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Influence of catechol-*O*-methyltransferase Val[158]Met polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia

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Abstract

Neurocognitive deficits are recognized as core features of schizophrenia and have a great impact on functional outcome. Recent reports have suggested that a functional polymorphism, Val[158]Met, of the catechol-*O*-methyltransferase (COMT) gene, partially influences cognitive performances (mainly cognitive flexibility and working memory) both in schizophrenic patients and in healthy controls, probably by modulating prefrontal dopamine function. While previous studies focused on single evaluation of cognitive functioning, we aimed to analyse the additive effect of COMT genotype and cognitive exercise on dynamic modulation of cognitive performances. We analysed the COMT Val[158]Met polymorphism in 50 patients with chronic schizophrenia randomly allocated to two treatment conditions for 3 months: standard rehabilitation treatment (SRT) alone and SRT plus specific cognitive exercise of impaired functions. We then divided our sample in four subgroups on the basis of genotype (Val/Val versus Met carriers) and treatment (placebo versus active). We assessed patients with a neuropsychological battery, the Positive and Negative Symptoms Scale (PANSS) and the Quality of Life Scale (QLS) at enrolment, after 3 months of therapy and after further 3 months of follow-up. We found significantly greater improvement of cognitive flexibility performance and QLS total score for Met carriers on active treatment in comparison to Val/Val on placebo. The findings support the hypothesis that COMT polymorphism influences individual capacity to recover from cognitive deficit through rehabilitation therapy after a wider intervention also including deficit-specific cognitive exercise as a potentiating tool.
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Keywords: Schizophrenia; Cognitive functions; Rehabilitation therapy; Catechol-*O*-methyltransferase (COMT); Genetic association

Catechol-*O*-methyltransferase (COMT) is an important enzyme in dopamine degradation, regulating dopamine's availability in the prefrontal cortex. A common functional polymorphism, an A to G substitution, at the codon 158 in the gene coding for Mb-COMT, results in the presence of Valine instead of Methionine, leading to a three to four-fold higher enzymatic activity. This polymorphism has been associated with diverse phenotypes in schizophrenia: symptom's severity and hospitalisation's rate, frequency of response to the different classes of antipsychotics, aggressive behaviour, and eye's movements [8,10,19,21,22], but the results are controversial. Several studies have evaluated the effect of the Val/Met polymorphism on cognitive functions, which are impaired in schizophrenic patients. Many authors, albeit not all, have found an association between the Met allele, leading to higher levels of prefrontal dopamine, and better performance in executive functions, measured by the number of perseverative errors at the Wisconsin Card Sorting Test (WCST), and working memory, evaluated with the N-back Test [5]. The same findings have also been replicated on unaffected relatives of schizophrenic patients and healthy subjects from the general population [5,15]. These previous studies focused on the association with cognitive performances, evaluated at a given time, while to our knowledge no research has been published about the possible influences of this polymorphism on the plasticity of cognitive resource through rehabilitation programs. Green and Nuechterlein [6] observed that the cognitive deficit has a great impact on functional outcome, representing by itself a limiting factor for patients to obtain the best results from classical rehabil-

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itation therapy. To overcome this limitation, a number of studies [1,2,24] suggested that cognitive exercise may be helpful, not only by itself, but also as a potentiating strategy.

We can argue that cognitive remediation protocols in schizophrenic patients act on the so-called "cognitive reserve" [18], specifically on both its hypothesized components: the neural reserve and the neural compensation. The first represents individual, innate (genetically ruled) or acquired (i.e. education) abilities: higher neural reserve leads to more efficient brain networks with greater capacity in the face of increased demand [18]. Schizophrenic patients are known to show decreased efficiency in prefrontal cortex (PFC) activation when performing specific tasks under brain imaging analyses [16]. This decreased efficiency was hypothesized to be related to lower signal to noise ratio, depending on dopamine hypoactivity in that area, therefore it may be, at least partially, under the genetic control of COMT enzyme activity. Supporting this hypothesis Ho et al. [9], showed, through functional Magnetic Resonance Imaging (fMRI), an association between the Met allele and increased prefrontal efficiency in schizophrenic patients performing the N-back task.

Our study aims to evaluate the effect of COMT polymorphism on the patient's ability to respond either to classical rehabilitation or to cognitive exercise of the specific functions of interest, added to the former.

The hypothesis is that Met allele, leading to higher PFC dopamine levels, could be associated with greater improvement after therapy.

The study group included 50 biologically unrelated, clinically stabilized outpatients meeting DSM-IV criteria for schizophrenia who were attending a long term treatment rehabilitation program since 3 months. Patients were responders to typical and atypical antipsychotics in monotherapy, doses were stable in the 3 months before enrolment and remained unchanged throughout the study duration. After complete description of the study, informed consent to participation was obtained. The protocol and informed consent followed the principles of the Declaration of Helsinki, furthermore it was accepted and approved by the local Ethical Committee.

All patients underwent a venous blood sample for genotypic analysis. Genomic DNA was extracted using EXTRAGEN 8C. PCR was performed with the following primers: 5′ ACT GTG GCT ACT CAG CTG TG 3′, 5′ CCT TTT TCC AGG TCT GAC AA 3′. PCR product was digested using *Nla*III (New England Biolabs, England, UK); fragments were separated in 3% Seakem agarose gels (BMA, BioWhittaker Molecular Applications. Rockland, ME, USA). The cleaved bands were visualized by ultraviolet light. Depending on the presence of one or two restriction *Nla*III sites, either two fragments 140 bp + 29 bp (allele G or Val) or three fragments 114 bp + 26 bp + 29 bp (allele A or Met) were produced [14,20,21].

Subjects were randomly assigned 1:1 to two different treatment conditions (active and placebo), both added to SRT (including non cognitive subprograms of IPT [4], social skills training and psychoeducation). The experimental condition consisted in three sessions a week (36 sessions) of 1 h each of function-specific computer-aided exercises, while the control condition consisted in 1 h of computer-aided treatment with a set of aspecific exercises, and 2 h of supplementary occupational treatment a week. Computer-assisted neurocognitive exercise was done using the Cogpack Software® with function-specific exercises and aspecific exercises. The program was set for adaptive exercises (applied as positive reinforcement following the 'errorless learning environment' theory [13]).

All patients were assessed at baseline and after 3 months of treatment with: PANSS [11] to evaluate symptoms severity; QLS [7] to assess daily functioning and a battery of neuropsychological tasks including BACS, WCST, for the evaluation of cognitive flexibility, and CPT for the evaluation of sustained attention. The BACS [12] is a recent and short battery of neuropsychological tests specifically designed in two versions (A and B) to evaluate patients before and after rehabilitation programs, without the results being influenced by recall. It consists of the following tests: *verbal memory* (words recall); *working memory* (digit sequencing); *token motor task* (psychomotor speed and coordination); *selective attention* (symbol coding); *semantic fluency*; *letter fluency*; *Tower of London*. QLS was administered to patients even after 3 months of follow-up after the end of the neurocognitive treatment; during this period the patients continued to attend the SRT. This evaluation at 6 months from the beginning of the study is the most reliable to observe the functional outcome, since possible classical rehabilitation results are expected in 6–9 months. We hypothesized that cognitive exercise may restore the patient's cognitive scaffold, intended as the target on which classical rehabilitation acts to rebuild skills.

Demographic and clinical characteristics were analysed for group differences with ANOVA and Chi-square test (for dichotomic variables).

A Repeated Measures ANOVA Mixed Model with Time as the random factor, Group as the fixed factor and neuropsychological actual performance as the dependent variable, was estimated. Each analysis was covaried for baseline score and years of education. Results were adjusted with Bonferroni Correction.

The sample was composed of 50 patients, 34 males and 16 females. DNA analysis showed an allelic distribution according to Hardy-Weinberg equilibrium: 13 patients Val/Val, 24 Val/Met and 13 Met/Met.

All subjects enrolled in this study but one completed the 3 months experimental treatment and the QLS evaluation after 3 months. All analyses were calculated on completers.

COMT alleles were distributed between treatment groups as following: the group treated with SRT included 6 Val/Val, 12 Val/Met and 4 Met/Met; the group on neuroremediation added to SRT was composed of 6 Val/Val, 12 Val/Met and 9 Met/Met. A Chi-square analysis did not show a significant difference in frequencies of alleles between treatment groups.

Because of the small sample size and taking into consideration previous studies showing no significant differences in cognitive performances between Met homozygous and Val/Met subjects [3,17], for analysis we grouped patients as Val/Val versus Met carriers. Patients were then divided into four groups, on the basis of the different combination between genotype and treatment (Val/Val versus Met carriers and Active versus Placebo

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