

SUPPLEMENTARY.

Table S1. Studies of the association between the rs4680 variant of the COMT gene and cognitive impairment in schizophrenia

No.	Article	Ethnicity	Cognitive functions under investigation	Cognitive function assessment scale	Number of subjects (schiz)	Number of subjects (control)	Medications taken	Hospitalization status	Results	Study quality
1	Sun et al., 2018 [1]	Han	Verbal fluency, executive functions, working memory and attention, information processing speed, thinking	Verbal Fluency Test, TMT A-B, SCWT, WCST	62 m 34 f	0	76 (38%) were drug-naïve, the others were receiving antipsychotic treatment at study enrollment	Inpatient setting	No significant genotypic association between rs4680 and cognitive functions was observed at baseline or after 8 weeks of antipsychotic treatment	Positive factors: the investigators accounted for the impact of confounding factors; homogeneous clinical attributes; blinded assessment of clinical and cognitive symptoms. Negative factors: dropouts differed in the distribution of genotypes from the group that completed the study; no Hardy-Weinberg equilibrium test was carried out
2	Lindenmayer et al., 2015 [2]	African American, Asian, Caucasian, Hispanic	Processing speed, attention, working memory, verbal and visual learning, reasoning, and problem solving	MCCB	125 m 13 f	0	A stable dose of atypical antipsychotic drugs for at least 4 weeks prior to inclusion in the study	Outpatient and inpatient settings	Subjects were assessed at baseline and at the end point after 12 weeks of CRT. The Met allele was associated with significant improvements in MATRICS domains, such as verbal learning, visual learning, and attention/vigilance of verbal learning, indicating its importance in learning and memory processes	Positive factors: the investigators took into account the influence of confounding factors; measurements were performed by experts who did not know the study hypothesis. Negative factors: there was no group without cognitive training; ethnicity, diagnosis, and hospitalization status were different between genotypes; no Hardy-Weinberg equilibrium test was carried out
3	Nkam et al., 2017 [3]	European	Attention, information processing speed, executive control, working memory, thinking	SCWT, Attention Network Test, WCST	36 m 16 f	19 m 34 f	Atypical antipsychotics	Outpatient setting	Patients with the Val/Val genotype showed an increase in the number of perseverative errors and worse executive functions	Positive factors: the investigators took into account the influence of confounding factors; homogeneity of the groups was ensured by limiting enrollment to outpatients taking only atypical antipsychotics, with a similar disease presentation. Negative factors: the distribution by age, education level, and gender was different between the control group and the patients with schizophrenia; the publication did not report whether the person conducting and assessing the tests was aware of the group to which the patient belonged; no Hardy-Weinberg equilibrium test was carried out

4	Sagud et al., 2023 [4]	Croatian	Impaired thinking, attention	PANSS: N5 (abstract thinking) and P2 (conceptual disorganization), G10 (disorientation) and G11 (poor attention)	544 m 385 f	0	Not described	Inpatient setting	Carriers of the Met allele had worse abstract thinking results than G homozygotes	Positive factors: the investigators took into account the influence of confounding factors. Negative factors: no data on the drugs taken were provided; groups of men and women differed in age and severity of the disease; no control group was used; the publication did not report whether the person conducting and assessing the tests was aware of the group to which the patient belonged
5	Loch et al., 2015 [5]	Brazilian	Thinking, working memory, attention, executive functions, information processing speed, verbal and visual memory, visuospatial function, intelligence	WAIS, WCST-FMS, TMT-A, SCWT, RCFT, FAS, IQ, estimated IQ (EIQ), execution IQ (EXIQ), and verbal IQ (VIQ)	40 m 18 f	43 m 67 f	51 (88%) took atypical antipsychotics, 9 (16%) received typical antipsychotics, 12 (21%) took mood stabilizers, 24 (41%) received antidepressants, 12 (21%) used benzodiazepines	Outpatient setting	Patients with the Val/Val genotype demonstrated a level of executive functions similar to the level in the control group. Executive functions became worse with an increase in the frequency of the Met allele	Positive factors: the investigators took into account the influence of confounding factors. Negative factors: different treatments; diagnoses of «schizoaffective disorder» and «schizophrenia»; age was lower in the control group, but the authors did not provide statistics; the publication did not report whether the person conducting and assessing the tests was aware of the group to which the patient belonged
6	Matsuzaka et al., 2017 [6]	Brazilian (Caucasian and non-Caucasian)	Working memory, visual memory, attention, information processing speed	VWM, Keep Track, Letter Memory Task	133	93	Not described	Inpatient setting	In the VWM and KTT tests, patients with the Met Met genotype had the lowest scores compared to the control group, but the highest among patients, for both tests	Positive factors: the investigators took into account the influence of confounding factors; the characteristics of the main and control groups did not differ. Negative factors: there is no description of how the control group was recruited, the drugs taken, and the duration of the disease; the publication did not report whether the person conducting and assessing the tests was aware of the group to which the patient belonged
7	Morozova et al., 2019 [7]	Slavic, Russian	Praxis, executive functions, working memory, verbal fluency, attention, impaired thinking	FAB, PANSS: N5 (abstract thinking) and P2 (conceptual disorganization), G10 (disorientation) and G11 (poor attention)	186 m 276 f	100 m 112 f	Not described	Inpatient setting	The Val allele was associated with lower «conceptualization» and «inhibitory control» results, but only in women	Positive factors: the investigators took into account the influence of confounding factors; homogeneous ethnicity; homogeneous group diagnosed with early-onset schizophrenia. Negative factors: there is no description of the drugs taken; the publication did not report whether the person conducting and assessing the tests was aware of the group to which the patient belonged

8	Bosia et al., 2014 [8]	Not described	Thinking, intelligence, executive functions, information processing speed, working memory	WCST WAIS	53 m 33 f	0	Not described	Outpatient setting	In the Val/Val group, the effect after 3 months of CRT was lower (executive functions) than in the group of Met carriers	Negative factors: the authors did not consider confounding factors, did not describe exclusion criteria and therapy; there was no control group and no patients without CRT; the publication did not report whether the person conducting and assessing the tests was aware of the group to which the patient belonged
9	Syamsuddin et al., 2023 [9]	Indonesian	Attention, information processing speed, working memory	TMT-AB	84 m 16 f	70 m 30 f	Risperidone	Inpatient setting	Patients with the Met allele tended to complete the TMT A and TMT B test faster than patients with the Val/Val genotype	Positive factors: homogeneous group in terms of treatment; sample size calculation; the influence of confounding factors was taken into account; the control group had the same characteristics as the experimental group. Negative factors: the publication did not report whether the person conducting and assessing the tests was aware of the group to which the patient belonged; no Hardy-Weinberg equilibrium test was carried out
10	Xu et al., 2022 [10]	Han	Working and visual memory, language, attention, and delayed memory	RBANS	181 m 63 f	168 m 229 f	Monotherapy with various antipsychotics	Inpatient setting	Val/Val carriers showed more severe memory and attention disorders than Met carriers	Positive factors: the investigators accounted for the impact of confounding factors; homogeneous ethnicity; independent evaluation by several psychiatrists. Negative factors: the publication did not report whether the person conducting and assessing the tests was aware of the group to which the patient belonged; age difference between control and healthy individuals
11	Bondrescu et al., 2024 [11]	European	Verbal memory, visual memory, reaction time, processing speed, cognitive flexibility, reasoning, social acuity, and working memory	CNS Vital Signs	30 m 24 f Schizophrenia spectrum disorders	0	Not specified	Inpatient setting	Patients with the Met allele showed better processing speed (especially patients with schizophreniform disorder)	Positive factors: sample size calculation; the influence of confounding factors was taken into account; the control group had the same characteristics as the experimental group. Negative factors: the publication did not report whether the person conducting and assessing the tests was aware of the group to which the patient belonged; no Hardy-Weinberg equilibrium test was carried out; there was no control group; the drugs taken were not specified

Note: COMT — catechol-O-methyltransferase; CRT — cognitive rehabilitation therapy; FAB — Frontal Assessment Battery; IQ — Intelligence Quotient; KTT — Keep Track Task; MCCB — MATRICS Consensus Cognitive Battery; PANSS — Positive and Negative Syndrome Scale; RBANS — Repeatable Battery for the Assessment of Neuropsychological Status; RCFT — Rey-Osterrieth Complex Figure Test; SCWT — Stroop Color Word Test; SNP — Single nucleotide polymorphism; TMT — Trail Making Test; VWM — Visual Working Memory; WAIS — Wechsler Adult Intelligence Scale; WCST — Wisconsin Card Sorting Test. f — females; m — males; schiz — schizophrenia.

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