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ORIGINAL ARTICLE

COMT and STH polymorphisms interaction on cognition in schizophrenia

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Abstract Catechol-*O*-methyltransferase (COMT) gene, a key regulator of prefrontal cortex (PFC) dopamine (DA) availability, has been extensively studied in relation to cognitive domains, mainly executive functions, that are impaired in schizophrenia, but results are still controversial. Since recent studies in patients affected by neurodegenerative and psychiatric disorders suggested a role of saitohin (STH) gene as a concurring factor in hypofrontality, we hypothesize that STH and COMT polymorphisms could have an additive effect on cognition in schizophrenia. Three forty three clinically stabilized patients with schizophrenia were assessed with a broad neuropsychological battery including the Brief Assessment of Cognition in Schizophrenia, the Wisconsin Card Sorting Test and the Continuous Performance Test and were genotyped for COMT Val108/158Met and STH Q7R polymorphisms. We observed the effects of COMT on speed of processing and executive functions, as well as a significant effect of STH on executive functions performances. Moreover, a significant interaction between COMT and STH polymorphisms was found on executive functions, with COMT Val/Val and STH R carriers performing worse. Our results showed a significant interaction effect of COMT and STH polymorphisms on cognitive performances, strengthening the involvement of STH in cognitive impairments, especially in the domains commonly impaired in schizophrenia.

Keywords COMT · Saitohin · Cognition · Hypofrontality · Schizophrenia · Neurodegeneration

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Introduction

Schizophrenia is a chronic mental illness affecting almost 1 % of the population, characterized by cognitive and functional deficits leading to poor functional outcome and social disruption [1].

In the past decades, several studies addressed to the biological bases of cognitive impairment in schizophrenia, evaluating the effects of different polymorphisms, mainly in genes involved in neurotransmission and also in neurodevelopment and neurodegeneration processes [2].

Most consistent results have been found for a single nucleotide polymorphism in the gene coding for Catechol-*O*-methyltransferase (COMT), an enzyme that significantly contributes to the removal of dopamine (DA) from the synapse in the prefrontal cortex (PFC). The substitution of Met for Val at codon 108/158 results in the transcription of a thermolabile variant with approximately 40 % less enzymatic activity, leading to greater availability of DA in the PFC [3]. Numerous studies identified associations between COMT genotype and cognition in patients with schizophrenia and their relatives, with homozygous for

Met allele performing better than Val homozygous in test evaluating cognitive functions relying on PFC [4]. Moreover, we previously reported an association between COMT genotype and improvement after cognitive remediation [5], also in relation to antipsychotic treatment [6]. However, there have also been negative findings [7], thus pointing out the need to further explore other contributing factors that may interact with COMT. In particular, a large study exploring the effect of COMT Val108/158Met polymorphism on executive functions, both in healthy controls and in patients with schizophrenia, concluded that the relationship between COMT polymorphism and executive performances was limited to the healthy control group [8].

Recent studies focused on the effect of saitohin (STH) gene, located in intron 9 of the human tau gene, in several neurodegenerative disorders, mainly dementia processes [9, 10]. STH gene contains a single nucleotide polymorphism (A/G), which changes glutamine residue 7 to arginine (Q7R) [11]. Interestingly, Borroni et al. [13, 14] found an association between H2 haplotype, in complete linkage disequilibrium with the STH R allele [12], and both greater anterior brain hypoperfusion and worse clinical prognosis in patients affected by frontotemporal dementia (FTLD). In an Italian sample of patients affected by sporadic dementia, Lorenzi et al. [15] observed significant interactions between STH and 5-HTTLPR, as a potential susceptibility factor for neurodegenerative diseases. Bosia et al. [16] evaluated the role of the STH polymorphism in the cognitive decline in schizophrenia, reporting an association between the R allele and poorer executive performances.

Based on these data, it appears worth of interest to study the possible interactions between COMT and STH polymorphisms, both hypothesized to be concurring factors contributing to PFC functions and cognitive performances, especially executive functions. In this study we thus analyzed the possible effects and interactions of STH and COMT polymorphisms on cognition in a sample of patients affected by schizophrenia.

Materials and methods

A sample of 343 Caucasian biologically unrelated outpatients were recruited at the San Raffaele Scientific Institute of Milan (Italy). Inclusion criteria were: diagnosis of schizophrenia (DSM-IV-TR criteria), age 18–70 years, stable antipsychotic treatment since at least 3 months and good response (defined as a reduction of 30 % or more in PANSS Total Score after 3 months of treatment). Exclusion criteria were: psychiatric comorbidities, mental retardation, substance abuse, neurological disorders and brain injury. After a complete description of the study, informed consent to participation was obtained. The protocol was approved by the local ethical committee and followed the principles of the Declaration of Helsinki.

Genotyping

All patients underwent a venous blood sample for genotypic analysis. DNA was extracted from whole blood by manual extraction, using the "Illustra blood genomicPrep Midi Flow kit" (GE Healthcare, Milan, Italy).

For COMT Val108/158Met, polymerase chain reaction (PCR) was performed with the following primers: 5′-ACTGTGGCTACTCAGCTGTG-3′, 5′-CCTTTTTCCAGGTCTGACAA-3′. The PCR reaction was carried out by ABI 9700 PCR thermal-cycler (Applied Biosystems, APPLERA) in a 10 µl volume containing 150 ng of genomic DNA, 5 pmol of each primer, 10 nmol of dNTPs' mix, 10× HotMaster Taq Buffer and 0.5 U of HotMaster Taq DNA Polymerase (Eppendorf, Milan, Italy). The amplified fragment was then purified by Multi-Screen Colum Loader (MILLIPORE), filled up and packaged with Sephadex G-50 (Sigma–Aldrich's) to remove residual PCR reagents. An aliquot of purified PCR product was then used to perform sequencing reaction, using DYEnamic ET Dye Terminator Cycle Sequencing Kit (GE Healthcare, Milan, Italy). In its turn, sequencing reaction product, was purified following the above-mentioned protocol, to remove the excess of fluorescent dyes not incorporated in the DNA fragment. The fragment was then sequenced by MegaBACE 500 genetic analyzer (GE Healthcare, Milan, Italy) under standard conditions.

For the STH Q7R polymorphism, a PCR was performed with the following primers: 5′-CCCTGTAAACTCTGACCACAC-3′ and 5′-ACAGGGAAGCTACTTCCCATG-3′. The PCR reaction was carried out by ABI 9700 PCR thermal-cycler (Applied Biosystems, APPLERA) as follows: after a first step at 94 °C for 3 min, steps of 94 °C for 30 min, 60 °C for 30 min, 70 °C 30 min for 35 cycles. Then, a final extension step at 70 °C for 6 min was added. PCR product was digested using *Hin*fI (New England Biolabs, England, UK) at 37 °C overnight; fragments were separated in 3 % Seakem agarose gel with ethidium bromide. The cleaved bands were visualized by ultraviolet light. Depending on the presence of one or two restriction *Hin*fI sites, either two fragments 171+55 bp (A or Q allele) or three fragments 97+74+55 bp (G or R allele) were produced.

Assessment

Basic clinical and demographic data were collected from clinical records.

Psychopathology was assessed by means of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), [17], administered by trained psychiatrists.

Neuropsychological performances were assessed with the following tests, administered by trained psychologists.

The Brief Assessment of Cognition in Schizophrenia (BACS), a brief evaluation of the main cognitive functions that are usually impaired in schizophrenic patients [18], includes the following tasks: verbal memory and learning (list of words), working memory (sequence of numbers), motor function (token motor task), speed of processing (symbol coding), verbal fluency (semantic categories), letter fluency, executive function, subcomponent of planning (Tower of London).

The Wisconsin Card Sorting Test (WCST) [19] evaluates visuospatial skills and the ability to classify, keep the set, switch the attentive focus, and inhibit interfering answers. The score results from the number of categories completed by the patient, a measure of abstract reasoning and the number of perseverative errors, evaluating more specifically cognitive flexibility.

The Continuous Performance Test (CPT) [19], a computerized test, presenting a sequence of stimuli to be recognized ignoring distractors, evaluates sustained and selective attention.

Data analysis

STATISTICA Software for Windows, version 8 (StatSoft Inc., Tulsa, OK, USA) was used to perform statistical analyses.

As in previous works, for analysis on COMT genotype we grouped patients as Val/Val and Met carriers [5], while for STH genotype we grouped patients in Q/Q homozygous and R carriers [12], given the low frequency of the G/G genotype.

For analysis on antipsychotics, we stratified patients into three groups: first generation antipsychotics (FGA), second generation antipsychotics (SGA) and clozapine.

Differences between COMT and STH genotypes and demographic and clinical characteristics were analyzed with one-way analysis of variance (ANOVA) for quantitative measures, or χ^2 test for dichotomic variables (gender and treatment class).

Effects of COMT and STH genotypes and their interaction on cognitive performances were analyzed by means of General Linear Model (GLM), with scores of BACS, WCST and CPT as dependent variables and COMT and STH genotypes as categorical factors. To be more conservative, given the unbalanced groups sizes, we used HSD Test for Unequal numbers to determine significant differences between genotypes groups.

Results

DNA analysis showed reliable results for COMT genotype in 339 subjects and for STH genotype in 342 subjects. Genotypes were distributed as follows: 68 Met/Met, 174 Met/Val and 97 Val/Val for COMT gene; 214 Q/Q, 113 Q/R and 15 R/R for STH gene. Allelic distributions followed Hardy–Weinberg equilibrium.

Demographic and clinical characteristics stratified by COMT and STH genotypes are reported in Table 1. No significant differences were observed between genotype groups.

All patients were taking antipsychotic treatments: 129 subjects were on clozapine, 112 on risperidone, 80 on haloperidol, 13 on olanzapine, 5 on aripiprazole, 3 on paliperidone and 1 on quetiapine. The χ^2 test showed no significant differences in genotypes distribution (COMT and STH both separately and in interaction) among

Table 1 Demographic and clinical features of the sample, stratified by COMT and STH genotypes

	COMT		ANOVA/χ^2	STH		ANOVA/χ^2
	Val/Val (mean ± SD)	Met carriers (mean ± SD)		Q/Q (mean ± SD)	R carriers (mean ± SD)	
Gender	M = 65; F = 32	M = 157; F = 85	NS	M = 137; F = 77	M = 88; F = 40	NS
Age (years)	35.70 ± 10.00	35.04 ± 9.92	NS	34.97 ± 10.03	35.78 ± 9.83	NS
Education (years)	10.54 ± 2.93	10.67 ± 2.87	NS	10.55 ± 2.77	10.76 ± 3.07	NS
Onset (years)	23.35 ± 5.06	22.95 ± 5.53	NS	23.05 ± 5.10	23.09 ± 5.85	NS
PANSS negative (score)	21.09 ± 8.02	19.83 ± 8.34	NS	20.53 ± 8.93	19.46 ± 7.00	NS
PANSS positive (score)	17.51 ± 6.85	16.74 ± 8.04	NS	17.61 ± 8.93	15.76 ± 5.07	NS
PANSS general (score)	35.00 ± 9.97	32.75 ± 10.46	NS	34.42 ± 11.00	31.42 ± 8.95	NS
PANSS total (score)	73.85 ± 22.77	69.40 ± 22.89	NS	72.56 ± 24.60	66.84 ± 19.15	NS

years years, *SD* standard deviation, *NS* not significant

Table 2 Antipsychotic treatment distribution, stratified by COMT*STH genotypes

	COMT Val/Val STH Q/Q *N* (%Tot)	COMT Val/Val STH R carriers *N* (%Tot)	COMT Met carriers STH Q/Q *N* (%Tot)	COMT Met carriers STH R carriers *N* (%Tot)	χ^2
Clozapine	23 (6.80)	15 (4.44)	67 (19.82)	24 (7.10)	NS
SGA	25 (7.40)	14 (4.14)	50 (14.79)	42 (12.43)	NS
FGA	13 (3.85)	7 (2.07)	34 (10.06)	24 (7.10)	NS

FGA first generation antipsychotics, *SGA* second generation antipsychotics, *SD* standard deviation, *NS* not significant

treatment groups (FGA, SGA and clozapine) as shown in Table 2.

The GLM Analysis with COMT and STH genotypes as categorical predictors and the score of cognitive tests as dependent variables showed significant effects only for Symbol Coding BACS' subtest and WCST number of categories completed.

Symbol Coding BACS' subtest evaluates selective attention and working memory, representing a global measure of speed of processing. The analysis on symbol coding revealed a significant overall model ($R^2 = 0.036$, $F = 3.79$, $p = 0.01$), with significant main effect of COMT genotype ($\eta_p^2 = 0.02$, $F = 4.93$, $p = 0.027$) and a trend of COMT*STH interaction ($\eta_p^2 = 0.011$, $F = 3.32$, $p = 0.069$). Post-hoc HSD for Unequal numbers on COMT main effect showed a significant difference between COMT Met carriers and COMT Val/Val ($p = 0.02$), the latter showing worse performances.

The analysis on WCST number of categories completed, a measure of abstract thinking, showed a significant overall model ($R^2 = 0.040$, $F = 4.14$, $p = 0.007$), with a slightly significant main effect of COMT genotype ($\eta_p^2 = 0.012$, $F = 3.67$, $p = 0.056$), a significant main effect of STH genotype ($\eta_p^2 = 0.021$, $F = 6.34$, $p = 0.01$) and a significant COMT*STH interaction ($\eta_p^2 = 0.033$, $F = 10.03$, $p = 0.002$). Post-hoc HSD for Unequal numbers showed that subjects carrying COMT Val/Val genotype and STH R allele performed worse than both COMT Val/Val and STH Q/Q carriers ($p = 0.019$) and COMT Met allele and STH R carriers ($p = 0.046$).

Mean scores of neuropsychological performances stratified by COMT and STH genotypes are reported in Table 3. Significant effects of COMT*STH interaction on WCST number of categories are displayed in Fig. 1.

Discussion

To our knowledge this is the first study evaluating interactions between COMT and STH polymorphisms on cognitive functions in a sample of patients with schizophrenia.

Our results confirm previous literature reporting an effect of COMT genotype on several cognitive measures. In detail, we observed a significant effect of COMT on Symbol Coding BACS subtest, with better performances among Met carriers and a similar trend on WCST "number of categories".

Results also revealed a significant main effect of STH genotype on WCST "number of categories", showing the patients carrying the STH R allele performed worse than Q/Q homozygous, supporting previous findings [16].

Moreover, analyses suggest an additive effect of COMT and STH polymorphisms. A significant interaction was found on WCST number of categories with subjects carrying COMT Val/Val genotype and STH R allele performing significantly worse than both COMT Val/Val and STH Q/Q carriers and COMT Met allele and STH R

Table 3 Mean scores of neuropsychological tests, stratified by COMT and STH genotypes

	COMT		STH	
	Val/Val (mean ± SD) *N* = 97	Met carriers (mean ± SD) *N* = 242	Q/Q (mean ± SD) *N* = 214	R carriers (mean ± SD) *N* = 128
Correct sequences	15.78 ± 5.02	16.73 ± 5.13	15.78 ± 5.02	16.73 ± 5.13
Tokens	67.11 ± 16.44	68.70 ± 18.88	60.25 ± 19.10	68.28 ± 16.70
Verbal fluency	33.44 ± 12.45	34.57 ± 13.38	33.59 ± 12.52	35.11 ± 13.93
Symbol coding	32.93 ± 10.61	37.13 ± 12.52	36.22 ± 11.58	35.34 ± 13.03
Tower of London	12.56 ± 4.22	12.85 ± 5.05	12.77 ± 4.12	12.85 ± 5.78
Verbal memory	31.97 ± 10.47	34.17 ± 10.97	32.66 ± 10.60	35.02 ± 11.15
WCST cat.comp.	3.64 ± 2.42	3.97 ± 2.28	4.00 ± 2.34	3.67 ± 2.27
WCST pers err	15.72 ± 10.99	16.00 ± 10.92	15.35 ± 10.75	16.79 ± 11.05
CPT missed	30.75 ± 29.04	30.95 ± 30.70	30.94 ± 29.28	32.98 ± 32.64
CPT hits	145.93 ± 28.84	142.92 ± 33.12	114.52 ± 30.30	141.19 ± 35.32

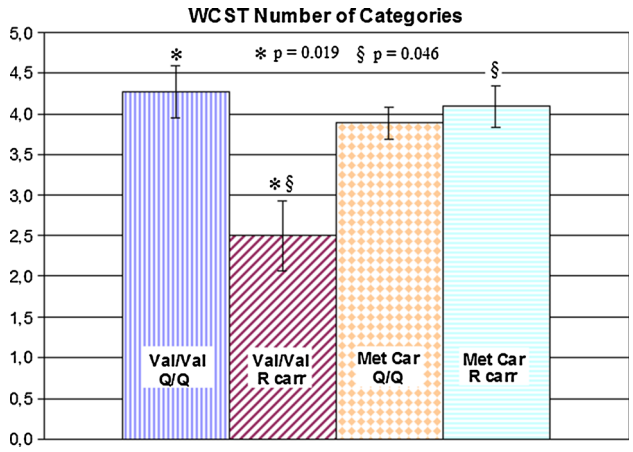

Fig. 1 Number of categories completed in the Wisconsin Card Sorting Test (WCST), stratified by COMT and STH grouped genotypes. General Linear Model: $F = 10.03$; $p = 0.002$

carriers. A trend of interaction between COMT and STH was also observed on Symbol Coding.

Our results thus suggest an interaction of COMT and STH polymorphisms on cognition, strengthening the involvement of STH in cognitive impairments, especially in domains commonly impaired in schizophrenia. Symbol Coding subtest represents a general measure of processing speed, a domain sensible to neurodevelopment insults and neurodegeneration processes, often used as an indicator of severity in schizophrenia [20]. Number of categories subtest, on the other hand, is a global measure of executive functioning, in particular abstract thinking, domains commonly impaired in patients with schizophrenia [21].

Interestingly, patients carrying STH R allele and COMT Val/Val performed significantly worse than the others. Although the specific effect of STH polymorphism is still unclear, some speculations are possible. Previous findings in patients affected by FTLD, sporadic dementia and schizophrenia pointed out R allele as a possible factor contributing to worse prognosis [13–16], suggesting that the STH genotype may be involved in disorders with a neurodegenerative component. The interaction observed between COMT and STH genotypes suggests an additive effect that may be explained hypothesizing that COMT functional effect on DA levels may be more critical in STH R carriers which could have an higher susceptibility to an early neurodegeneration.

A number of limitations should be taken into account. First of all, we tested the interaction of COMT and STH polymorphisms only in a sample of patients affected by schizophrenia, thus the lack of a healthy control group limits the possibility of truly disclosing the role of the studied polymorphisms within schizophrenia. Testing the possible interaction effect on cognition in a group of healthy controls and in a group of controls affected by FTLD may be helpful to understand physiologic mechanisms underlying cognitive processes. Second, focusing on single polymorphisms may be restrictive and we cannot exclude that our results may depend on interaction with different polymorphism or on other unexplored factors, such a downstream effect in the pathway where COMT and STH are normally involved.

Although explanation of our results is far from clear and the effect that we observed may depend on a set of interacting neurobiological factors, the role of STH genotype on cognitive functions appears to be worthy of further investigation, that might help understanding its neurophysiologic value.

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