COMT GENOTYPE IN SCHIZOPHRENIA: COGNITIVE PERFORMANCE AND BRAIN CIRCUITS

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BACKGROUND

Dopamine levels In the prefrontal cortex seem to play a crucial role in cognitive functioning in schizophrenia. The functional polymorphism of the COMT (catechol-o-methiltransferase) enzyme could mediate the relationship between dopamine levels, cognitive functioning and neural activity of the prefrontal cortex (1). The val allele results in a high functioning enzyme which degrades dopamine from the synapsis more rapidly than the low functioning enzyme (met allele). The val/val polymorphism should be associated with less dopamine in the prefrontal cortex and therefore with poorer cognitive performance and dysfunctional brain activity in the prefrontal cortex than the met/met polymorphism. Context processing deficits have been shown to be specifically present in schizophrenia and linked to hypofrontality (2). This specific measure of executive functioning should be more related to genetic variations than more general cognitive deficits (3).

GOALS:

1. To investigate the impact of the val158met COMT polymorphism on several neuropsychological and cognitive domains in schizophrenia.
2. To study the impact of the val158met COMT polymorphism on prefrontal cortical function in schizophrenia during context processing tasks.

METHODS

Neuropsychological testing: MATRICS battery

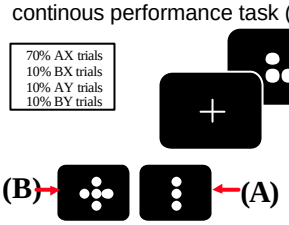
We studied a sample of 68 schizophrenia spectrum disorder patients. Subjects performed several tests of the **MATRICS** Consensus Cognitive Battery to measure the performance in the cognitive domains of speed of processing, working memory, verbal learning and visual learning.

Genotyping for COMT val158met polymorphism was accomplished by PCR-RFLP analysis.

Cognitive testing: DPX Task

36 schizophrenia spectrum disorder patients performed the Dot version of the expectancy AX continous performance task (DPX task).

70% AX trials
10% BX trials
10% AY trials
10% BY trials



Good context processing: few BX errors

Subjects view a series of dot patterns and identify each pattern as a target or non-target. Target: specific dot pattern (X) that follows another specific dot pattern (A). Non-targets: any other stimuli.

Functional Imaging: fMRI

fMRI Acquisition and preprocessing

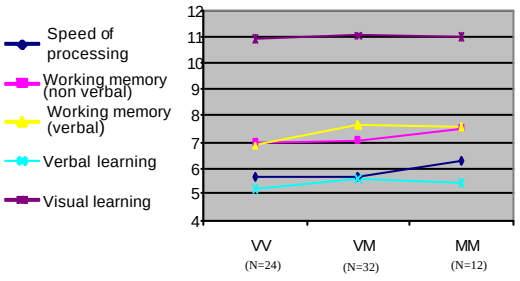
- Preliminary data are shown on 6 controls and 6 val/valpatients
- DPX task during the fMRI (4 blocks, 30 trials/block)
- 3 Tesla TRIO Siemmens scanner with standard head coil
- T2*-weighted EPI scanning, (TR = 2000 ms, 36 axial 3.5 mm thick slices). MPRAGE for each subject.
- Spatial realignement, slice timing, spatial normalization, segmentation, smoothing (8 mm FWHM)

fMRI Analysis

- SPM5
- Contrast of interest: BX vs AX trials
- P < 0,05 (uncorrected)

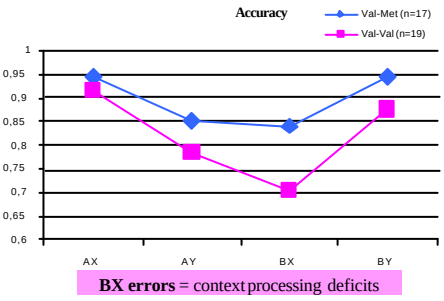
RESULTS

MATRICS BATTERY



Val/val patients performed worse than met/met patients in all the neuropsychological domains.

DPX TASK

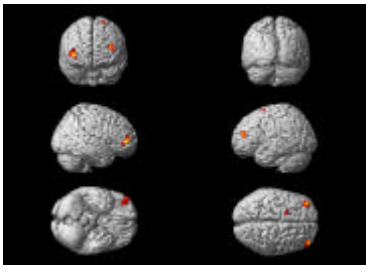


BX errors = context processing deficits

Val/val patients showed a context processing deficit pattern (more errors and slower RT on BX trials) than Val/met and met/met patients.

fMRI

val/val patients showed less bilateral prefrontal activation than controls



CONCLUSIONS

Our results show that the COMT genotype impacts in the neuropsychological and cognitive performance of schizophrenia spectrum patients probably through dopamine availability in the prefrontal cortex. Prefrontal brain activity of context processing deficits in schizophrenia may be mediated by COMT genotype effects. COMT genotype may be relevant to schizophrenia treatment through its involvement in dopamine metabolism.

REFERENCES

1. Alfimova MV, Golimbet VE, Gritsenko IK et al. Interaction of dopamine genes and cognitive functions in patients with schizophrenia and their relatives and in healthy subjects from the general population. Neurosci Behav Physiol 2007;37(7):643-50.

2. MacDonald AW, Carter CS, Kerns JG, Ursu S, Barch DM, Holmes AJ, Stenger VA and Cohen JD. Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. Am J Psychiatry 2005; 162:475-484.

3. MacDonald AW, Flory JD, Carter CS, Ferrell RE and Manuck SB. COMT Val158Met and executive control: a test of the benefit of specific deficits to translational research. Journal of Abnormal Psychology 2007; 116(2):306-312.

AUTHORS DISCLOSURE NO POTENTIAL CONFLICT OF INTEREST