Variants in Catechol-O-Methyltranserfase gene are associated with impulsivity and executive function: relevance for major depression

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Introduction

- COMT is important in PFC to eliminate DA from the synaptic cleft(1)
- the Val to Met substitution in COMT results in different enzyme activity(2)
- COMT activity related changes in dopaminergic neurotransmission are critical for modulating cognitive functions subserved by the PFC, such as working memory, executive functions, cognitive flexibility, impulsivity (3)
- impulsivity is a multidimensional personality trait that includes the inability to delay gratification and acting without regard to future consequences
- it is a characteristic of several psychiatric conditions, such as mood disorders, and it has a strong heritable component suggesting that it can be an intermediate phenotype, and important risk factor for major depression(4)
- our aim was to investigate the role of impulsivity and dopaminergic system in depression by analysing cathecol-O-methyltransferase (COMT) gene

Methods

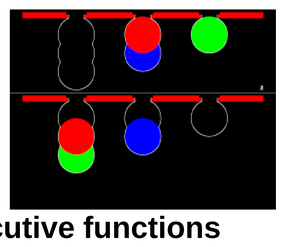
- all participants provided buccal cell DNA and filled out the NewMood booklet consisted standard, validated psychiatric questionnaires

LEVEL1:

- big number of Caucasian participants from Manchester, UK (1267), and Budapest, Hungary (942)
- used questionnaires for MODEL1:
  - *Impulsiveness-Venturesomeness-Empathy Scale (IVE)* for **impulsivity**,
  - *Big 5* neuroticism items for **neuroticism**,
  - *Brief Symptom Invnetory (BSI)* for **depressive symptoms**,
  - *Background questionnaire* for **reported lifetime depression**

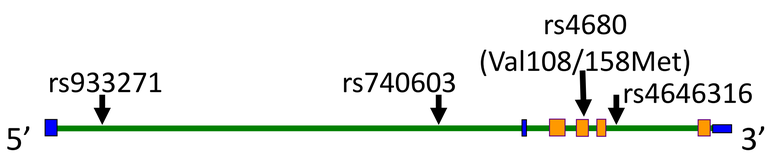
LEVEL2:

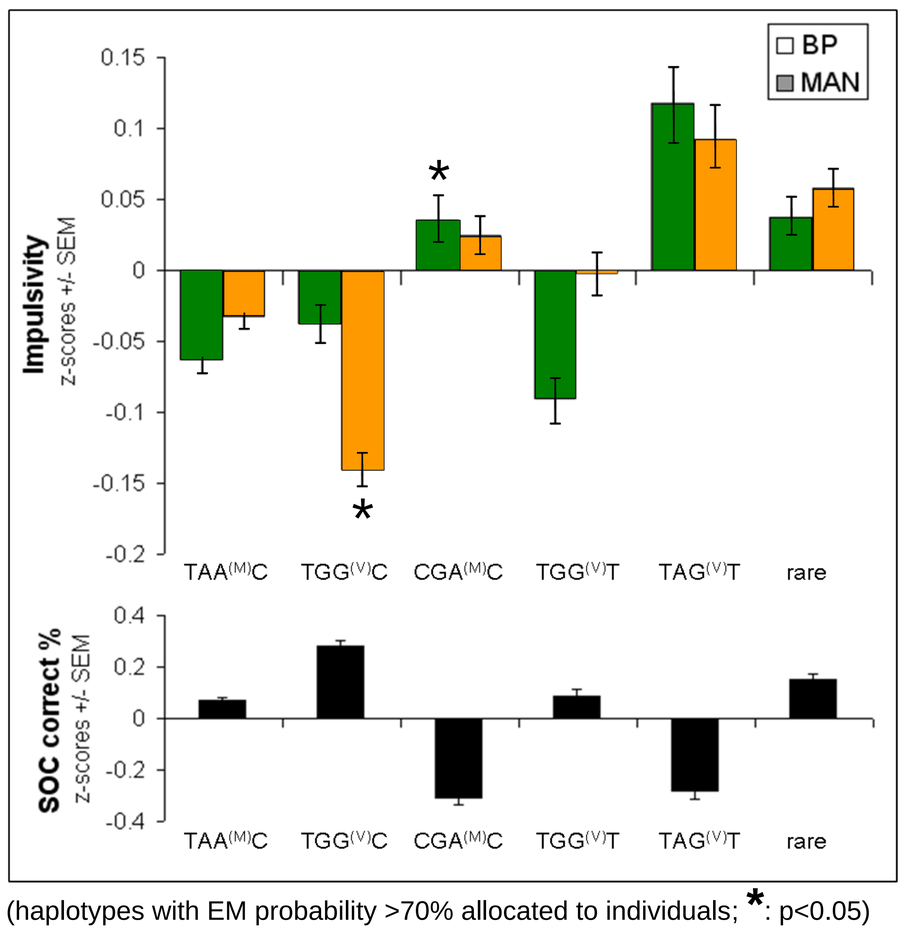
- smaller interviewed Manchester population (207)
- used questionnaires, tasks for MODEL2:
  - *NEO-PI-R* for **neuroticism**,
  - *Stockong of Cambridge (SOC)* spatial planning task for **executive functions**



Results

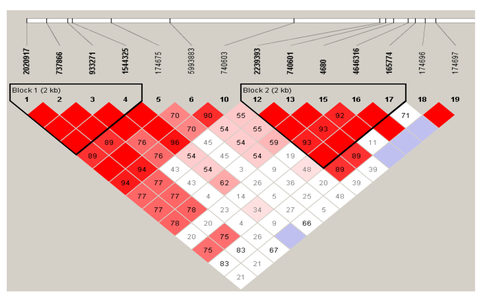
Selected htSNP-s and their location on the COMT gene
(all the SNPs were in Hardy-Weinberg equilibrium in both populations)



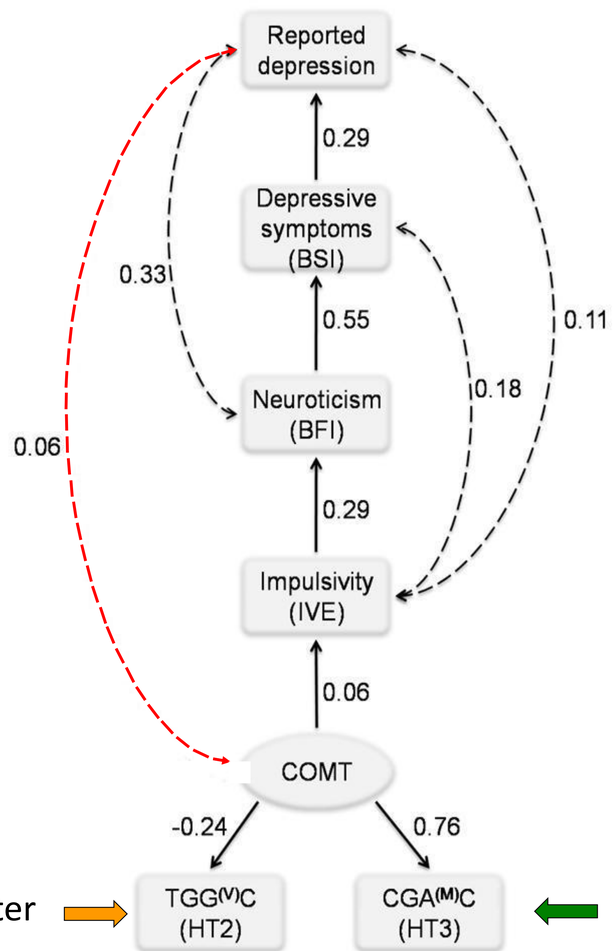


(haplotypes with EM probability >70% allocated to individuals; *: p<0.05)

LD R^2



MODEL 1

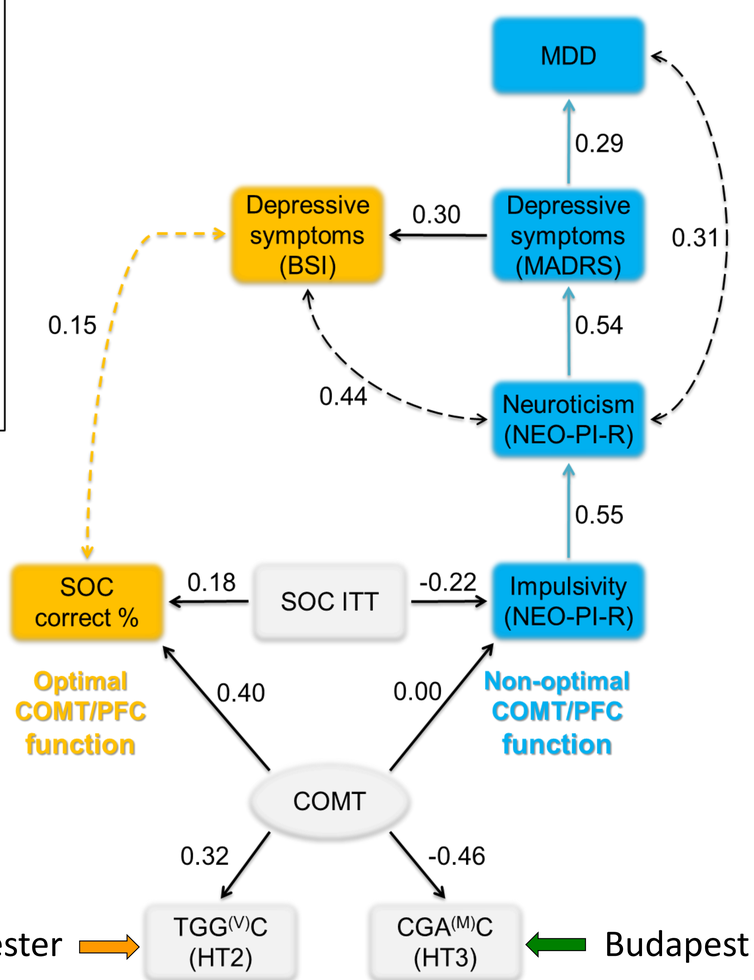


Haplotypic association with impulsivity* in Manchester and Budapest Level1

	Manchester			Budapest		
Regressor	Frequency	B	p	Frequency	B	p
T,A,A(M),C	30.86%	-0.044	0.136	31.86%	0.042	0.151
T,G,G(V),C	17.70%	-0.127	0.001	16.63%	0.075	0.092
C,G,A(M),C	12.80%	0.039	0.480	10.32%	0.184	0.002
T,G,G(V),T	11.26%	0.054	0.214	11.78%	0.047	0.330
T,A,G(V),T	5.23%	-0.054	0.606	5.61%	0.119	0.164
rare	22.15%			23.79%		

(*age and sex were covariates)

MODEL 2



Conclusions

- people with current or lifetime depression scored higher on impulsivity scales, and impulsivity is negatively associated with executive functions
- variations in the COMT gene are significantly associated with self reported impulsivity in two independent European populations
- according to our results self-reported impulsivity is a possible trait marker for depression
- the COMT haplotypic association with impulsivity was in opposite direction to the COMT effect on cognitive function.
- SEM models demonstrated that COMT and impulsivity acted both together, through neuroticism, and also independently, and increase the risk of depression
- these effects were modulated by cognitive function
- these results emphasize how important to investigate intermediate phenotypes in relation to genotypes to interpret their relevance in the development of neuropsychiatric disorders

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