.32	−0.190	−1.070	0.282	11.34	−0.091	−0.876	0.382
T.G.G$^{(V)}$.T	11.78	−0.011	−0.074	0.941	11.44	0.133	1.891	0.060
T.A.G$^{(V)}$.T	5.61	0.310	1.192	0.232	6.85	−0.149	−1.599	0.112
rare	23.79				20.45			
	p (full vs. reduced model)			0.009	p (full vs. reduced model)			0.034
	p (permutated)			0.008	p (permutated)			0.028

BSI, Brief Symptom Inventory; SOC, Stocking of Cambridge task; SOC%, percentage of correctly solved problems in the specified minimum number of moves in SOC. Age and sex were covariate in all calculations and the order of the htSNPs in the haplotypes corresponds to the SNP order in Figure 1.

and higher impulsivity scores. Despite these differences the effect of the haplotypes showed concordant direction in both populations. Furthermore, based on these cohorts plus a study with interviewed subjects, we demonstrated that self-reported impulsivity is a possible trait marker for depression, but also shows positive correlation with state dependent depressive symptoms, extending findings from previous, relatively small, studies [Corruble et al., 1999, 2003; Peluso et al., 2007; Strakowski et al., 2010].

Although, impulsivity is a core feature of mood disorders, it is a multidimensional and complex trait, difficult to define and measure. It has been suggested that depression is associated with the non-planning aspect of impulsivity [Corruble et al., 2003; Swann et al., 2008], consistent with the questions in Eysenck's impulsivity questionnaire reflecting non-planned actions [Whiteside and Lynam, 2001]. In addition, the NEO-PI-R impulsivity facet, that measure urgency rather than non-planning impulsivity, showed a negative correlation with initial thinking time on the SOC task suggesting that it partially overlaps the non-planning components of impulsivity. It is important to note that neither Eysenck's impulsivity questionnaire (similarly to our previous finding [Horn et al., 2003]) nor NEO-PI-R impulsivity facet show correlation with the Stop task, which is the most frequently used state dependent motor impulsivity measure and has been related to the manic phase of bipolar disorder [Swann et al., 2008].

Despite the apparent relationship between impulsivity and depression, the association between these phenotypes and COMT is not straightforward but rather a complex interplay with other factors. Using structural equation modelling, we found that COMT and impulsivity acted both independently and through neuroticism to increase the risk of depression. In addition, consistent with previous proposals that the COMT gene is associated with cognitive function [Akil et al., 2003; Egan et al., 2001; Tunbridge et al., 2006], we found a nominal haplotypic association with a measure of executive function (the percentage of correctly solved problems on the SOC task). Previously, it has been demonstrated that COMT haplotypes influence the prefrontal cortical response during working memory task [Meyer-Lindenberg et al., 2006] and verbal inhibition in children [Barnett et al., 2009]. As expected (based on the results from previous studies), the pattern of haplotypic effect on SOC% was opposite of that associated with impulsivity. Thus, the finding that executive function positively correlated with depressive symptoms in our second model (Fig. 4) is not straightforward to explain. One possibility discussed further below is that high executive function could be linked to cognitive inflexibility and represents a risk factor for depression. In summary, our second model suggests that both optimal and non-optimal COMT function can exert effects on susceptibility to depression making it difficult to distinguish between risk and no-risk genetic variants.

As discussed in Introduction Section, COMT is required in the PFC to eliminate dopamine (DA) from the synaptic cleft; thus playing an important role in controlling DA levels [Chen et al., 2004]. PFC DA level is hypothesised to have a dual action on cognition according to the tonic-phasic DA model hypothesis: tonic DA signalling, primarily via D_1 receptors, maintains stability by preventing uncontrolled, spontaneous switches, while phasic DA signalling, via D_2 receptors, promotes flexibility by constantly updating novel relevant information [Bilder et al., 2004; Winterer and Weinberger, 2004; Cools and D'Esposito, 2011]. According to the hypothesis, PFC D_1 receptors exert their effects by a negative feedback control of striatal DA level, which is especially important as increased striatal DA signalling plays a crucial role in human impulsivity [Buckholtz et al., 2010; Colzato et al., 2010]. As impulsivity represents extreme flexibility and distractibility, whereas good performance on executive function task requires stability and non-distractibility, our results showing opposite haplotypic effect on impulsivity and SOC% are consistent with this hypothesis. Thus more active COMT gene variants are hypothesised to decrease PFC DA level and enhance impulsivity, while less active variants should increase PFC DA level and improve executive function [Nolan et al., 2010a,b; Rosa et al., 2010].

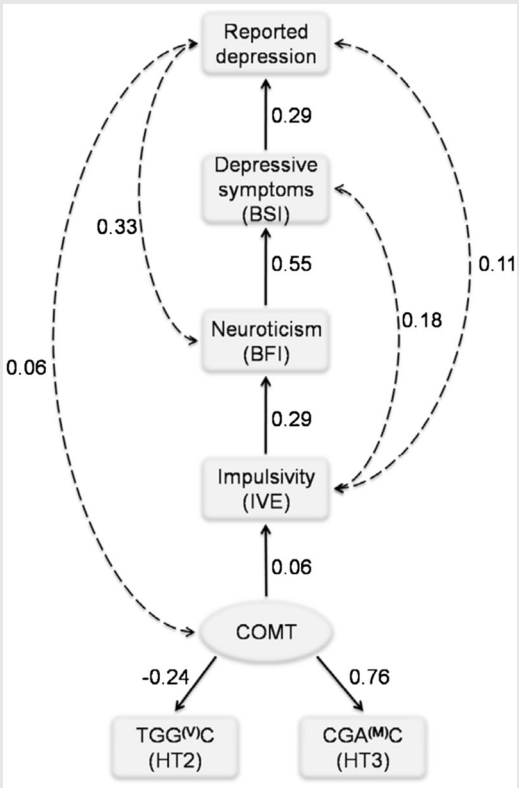

FIG. 3. Best-fit structural equation model for the population cohort study. Based on our genetic association results and the scientific literature we draw a preliminary structural equation model using the combined dataset that contained two genetic variables (T,G,G$^{(V)}$,C and C,G,A$^{(M)}$,C haplotypes), impulsivity, neuroticism, depressive symptoms, and reported depression, and their relationship as it can be seen in this figure with four exceptions: Reported depression covaried significantly with neuroticism, with COMT and with impulsivity, and depressive symptoms with impulsivity so we added these significant paths based on modification indices. One-headed arrows with numbers represent standardised regression coefficients. Two-headed arrows and numbers represent correlation coefficients. Observed variables are depicted in rectangles and latent variables in ovals. All variables have estimated residual variance not shown in the figure. Reported depression based on the background questionnaire and was validated in our previous study [Juhasz et al., 2011]; BFI, Big Five Inventory; BSI, Brief Symptom Inventory; IVE, Eysenck's Impulsivity, Venturesomeness and Empathy Questionnaire.

TABLE V. Global Haplotypic Association With the Tasks in the Manchester Interviewed Sample

	Interviewed sample			
Full vs. reduced model	F	df	*P*	p (perm)
SOC%	2.468	7, 2	0.034	0.028
SOC-ITT	1.493	7, 2	0.194	0.197
SSRT	0.443	7, 2	0.818	0.754

Age and sex were covariate in all calculations. Linear and logistic haplotype trend regression analysis as implemented in HelixTreeTM 6.4.3 (Golden Helix) software was used to calculate associations.

In apparent contradiction to this interpretation, however, was the lack of association between the Val^{158}/^{108}Met polymorphism of the COMT gene and measures of impulsivity and executive function. Based on in vitro data, this SNP is functional with the Val variant of the protein have 40% higher enzyme activity [Lotta et al., 1995; Chen et al., 2004]. One possible explanation lies in the complexity of the COMT gene [Mukherjee et al., 2008]. In vitro functional studies demonstrated that haplotypes of the COMT gene were associated with stronger functional effect than the Val^{158}/^{108}Met polymorphism alone, possibly by influencing mRNA stability and thus enzyme synthesis. In addition, the most active and the less active haplotypes both carried the Val allele of the Val^{158}/^{108}Met polymorphism with the Met allele carriers represented an intermediate phenotype. This pattern suggests that polymorphism within the haplotype functionally interact with each other [Nackley et al., 2006], which is in line with our results. The conflicting results regarding COMT gene effects can be explained by an inverted U-shape model, which suggests that both sub- and super-optimal PFC DA levels impair PFC function [Goldman-Rakic et al., 2000; Meyer-Lindenberg and Weinberger, 2006; Tunbridge et al., 2006]. Combinations of genetic variants throughout the COMT gene may well result in an evenly distributed COMT function on this inverted U-shape model, making it difficult to identify the effect of any individual SNP.

As discussed above, it appears at first sight counter intuitive that executive function (SOC%) showed a positive correlation with depressive symptoms, and also that the haplotypic association between COMT and depressive symptoms in the Budapest population showed a similar pattern for SOC% but not for impulsivity. One possibility is that cognitive stability might reduce the ability to flexibly disengage from negative emotions, thus genetic variants advantageous for executive function may represent risk factors for mood disorders [Smolka et al., 2005; Drabant et al., 2006; Yacubian et al., 2007; Mier et al., 2010; Juhasz et al., 2011]. However, it is important to note that most of these genetic studies investigated healthy volunteers similar to our second model, which was based on healthy and remitted depressed subjects, and to the Budapest cohort, which reported much less depression (19%) than the Manchester cohort (53%). As depression is a polygenic multifactorial disorder, it is possible that other genetic and environmental effects masked the relationship between the COMT gene and depressive symptoms in the Manchester population. Indeed, it was in this population that we did not find haplotypic association between COMT and depressive symptoms ($p_{perm} = 0.325$). In a post hoc analysis in the combined population, after excluding those subjects who reported lifetime depression, the association between COMT haplotypes and depressive symptoms became significant ($n = 1{,}350$, $p_{perm} = 0.017$; Supplementary Table S6), showing the same pattern as SOC%. These results suggest that in patient populations the effect of COMT gene on depression may be masked by widespread disruption in emotion regulation neuronal networks

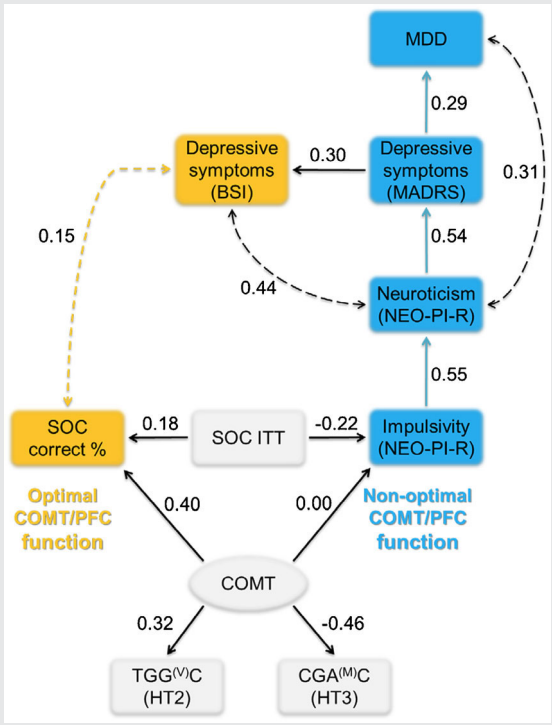

FIG. 4. Best-fit structural equation model for the phenotypic data of the interviewed population. This model is based on the population cohort SEM model but reported depression has been replaced with major depression diagnosis (MDD), for neuroticism and impulsivity measurement NEO-PI-R has been used, and interviewer rated depressive symptoms has been added (MADRS). One-headed arrows with numbers represent standardised regression coefficients. Two-headed arrows and numbers represent correlation coefficients. Observed variables are depicted in rectangles and latent variables in ovals. All variables have estimated residual variance not shown in the figure. Orange shaded figures represent the dominant path in the presence of optimal COMT activity, while blue represents the dominant path in non-optimal situations. BSI, Brief Symptom Inventory; MADRS, Montgomery Asberg Depression Rating Scale; MDD, major depressive disorder based on the Structured Clinical Interview for DSM-IV (SCID); NEO-PI-R, NEO Personality Inventory Revised; SOC, Stocking of Cambridge task; SOC correct %, percentage of correctly solved problems in the specified minimum number of moves in SOC; SOC-ITT, initial thinking time in SOC. Note that the very low standardised regression coefficients between COMT and impulsivity can be explained by the insufficient power in this sample to show genetic effects of COMT on impulsivity (see Supplementary document).

[Johnstone et al., 2007; Phillips et al., 2008; Elliott et al., 2011] or changed by genotype dependent epigenetic processes that selectively modulate the function of the PFC [Ursini et al., 2011]. However, further studies are clearly required to replicate our findings and to test this hypothesis.

Our study has some limitations. First of all, some associations in the replication samples did not survive correction for multiple testing and can therefore only be regarded as provisional. However, adapting a lenient significance threshold during replication with additional criteria, namely the expectation of the concordant direction of effect, might be able to reduce both type-1 and type-2 errors [Sklar et al., 2011]. A second limitation is that we used only four polymorphisms to cover the COMT gene, and it would be desirable to use more variants. Nonetheless, recent studies demonstrated that with these variants we were able to capture those haplotype blocks that are prevalent in the Caucasian population and possibly related to function [Mukherjee et al., 2008]. Another weakness is that the relatively small number of interviewed subjects limited our power to detect a possible association between haplotypes and SOC, which would survive correction for multiple testing, and that our results are constrained by the limited impulsivity measures that we used to cover a complex trait.

In summary, our study showed that genetic variants in the COMT gene are associated with impulsivity, measured by the Eysenck's Impulsivity scale, in a European population cohort from Manchester and Budapest showing concordant direction of effect in both populations. Further investigation suggested that, although impulsivity is an important risk factor for depression, the COMT gene might also exert its influence through its effects on PFC function, possibly through top–down control of emotional information processing. Further, studies are required to investigate the role of COMT gene in depression using intermediate phenotype approach, and modelling the interplay between these phenotypes.

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