Review Paper

COMT, neuropsychological function and brain structure in schizophrenia: a systematic review and neurobiological interpretation

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Background: Endophenotypes in genetic psychiatry may increase our understanding of the molecular mechanisms underlying disease risk and its manifestations. We sought to investigate the link between neuropsychological impairments and brain structural abnormalities associated with the COMT Val^{158}Met polymorphism in patients with schizophrenia to improve understanding of the pathophysiology of this disorder. **Methods:** We performed a systematic review using studies identified in PubMed and MEDLINE (from the date of the first available article to July 2012). Our review examined evidence of an association between the COMT Val^{158}Met polymorphism and both neuropsychological performance and brain structure in patients with psychosis, in their relatives and in healthy individuals (step 1). The review also explored whether the neuropsychological tasks and brain structures identified in step 1 met the criteria for an endophenotype (step 2). Then we evaluated evidence that the neuropsychological endophenotypes identified in step 2 are associated with the brain structure endophenotypes identified in that step (step 3). Finally, we propose a neurobiological interpretation for this evidence. **Results:** A poorer performance on the n-back task and the Continuous Performance Test (CPT) and smaller temporal and frontal brain areas were associated with the COMT Val allele in patients with schizophrenia and their relatives and met most of the criteria for an endophenotype. It is possible that the COMT Val^{158}Met polymorphism therefore contributes to the development of these neuropsychological and brain structural endophenotypes of schizophrenia, in which the prefrontal cortex may represent the neural substrate underlying both n-back and CPT performances. **Limitations:** The association between a single genetic variant and an endophenotype does not necessarily imply a causal relationship between them. **Conclusion:** This evidence and the proposed interpretation contribute to explain, at least in part, the biological substrate of 4 important endophenotypes that characterize schizophrenia.

Introduction

The catechol-O-methyltransferase (*COMT*) gene is one of the most investigated candidate genes for schizophrenia because of its role in the degradation of dopamine (DA). This gene contains a common functional variant, the Val^{158}Met polymorphism, which impairs the thermostability of the mature protein, altering DA levels in several brain regions and specifically in the prefrontal cortex.[1,2] To date, several meta-analyses have investigated the association between the COMT Val^{158}Met polymorphism and schizophrenia: although the evidence is controversial, the most recent meta-analysis points to a weak association between the COMT Val^{158}Met polymorphism and schizophrenia (from the Schizophrenia Research Forum, www.szgene.org/meta.asp?geneID=420).[3–6]

Interestingly, the dopaminergic system is also involved in some of the neuropsychological impairments frequently described in patients with schizophrenia.[7] These impairments are thought to represent the functional correlate of abnormalities in the structure of the brain areas involved in these functions (for a review, see Antonova and colleagues[8]).

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Interestingly, there is evidence that the COMT Val allele itself may be associated with abnormalities in these areas in patients with schizophrenia.[9–11]

The COMT Val^{158}Met polymorphism may therefore contribute to the risk for schizophrenia by influencing specific neuropsychological impairments and brain structural abnormalities, which have been proposed as endophenotypes for this disorder.[12,13] Endophenotypes are heritable traits that possibly represent a causal link between genes and observable phenotypes.[14] They have the advantage of being measurable using strategies that involve quantitative units of analysis, and of being amenable to assessment in the laboratory.[15] Furthermore, the association between a specific endophenotype and certain genetic variants could be stronger than that with the illness itself.[14] According to Gottesman and Gould,[14] an endophenotype should

- be associated with the illness in the population of interest,
- be heritable,
- be primarily state independent,
- cosegregate with the illness within families, and
- be present in nonaffected family members more frequently than in the general population.

Endophenotypes in genetic psychiatry may increase our understanding of the molecular mechanisms underlying disease risk and its manifestations. Thus, investigating the link between neuropsychological impairments and brain structural abnormalities associated with COMT Val^{158}Met in schizophrenia may provide a better understanding of the pathophysiology of this disorder.

Although many studies have investigated the relationship between the COMT Val^{158}Met polymorphism and neuropsychological impairments or brain structural alterations in patients with schizophrenia, in their relatives and in healthy individuals, to our knowledge, no systematic review has critically appraised this evidence and explored the potential relationship between this polymorphism and neuropsychological impairments or the brain structural alterations. We sought to fill this gap with the present systematic review.

Methods

A flow chart of the methodology is presented in Figure 1. In step 1, we searched the PubMed and MEDLINE databases, from the date of the first available article to July 2012, to systematically identify the neuropsychological tasks and brain structural variations reported, as related to the COMT Val^{158}Met polymorphism, across disorders in the psychosis spectrum. To investigate the association between COMT and neuropsychological tasks, we used the terms "catechol-O-methyltransferase" or "COMT" AND "cognitive" or "cognition" or "neuropsychological" or "neuropsychology" or "attention" or "memory" or "executive function" AND "schizophrenia" or "psychosis" or "schizoaffective" or "schizophreniform" or "healthy." To investigate the association between COMT and brain structure we used the terms "catechol-O-methyltransferase" or "COMT", AND "MRI" or "magnetic resonance imaging" or "imaging" or "voxel" or "brain structures" AND "schizophrenia" or "psychosis" or "schizoaffective" or "schizophreniform" or "healthy." We also manually searched the reference lists of the articles identified in our search. Unpublished studies, conference abstracts and poster presentations were not included. One of us (E.I.) selected the articles, which 2 of us (P.D. and S.T.) then checked against our inclusion criteria.

We included studies that fulfilled the following criteria. First, studies must have evaluated the association between the COMT Val^{158}Met polymorphism and neuropsychological tasks in patients with diagnosed schizophrenia-spectrum disorders (i.e., schizophrenia, schizophreniform disorder, schizoaffective disorder) and/or in healthy controls and/or in relatives of patients with psychosis. We included only studies conducted using a standardized cognitive measure in adult participants. Behavioural data from functional magnetic resonance imaging (fMRI) studies were also included when reported. Second, studies must have evaluated the

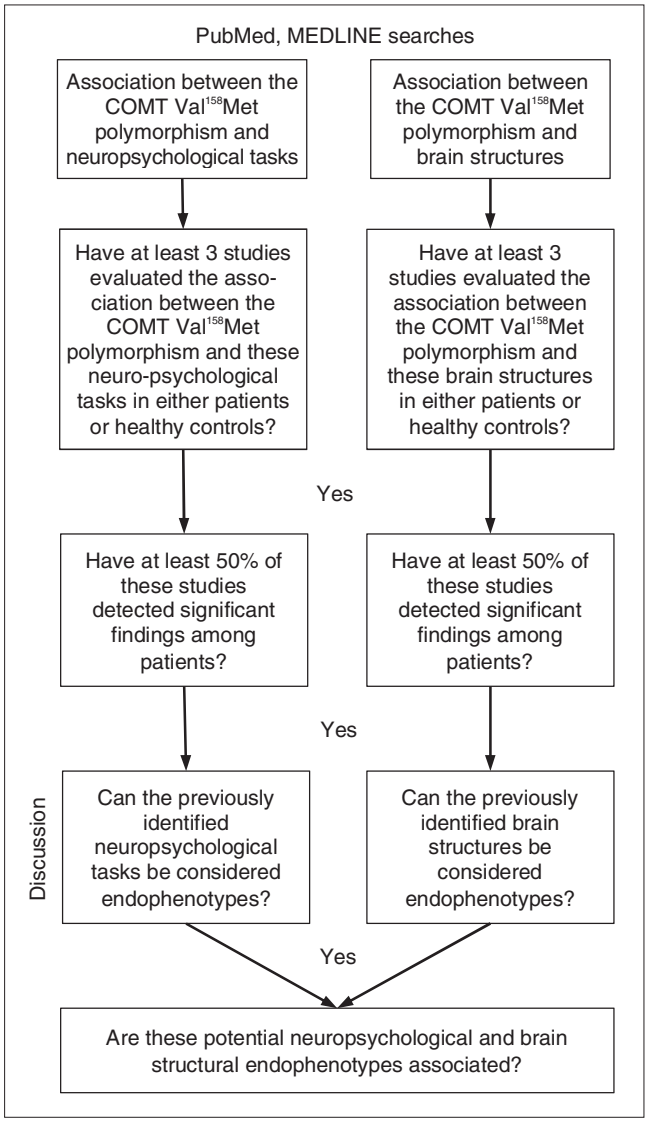

Fig. 1: Systematic review methodology.

association between the COMT Val[158]Met polymorphism and brain volumes using structural MRI in patients with diagnosed schizophrenia-spectrum disorders and/or in healthy controls and/or in relatives of patients with psychosis.

From the studies reviewed, we selected neuropsychological tasks and brain structures strongly associated with the COMT Val[158]Met polymorphism according to the following criteria. First, at least 3 studies must have evaluated the association between *COMT* and those neuropsychological tasks or brain structures in either patients or healthy controls. Second, at least 50% of these studies must have reported an association in patients.

In step 2, we considered each neuropsychological task and brain structure identified in step 1 to establish whether they satisfied the criteria for endophenotypes.

In step 3, we systematically searched the PubMed and MEDLINE databases, from the date of the first available article to July 2012, to verify whether the neuropsychological and the brain structural endophenotypes identified in step 2 were associated with each other. We used the name of each neuropsychological task as a search term combined with the terms "MRI" or "magnetic resonance imaging" or "imaging" or "voxel" or "brain structures" AND "schizophrenia" or "psychosis" or "schizoaffective" or "schizophreniform" or "healthy." In addition, we manually searched the reference lists of the articles identified in our search. Unpublished studies, conference abstracts and poster presentations were not included.

Results

Step 1a: association between the COMT Val[158]Met polymorphism and neuropsychological tests

We identified 53 studies (Table 1) that explored the association between the COMT Val[158]Met polymorphism and various neuropsychological tests. We present the neuropsychological tests that satisfied our first criterion (i.e., at least 3 studies evaluated the association between the COMT Val[158]Met polymorphism and those neuropsychological tests in either patients or healthy controls).

N-back task

The n-back task is conceptualized as a measure of working memory and includes executive functions, such as encoding, updating, sequence maintenance, comparing and deciding.[44] Eleven studies satisfied our inclusion criteria and together suggest that while the COMT Val[158]Met polymorphism seems to be associated with performance on the n-back task in patients with schizophrenia and schizoaffective disorder and in their siblings, this association is not present in healthy individuals. Three studies resported a significant or trend-level association between the Val/Val genotype and a worse performance (accuracy and reaction time) on the n-back task in patients with schizophrenia, schizophreniform disorder and schizoaffective disorder[26,40,64] and in their relatives,[40,64] whereas 1 study found no association.[27] Interestingly, the 3 studies that detected a significant association used a version of the n-back task that requires a higher cognitive load, suggesting that the association between the COMT Val[158]Met polymorphism and performance on the n-back task in patients with schizophrenia-spectrum disorders may become apparent when a more challenging performance is required (for details about the different versions of the tasks used, see Appendix 1, Table S1, available at cma.ca/jpn). In healthy individuals, 3 studies found a significant association between the COMT Val[158]Met polymorphism and performance on the n-back task.[30,40,64] In 2 of these studies the Val/Val genotype was associated with worse performance,[40,64] whereas in the third one participants with the Val/Met genotype performed worse than those with the Met/Met or Val/Val genotype.[30] Eight studies did not find a COMT Val[158]Met genotype effect on n-back task performance in healthy individuals.[18,21,26,27,41,44,47,58]

Continuous Performance Test (CPT)

The CPT is conceptualized as a behavioural assessment of attentional modulation; it can detect deficits in vigilance, selective attention and sustained attention.[68] Ten studies satisfied our inclusion criteria, reporting inconsistent findings on the association between the CPT and the COMT Val[158]Met polymorphism in both patients with schizophrenia and healthy individuals. In patients, 3 studies found a significant association between the Val/Val genotype and a poorer performance in terms of number of errors[57,69] and a better performance in terms of signal discrimination.[32] In contrast, 2 studies found no association either in patients with schizophrenia and schizoaffective disorder or in their relatives.[40,64] In healthy individuals, the Val/Val and Val/Met genotypes have been associated with worse performance in terms of commission errors,[47] context processing[44] and reaction time variability in some studies,[55] whereas other studies reported no association.[23,40,42,64] This inconsistency may be related to the use of different versions of the CPT across studies (for details about the different versions of the tasks used, see Appendix 1, Table S1). Interestingly, 1 study reported an interaction between the COMT Val[158]Met polymorphism and the DAT 40 bp variable number tandem repeat; participants homozygous for both the COMT Val allele and the DAT 10 allele exhibited worse performance in terms of commission errors.[47] This result suggests that the COMT Val[158]Met polymorphism may affect CPT performance by interacting with other genes, which may also explain inconsistencies in previous findings.

Wisconsin Card Sorting Test (WCST)

The WCST is regarded as a neuropsychological marker of the efficiency of executive functions.[70] While the *COMT* gene appears to have no effect on WCST performance in patients with psychosis, it seems to have an effect in healthy individuals. A meta-analysis has been conducted to assess the effect of the COMT Val[158]Met polymorphism on WCST perseverative errors in patients with schizophrenia-spectrum disorders and in healthy controls;[48] this included 11 studies that met our inclusion criteria.[1,49,50,56–58,60,63,65–67] The meta-analysis revealed a small but significant association between the COMT Val[158]Met polymorphism and executive function in healthy individuals,

Table 1: Studies evaluating the association between the COMT Val[158]Met polymorphism and neuropsychological tests (part 1 of 3)

Study	No. patients	Diagnosis	No. controls (relatives)	Cognitive measures	Main results*
Green et al.[16]	—		160	MSIT, WASI (vocabulary, similarities, block design, matrix reasoning)	• MSIT (accuracy and reaction time): Val/Val ↓ • WASI: Val/Val ↓
Gong et al.[17]	—		700	Digital and spatial working memory spans	No association between COMT and digital and spatial working memory spans
Blanchard et al.[18]	—		291	Spatial n-back task	No association between COMT and n-back task
Greenwood et al.[19]	87	Schizophrenia	—	WCST, WAIS-R (digit span)	• WCST (category achievement): Val/Met ↓ • No association between COMT and WCST (perseverative errors) and digit span
Wishart et al.[20]	—		95	TMT A–B, D-KEFS (trail-making subtest)	• TMT-B: Val/Val Val/Met ↓ • No association between COMT and TMT A • TMT-B: COMT x ANKK1 interaction: Val carriers + T carriers ↓
Stokes et al.[21]	—		50	Spatial n-back, go/no-go, Tower of London tasks	No association between COMT and any cognitive measure
Rosa et al.[22]	67	Schizophrenia and schizoaffective disorder	186	Modified Stroop test (manipulating level of required cognitive stability)	• Patients and controls: task requiring cognitive stability: Val/Val ↓ • No association between COMT and task requiring cognitive flexibility
Solís-Ortiz et al.[23]	—		74 F	WCST, Stroop test, CPT (test single and AX task), verbal fluency test	• WCST (commission errors) – Stroop test: Val/Val ↑ • No association between COMT and CPT and verbal fluency test
Uçok et al.[24]	99	Schizophrenia	—	WCST, CPT (ZA task)	• CPT (commission errors): Val/Val Val/Met ↓ • No association between COMT and WCST
Wilkosc et al.[25]	—		200	WCST	WCST (percentage of nonperseverative errors): Val/Val Val/met ↓ (in males only)
Wirgenes et al.[26]	315	Schizophrenia-spectrum disorders • 137 schizophrenia • 27 schizoaffective disorder • 7 schizophreniform disorder	340	Bergen n-back task, digit symbol coding test, CVLT, D-KEFS (colour-word interference test, verbal fluency test)	• Schizophrenia: n-back task: Val/Val ↓ • No association between COMT and other cognitive measures • Controls: no association between COMT and any cognitive measures
Pomarol-Clotet et al.[27]	42	Schizophrenia	31	N-back task (sequential letter version)	No association between COMT and n-back task
Dennis et al.[28]	—		496 to 1218	CANTAB (paired associates learning, spatial working memory, verbal recognition memory—immediate recall, ID/ED, rapid visual processing, spatial span, spatial recognition memory), Green's story recall (immediate and delayed), TMT A–B, WAIS-III (forward and backward digit span, digit symbol, symbol search), COWAT, semantic fluency, Stroop colour-word interference	No association between COMT and any cognitive measures
Van den Bos et al.[29]	—		70	IGT	Val/Val ↑
Yue et al.[30]	—		21	N-back task (sequential number version)	Val/Met ↓, Val/Val ↑
Krug et al.[31]	—		80	Verbal fluency	No association between COMT and verbal fluency
Neuhaus et al.[32]	111	Schizophrenia	—	CPT-IP	Val/Val ↑
Prata et al.[33]	42	Schizophrenia	48	Verbal fluency task	• Schizophrenia: Val/Val Val/Met ↓ • Controls: no association between COMT and verbal fluency task
Schmack et al.[34]	—		44	Monetary incentive delay	No association between COMT and monetary incentive delay
Sheldrick et al.[35]	—		522	D2 Test of Attention, MWT-B, LNS, TMT B, verbal fluency, Wechsler Memory Scale (spatial span)	• TMT-B: Val/Val ↓ • No association between COMT and other cognitive measures
Roussos et al.[36]	—		107	SoC, IGT	• SoC: Val/Val ↓ • IGT: Val/Val ↑
Roffman et al.[37]	185	Chronic schizophrenia	—	WCST	• No association between COMT and WCST (perseverative errors and category achievement) • COMT x MTHFR mutation interaction: Val/Val +T carriers ↓(perseverative errors)
Opgen-Rhein et al.[38]	63	Schizophrenia	40	ANT	Schizophranie–controls: Val/Val ValMet ↓ reaction time and ↑ conflict effect scores

Table 1: Studies evaluating the association between the COMT Val[158]Met polymorphism and neuropsychological tests (part 2 of 3)

Study	No. patients	Diagnosis	No. controls (relatives)	Cognitive measures	Main results*
Mata et al.[39]	130	First-episode nonaffective psychosis	—	• General verbal ability: WAIS-III (vocabulary, similarities, information, and comprehension subtests) • Attention and processing speed: CPT (correct trials), WAIS-III (digit symbol coding), WAIS-III (forward digits), TMT-A • Executive and perceptual organization function: WAIS-III (backward digits, letter fluency, category fluency), TMT-B • Verbal memory: Rey Auditory Verbal Learning Test (initial learning, total learning, short-term recall, long-term recall, recognition) • Visual memory: Rey complex figure (immediate reproduction, delayed reproduction) • Motor function: Grooved Pegboard Test (dominant and nondominant hand), finger tapping test (dominant and nondominant hand)	No association between COMT and any cognitive domain
Diaz-Asper et al.[40]	325	Schizophrenia, schizoaffective disorder	330 (359)	Spatial n-back task, WCST, CPT 1–9, WAIS-R (short form: arithmetic, similarities, picture completion and digit symbol), ID/ED	Patients, controls, relatives: • N-back task: Val/Val ↓ • No association between COMT and other cognitive measures
Bertolino et al.[41]	—		82	Spatial n-back task, recognition memory paradigm	No association between COMT and any cognitive measures
Aguilera et al.[42]	—		521	WCST, CPT-IP, WMS-R (backward visual span), WAIS III (LNS)	• LNS: Val/Val ↓ • No association between COMT and other cognitive measures
Woodward et al.[43]	86	Schizophrenia	—	ACTT, WCST, WISC-R (mazes), BSRT, CIGT, COWAT, WAIS-R (digit symbol)	• ACTT and WCST (perseverative errors): Val/Val ↓ • No association between COMT and other cognitive measures
MacDonald et al.[44]	—		464	N-back task (sequential letter version), CPT (AX/DPX tasks)	• CPT (DPX): Val/Val ↓ • No association between COMT and performance on N-back
Ehlis et al.[45]	56	Schizophrenia-spectrum disorders	—	Stroop test, TMT A–B, verbal fluency test	• Stroop test: Val/Val Val/Met ↓ (trend significance) • No association between COMT and other cognitive measures
Dickerson et al.[46]	364	Schizophrenia	—	RBANS: immediate memory (list learning and story memory tasks), visuospatial/constructional (figure copy and line orientation tasks), language (picture naming and semantic fluency tasks), attention (digit span and coding tasks) and delayed memory (list recall, story recall, figure recall and list recognition tasks)	No association between COMT and any of the RBANS index
Caldú et al.[47]	—		75	WCST, Conners' CPT II, n-back task, WAIS (vocabulary)	• WCST and CPT (commission errors): Val/Val Val/Met ↓ • No association between COMT and other cognitive measures • CPT (commission errors): COMT x DAT interaction: Val/Val and 10/10 ↓
Barnett et al.[48]	822	Schizophrenia-spectrum disorders	1088	WCST	• Patients: no association between COMT and WCST (perseverative errors) • Controls: WCST (perseverative errors): Val/Val ↓
Szöke et al.[49]	66	Schizophrenia	50 (57 SCZ)	TMT A–B, WCST	Patients, controls, relatives: no association between COMT and any cognitive measure
Rybakowski et al.[50]	79	Schizophrenia	—	WCST	• WCST: Val/Val male ↑ (perseverative errors) • Val/Val female ↓ (nonperseverative errors)
Krabbendam et al.[51]	23	Schizophrenia	21 (33)	CPT (Flanker version)	Patients, controls, relatives: Val/Val ↓ (correct responses)
Han et al.[52]	132M	First-episode schizophrenia, schizoaffective disorder	—	WAIS (information, digit span, vocabulary. arithmetic comprehension, similarity, picture, picture arrangement, block design, object assembly, digit symbol)	• Digit span: Val/Val ↓ • Similarity: Val/Val ↑
Golimbet et al.[53]	124	Schizophrenia	116 (79)	Long-term memory, short-term memory, verbal fluency, selectivity of speech relations, calculating with switching over	No association between COMT and any cognitive measure
Bertolino et al.[54]	—		27	Recognition memory paradigm	Val/Val ↓ (accuracy at retrieval)
Stefanis et al.[55]	—		527	CPT-IP version	Val/Val Val/Met: higher reaction time variability
Ho et al.[56]	159	Schizophrenia	84	WCST, digit span backward, TMT A–B	No association between COMT and any cognitive measure

Table 1: Studies evaluating the association between the COMT Val[158]Met polymorphism and neuropsychological tests (part 3 of 3)

Study	No. patients	Diagnosis	No. controls (relatives)	Cognitive measures	Main results*
Galderisi et al.[57]	106	Schizophrenia	—	CPT (AX task), WCST	CPT (AX errors) and WSCT (perseverative errors): Val/Val ↓
Bruder et al.[58]	—		402	SDR, WSPT, N-back (sequential letter version), LNS, WCST (n = 246)	• WCST and LNS: Val/Val ↓ • No association between COMT and other cognitive measures
Blasi et al.[59]	—		23	Variable attentional control task	Val/Val Val/Met ↓
Rosa et al.[60]	89	Schizophrenia, schizoaffective disorder, psychotic mood disorder, schizophreniform disorder, brief psychotic disorder, delusional disorder, atypical psychosis	(89)	WCST	• Patients: no association between COMT and performance on WCST • Relatives: Val/Val ↓ (perseverative errors)
Nolan et al.[61]	26	Schizophrenia, schizoaffective disorder	—	Competing programs task	Val/Val Val/Met ↓ cognitive stability and ↑ cognitive flexibility
de Frias et al.[62]	—		286 M	Episodic memory (recall test, recognition test), semantic memory (knowledge test, fluency test)	• Recall test: Val/Val Val/Met ↓ • No association between COMT and other cognitive measures
Tsai et al.[63]	—		120 F	WCST	No association between COMT and WCST (perseverative errors)
Goldberg et al.[64]	74	Schizophrenia, schizoaffective disorder (depressed type)	68 (108)	Spatial n-back task, CPT 1–9, WAIS-R (IQ similarities, arithmetic, picture completion and digit symbol)	• **Patients**, controls, relatives: n-back task: Val/Val ↓ • No association between COMT and other cognitive measures
Malhotra et al.[65]	—		73	WCST	WCST (perseverative errors): Val/Val Val/Met ↓
Joober et al.[66]	94	Schizophrenia	31	WCST	• Patients: WCST (perseverative errors): Val/Val Val/Met ↓ • Controls: no association between COMT and WCST (perseverative errors)
Bilder[1]	58	Schizophrenia, schizoaffective disorder	—	• General executive and perceptual organization: LNS, WCST, category fluency, letter fluency, block design, visual reproductions I and II • Declarative verbal learning and memory: paragraph recall I and II, word list learning I and II • Processing speed and attention: TMT A–B, digit symbol	Processing speed and attention domain: Val/Val ↓
Egan et al.[67]	175	Schizophrenia	55 (219)	WCST, WAIS-R, WRAT	Patients, controls, relatives: WSCT (perseverative errors): Val/Val ↓

ACTT = Auditory Consonant Trigram Test; ANT = Attention Network Test; BSRT = Buschke Selective Reminding Test; CANTAB = Cambridge Neuropsychological Test Automated Battery; CIGT = Category Instance Generation Test; COMT = catechol-O-methyltransferase; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Test; CPT-IP = Continuous Performance Test, Identical Pairs version; CVLT = California Verbal Learning Test; DAT = dopamine transporter; D-KEFS = Delis–Kaplan Executive Function System; F = female; DPX = Dot Pattern Expectancy task; ID/ED = intradimensional/extradimensional shift task; IGT = Iowa Gambling Task; LNS = letter and number sequencing; M = male; MSIT = Multi-Source Interference Task; MWT-B = Mehrfachwahl-Wortschatz- Intelligenztest B; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SDR = Spatial Delayed Response; SoC = Stockings of Cambridge; TMT = Trail Making Test; WAIS = Wechsler Adult Intelligence Scale; WAIS III = Wechsler Adult Intelligence Scale-III; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WASI = Wechsler Abbreviated Scale of Intelligence; WCST = Wisconsin Card sorting Test; WISC-R = Wechsler Intelligence Scale for Children-Revised; WMS-R = Wechsler Memory Scale-Revised; WRAT = Wide Range Achievement Test; WSPT = Word Serial Position Test.

with Met/Met carriers performing slightly better than Val/Val carriers. However, this association was not found in patients with schizophrenia.

Subsequent studies have partially confirmed these findings, reporting an association between Val/Val and Val/Met genotypes and a higher number of perseverative errors[47] and nonperseverative errors[25] and fewer commission errors[23] in healthy individuals than in patients with schizophrenia and schizoaffective disorder.[24,37,40] In contrast, other studies found the Val/Val genotype to be associated with worse performance in terms of perseverative errors[43] and found the Val/Met genotype to be associated with lower number of categories achieved[19] in patients with schizophrenia but not in healthy individuals[42] or unaffected relatives.[40] Moreover, an interaction between the COMT Val[158]Met polymorphism and the MTHFR C677T mutation on WCST performance has been found in patients with schizophrenia, with COMT Val/Val carriers who had at least 1 copy of the MTHFR T allele making more perseverative errors.[37]

Trail Making Test (TMT) A and B

The TMT-A requires sequencing, psychomotor speed and visuoperceptual ability; part B also requires cognitive flexibility and working memory.[71,72] Performance on the TMT-A has not been found to be associated with the COMT Val[158]Met polymorphism in patients with schizophrenia[45,49,56] or healthy individuals.[20,28,56] Worse performance on the TMT-B has been found to be associated with Val/Val and Val/Met genotypes in healthy individuals in 1 study[20] but not in others,[28,56] nor in those evaluating patients with schizophrenia.[45,49,56]

Interestingly, an association between the COMT Val^{158}Met polymorphism and worse TMT-B performance has been reported in healthy individuals carrying both the COMT Val allele and the ANKK1 (rs1800497) T allele.[20]

Verbal fluency

Verbal fluency is considered to be an executive function task and a semantic memory measure.[53] Both Val/Val and Val/Met carriers with schizophrenia have been reported to perform worse in 1 study,[33] but this association has not been confirmed by other studies involving patients with schizophrenia,[26,53] their relatives[53] or healthy controls.[23,28,33,53,62,73]

Digit span

Composed by 2 parts, forward and backward, the digit span test is considered to be a short-term memory measure, with the digit span backward also involving working memory.[56] A worse performance on digit span has been found to be related to the Val/Val genotype in patients with schizophrenia and schizoaffective disorder in 1 study,[52] but not in another study involving patients with schizophrenia.[19] Of note, the sample size of the former study[52] was considerably larger than that in the latter study.[19] Only the digit span backward has not been found to be associated with the COMT Val^{158}Met polymorphism in patients with schizophrenia.[74]

According to our criteria, only the n-back task and the CPT can be considered strongly related to the COMT Val^{158}Met polymorphism in patients with schizophrenia. In healthy controls, these associations seem to be weaker or absent. Interestingly, some fMRI studies that used an n-back paradigm detected a significant association between the COMT Val^{158}Met polymorphism and the activation of the frontal cortex in patients with schizophrenia[26] and healthy controls[21,26,41,75] regardless of n-back task performance. Thus, fMRI may be a more sensitive approach to the evaluation of the neuronal circuitry affected by variation in the *COMT* gene and n-back task performance and when cognitive performance is not affected.

The n-back task and the CPT assess working memory and attention modulation, respectively. Interestingly, although the evidence available is not yet sufficient to make them satisfy our criteria of performance in other working memory tasks (e.g., letter and number sequencing, Auditory Consonant Trigram Test) and in tasks of attentional modulation (e.g., Attention Network Test, Variable Attentional Control Task), these tasks seem to be associated with the COMT Val^{158}Met polymorphism in patients with schizophrenia. On the other hand, verbal fluency and digit span backward have not been found to be associated with the COMT Val^{158}Met polymorphism in patients with schizophrenia or in healthy controls. However, this result may reflect the lack of association between the COMT Val^{158}Met polymorphism and semantic and short-term memory, respectively, which are both required for performing these tasks.

The WCST, which assesses executive function, has been related to the COMT Val^{158}Met polymorphism in healthy controls but not in patients with psychosis.[48] It is plausible that other COMT polymorphisms or other genetic variants or nongenetic factors might influence the performance on this task in individuals with psychosis.

Step 1b: Association between the COMT Val^{158}Met polymorphism and brain structure

We identified 13 studies (Table 2) exploring the association between brain structure (global or regional volumes of grey and white matter) and the COMT Val^{158}Met polymorphism. We report the regions that satisfied the first criterion (i.e., at least 3 studies evaluated the association between the COMT Val^{158}Met polymorphism and those brain areas in either patients or healthy controls).

Temporal regions

The most consistent finding has been that of an association with temporal areas. In patients with schizophrenia, a smaller volume of the hippocampus,[9] amygdala-uncus[9,11] and middle temporal gyrus[11] has been associated with the Val/Val and Val/Met genotypes. Interestingly, this association has not been found in studies that included patients with any psychosis,[79,80,83] indicating that the association may be specific to schizophrenia. In healthy individuals, smaller hippocampal,[9,78,81,82] amygdalar,[9] total and grey matter temporal lobe[82] volumes as well as reduced thickness of the right superior temporal sulcus[77] have been reported in Val/Val carriers. In contrast, other studies have failed to find a significant association between the COMT Val^{158}Met polymorphism and temporal lobe volumes in healthy individuals or in unaffected relatives of patients with psychosis.[11,79,84]

Frontal areas

The Val/Val genotype has been associated with smaller grey matter density in the anterior cingulate cortex in a population at high risk for psychosis[10] and with smaller grey matter volume in the left anterior cingulate cortex in patients with chronic schizophrenia.[11] However, these findings have not been replicated by other studies.[9,56,83] Interestingly, carriers of both the COMT Val allele and the PRODH GT or TT genotypes for rs20086720 have been found to have larger white matter volume of the inferior frontal area.[80] This may suggest that the COMT Val^{158}Met polymorphism affects frontal region morphology via an interaction with other genes, which may help explain the inconsistency found in the association between the COMT Val^{158}Met polymorphism and frontal volumes. In healthy individuals, both the Val/Val and Val/Met genotypes have been associated with greater grey matter volume of the prefrontal,[81] and (albeit at trend level) dorsolateral prefrontal cortex[78] and with a reduced thickness of the right inferior prefrontal sulcus;[77] however, these findings have not been confirmed by other studies.[9,11,56,76,84]

Lateral ventricles

In patients with first-episode schizophrenia with nonaffective psychoses, a significant enlargement of lateral ventricles has been reported in both Met/Met and Val/Met carriers.[83] This finding has not been replicated in studies involving patients

with any psychosis,[11,79] in unaffected relatives[79] or in healthy individuals.[11,79,84]

Thalamus

A reduced volume of the left thalamus has been associated with the COMT Val allele in patients with chronic schizophrenia,[11] but not in healthy controls.[11,84] Subsequent studies have not confirmed this association in patients.[80,83]

According to our criteria, only temporal and frontal volumes can be considered to correlate with the COMT Val[158]Met

Table 2: Studies evaluating the association between brain structures (global or regional grey and white matter volumes) and the COMT Val[158]Met polymorphism

Study	No. patients	Diagnosis	No. controls (relatives)	MRI analysis (Tesla)	Regions evaluated	Main results
Barnes et al.[76]	—		82	Automated (1.5 T)	Total grey matter volume, DLPFC	No association
Cerasa et al.[77]	—		149	Automated (3 T)	Whole brain	Val/Val ↓ thickness of the right inferior prefrontal sulcus and right superior temporal sulcus
Ehrlich et al.[9]	98	Schizophrenia	114	Automated (3 T and 1.5 T)	Whole brain, frontal lobe, hippocampal and amygdala volumes	Patients: Val/Val Val/Met ↓ bilateral amygdala and right hippocampal volumes; no association between COMT and whole brain and frontal regions Controls: Val/Val Val/Met ↓ bilateral amygdalae and right hippocampal volumes; no association between COMT and whole brain and frontal regions
Honea et al.[78]	—		151	Automated VBM/ROI (1.5 T)	Whole brain, DLPFC, hippocampal volumes	Val/Val Val/Met ↓ grey matter volume in hippocampus and parahippocampal gyrus; Val/Val ↑ (trend) grey matter volume in DLPFC; no association between COMT and whole brain
Dutt et al.[79]	128	Schizophrenia, bipolar disorder, schizoaffective disorder, psychotic disorder NOS	61 (194)	Automated (1.5 T)	Left hippocampal volume, right hippocampal volume and total lateral ventricular volume	No association
Zinkstok et al.[80]	51	Schizophrenia, schizoaffective disorder	—	Automated VBM (1.5 T)	Regional grey and white matter density and total grey and white matter volume	No association between COMT and grey or white matter density; COMT x PRODH rs20086720: Val allele T allele ↑ white matter density in the left inferior frontal lobe
Cerasa et al.[81]	—		57	Automated VBM (1.5 T)	Hippocampus and prefrontal cortex volumes	Val/Val ↓ hippocampal grey matter volumes bilaterally; Val/Val Val/Met ↑ prefrontal cortex greater grey matter volume bilaterally and ↓ tissue volume of the hippocampus bilaterally
Taylor et al.[82]	—		31	Automated (1.5 T)	Whole brain, hippcampus, amygdala, caudate and temporal lobe volumes	Val/Val ↓ temporal lobe (total and grey matter) and hippocampus volumes; no association between COMT and whole brain, caudate and amygdala volumes.
McIntosh et al.[10]	—	High-risk for schizophrenia	15 (78)	Automated VBM (1 T)	Prefrontal cortex	Val/Val Val/Met ↓ anterior cingulate cortex grey matter density
Crespo-Facorro et al.[83]	75	Schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis NOS, brief reactive psychosis	—	Automated (1.5 T)	Global and lobar volumes of grey matter and CSF	Met/Met Val/Met ↑ lateral ventricles, right lateral ventricle and left lateral ventricle
Zinkstok et al.[84]	—		154	Automated VBM (1.5 T)	Total and regional grey matter and white matter density	No association between COMT and grey or white matter volumes and densities
Ohnishi et al.[11]	47	Schizophrenia	76	Automated TBM/whole brain and ROI (1.5 T)	Whole brain morphology, DLPFC	Controls: no association between COMT and any brain structure Patients: Val/Val ↓ left amygdala-uncus, bilateral anterior cingulate cortex, right middle temporal gyrus, left thalamus; no association between COMT and DLPFC
Ho et al.[56]	100	Schizophrenia	49	Automated (1.5 T)	Frontal lobe grey matter, white matter and CSF volumes	Controls: no association between COMT and frontal lobe morphology Patients: no association between COMT and frontal lobe volume

COMT = catechol-O-methyltransferase; CSF = cerebrospinal fluid; DLPFC = dorsolateral prefrontal cortex; MRI = magnetic resonance imaging; NOS = not otherwise specified; ROI = region of interest; TBM = tensor-based morphometry; VBM = voxel-based morphometry.

polymorphism in schizophrenia, with temporal volumes also associated with this genotype in healthy controls. Interestingly, the association between the COMT Val[158]Met polymorphism and temporal and frontal areas has also been explored in fMRI studies. The Val allele has been reported to be associated with a reduced activation of the medial temporal lobe during an episodic memory task in healthy controls,[54,85] whereas in schizophrenia the Met allele has been reported to be associated with a reduced activation in this area.[86] Moreover, a recent meta-analysis[87] that evaluated 20 studies involving mostly healthy individuals showed a significant association between the Val allele and increased prefrontal activation. This finding has also been reported in patients with schizophrenia and in their relatives.[27,67]

Step 2a: Can the neuropsychological tasks identified (n-back and CPT) be considered endophenotypes?

N-back task

Association with the illness: Several studies suggest that patients with schizophrenia have worse n-back accuracy during high working memory load conditions and longer reaction time.[40,64,88]

Heritability: The n-back heritability seems high, at 72.9% for accuracy and 56.4% for reaction time, as found in healthy twins.[89]

State independence: Impairment in the n-back task has been reported in patients with schizophrenia at various illness stages,[90–92] before and after antipsychotic treatment[92] and independent of illness duration.[91]

Cosegregation with illness within family: Cosegregation is suggested by evidence that this impairment is present in relatives of patients with schizophrenia, who perform better than probands.[40,64,88,93] Moreover, a significant influence of familial loading on visuospatial working memory has been detected in patients with schizophrenia but not in patients with schizoaffective disorder.[94]

Presence in unaffected relatives: With the exception of 2 studies,[95,96] n-back performance has been found to be impaired in unaffected relatives of patients with schizophrenia in comparison to healthy controls.[40,64,88,93]

Continuous Performance Test

Association with the illness: Schizophrenia has been consistently associated with impairment in CPT discrimination accuracy and reaction time.[12,40,64,97,98]

Heritability: The heritability for *d'* of the CPT, Identical Pairs version (CPT-IP), has been estimated at around 39% for verbal and 49% for spatial attention.[99] For the X-CPT, the heritability has been reported to vary between 48% and 62%.[100,101]

State independence: It has been reported that at-risk offspring in whom a schizophrenia-spectrum disorder later developed had attentional deficits as early as age 12 years, with the impairment persisting over the following 15 years.[102]

Cosegregation with illness within family: CPT impairment may cosegregate with psychosis, as suggested by its presence among family members of patients with schizophrenia.[12] Moreover, there is evidence that nonpsychotic siblings from multiplex families exhibit worse performance on a degraded CPT version as well as less proficiency in processing the perceptual load when compared with those from simplex families.[103]

Presence in unaffected relatives: Unaffected relatives of patients with schizophrenia show impairment in discrimination accuracy at the CPT-IP.[12] However, studies that used different versions of the CPT have not reported impairment in discrimination accuracy.[40,64] Relatives of patients with schizophrenia have also been found to have an impairment in hit reaction time in comparison to healthy controls.[98]

Both the n-back and the CPT can be considered useful endophenotypes for schizophrenia.

Step 2b: Can the previously identified brain structures (temporal and frontal areas) be considered endophenotypes?

Temporal areas

Association with the illness: Meta-analyses suggest that a reduction of total and medial temporal (amygdala–uncus–hyppocampus) volumes is present in patients with schizophrenia, particularly in the hippocampus.[104–110]

Heritability: A moderate heritability (40%–69%) for hippocampal volume has been reported in twin studies in healthy controls.[111]

State independence: Hippocampus reductions seem to be state-independent and have been reported in patients at both first episode and chronic illness stages.[112]

Cosegregation with illness within the family: Cosegregation is suggested by the presence of hippocampal volume reduction among relatives of patients with schizophrenia,[113] particularly in multiplex families.[114]

Presence in unaffected relatives: Results from a meta-analysis indicate that amygdalar and hippocampal volume reductions are also present in relatives of patients with schizophrenia.[113]

Frontal areas

Association with the illness: Various meta-analyses have consistently reported volume reductions in medial prefrontal and anterior cingulate cortices[104–106,115] in patients with schizophrenia.

Heritability: The heritability of total frontal lobe volumes seems to be high (90%–95%); changes in ventrolateral prefrontal cortex, anterior cingulate gyrus, superior frontal cortex and anterior cingulate volumes have also been found to be highly heritable.[111] Moreover, a twin study has reported an association between smaller prefrontal grey matter volume and increasing genetic proximity to a patient with schizophrenia (monozygotic co-twins > dizygotic co-twins > control twins).[116]

State independence: Decreased prefrontal and cingulate grey matter volumes have been reported in high risk individuals who subsequently transition to psychosis[117,118] as well as in patients with first-episode and chronic schizophrenia.[104,110,115] Reductions in some regions of the frontal cortex seem to be a feature of high-risk people in whom schizophrenia or schizoaffective disorder subsequently develops.[119]

Cosegregation with illness within family: Cosegregation of the smaller prefrontal cortex within schizophrenia families is suggested by evidence of smaller volumes in this region in family members, albeit to a lesser extent than in affected relatives.[120,121] Moreover, there is evidence of a negative correlation between grey matter volume and increasing genetic risk for schizophrenia.[122]

Presence in unaffected relatives: Relatives of patients with schizophrenia show grey matter volume reductions in the total frontal lobe,[120] prefrontal cortex[123] and anterior cingulate gyrus[110,115,121] in comparison to healthy individuals. However, this finding has not been replicated in other studies.[124,125]

Reduced grey matter volume in the medial temporal and prefrontal cortices can be considered a useful endophenotype for schizophrenia.

Step 3: Are the previously identified neuropsychological endophenotypes associated with these brain structural endophenotypes?

Six studies (Table 3) have examined the association between the n-back and CPT and the brain structural endophenotypes we identified in step 2 (grey matter volume of medial temporal and prefrontal cortices).

N-back task

Although the association between n-back task and prefrontal brain function has been frequently explored with fMRI in patients with schizophrenia[88,126–129] and in their relatives,[95] the association between this test and prefrontal (or temporal) volume in patients with schizophrenia has not been explored. In healthy controls, only 1 study has been conducted, reporting no association between n-back performance and hippocampal and amygdalar volume.[130] However, reduced prefrontal activation during the n-back task has been associated with a reduction in prefrontal volume in people at ultra-high risk for psychosis, suggesting that "these 2 fundamental pathophysiological features of the disorder are interrelated."[117] Moreover, 2 studies that adopted working memory tasks similar to the n-back task (the Wechsler Adult Intelligence Scale arithmetic subtest and digit span backward, respectively) reported a association between worse working memory performance and reduced frontal, prefrontal and temporal lobe volumes in patients with schizophrenia.[131,132] Taken together, these data suggest that worse n-back performance is associated with reduced prefrontal and temporal lobe volumes. Interestingly, an impaired performance on the n-back task has also been described in individuals with focal prefrontal damage,[133] suggesting that this

Table 3: Studies evaluating the association between the n-back task and Continuous Performance Test and brain structure

Study	No. patients	Diagnosis	No. controls (relatives)	MRI analysis (Tesla)	Regions evaluated	Cognitive measures	Main results*
Piras et al.[130]	—	—	181	ROI (3 T)	Caudate, putamen, pallidum, thalamus, hippocampus and amygdala	N-back task	No association
Crespo-Facorro et al.[136]	142	Psychosis • 82 schizophrenia • 36 schizophreniform disorder • 24 patients with nonschizophrenic, nonaffective psychoses	83	Automated segmentation global volumes and ROIs (1.5 T)	Volumes of whole brain, total grey matter, total white matter, cortical CSF and lateral ventricles, grey matter volumes of cortical (occipital, parietal, temporal and frontal lobes) and subcortical (caudate nucleus, thalamus and putamen) regions	CPT	Controls: ↑ CPT, ↓ lateral ventricle volume Patients: no association
Laywer et al.[135]	71	Schizophrenia	65	Semiautomated and fully manual (1.5 T)	Frontal, occipital, parietal, temporal and occipital lobes, subcortical region, CSF volume of the ventricles I, II and III, intracranial volume, corpus callosum, caudate, putamen, hippocampus, cerebellum, the posterior superior, posterior inferior and anterior vermis, and cerebellar tonsil	CPT	Controls/patients: association with putamen volumes and vermis regions
Salgado-Pineda et al.[134]	13	Antipsychotic-naive schizophrenia	13	Automated VBM and ROI (1.5 T)	Whole brain grey matter, white matter and CSF, thalamus	CPT	Controls: no association Patients: ↑ CPT (*d'* scores), ↑ grey matter density in the left thalamic nucleus, left angular, supramarginal gyrus, left inferior frontal and postcentral gyri, grey matter density of the left and right thalamus
Antonova et al.[8]	45	Schizophrenia	43	Automated VBM (1.5 T)	Whole brain volume and grey matter	CPT	Controls/patients: no association
Goldberg et al.[137]	14	Schizophrenia	(14 co-twins)	Automated (1.5 T)	Hippocampus, third ventricle and a large section of the lateral ventricles	CPT	Patients/relatives: no association

CPT = Continuous Performance Test; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; ROI = region of interest; VBM = voxel-based morphometry.
*↑ (neuropsychological task) = better performance.

deficit may be shared by other disorders that primarily affect the prefrontal cortex.

Continuous Performance Test

A worse CPT performance has been associated with smaller prefrontal volume in patients with schizophrenia,[134] but not in studies that included patients with any psychosis[8,135,136] or healthy individuals.[8,134–136] Studies in patients with schizophrenia, their unaffected co-twins and healthy controls have found no association between CPT performance and hippocampal volume.[8,134–137]

These findings suggest that worse performance on the n-back task is associated with smaller prefrontal and medial temporal volumes and that worse CPT performance is associated with smaller prefrontal volume in patients with schizophrenia. Consistent with this evidence, a meta-analysis of fMRI studies reported that the dorsolateral prefrontal cortex and the anterior cingulate cortex were less activated during the n-back task in patients with schizophrenia.[128] On the other hand, prefrontal cortex activation has been found to be associated with the CPT in patients with schizophrenia[138–140] and in their relatives.[141]

Discussion

To our knowledge, this is the first systematic review to comprehensively evaluate evidence on the link between the COMT Val^{158}Met polymorphism and neuropsychological performance and brain structures in patients with schizophrenia, in their relatives and in healthy controls. We found that the n-back task and the CPT (a working memory task and an attentional modulation task, respectively) are the only 2 neuropsychological tasks strongly associated with the COMT Val^{158}Met polymorphism in patients with schizophrenia. More specifically, among patients, the Val/Val carriers showed a worse performance in both the n-back task and the CPT, with a greater number of errors, but a better performance in signal discrimination. Interestingly, evidence from fMRI studies suggests that performance on these 2 tasks is positively correlated with lower prefrontal cortex activation in patients with schizophrenia. This suggests that the cognitive domains assessed by these tasks reflect "the operation of a common underlying cognitive control mechanism supported by the prefrontal cortex."[142] Moreover, this evidence is consistent with the tonic–phasic DA hypothesis,[143] which suggests that tonic DA may stabilize and maintain relevant information ("cognitive stability") principally via D_1 receptors, while phasic DA is important for updating and manipulating information ("cognitive flexibility"), principally via D_2 receptors.[144] In the COMT Val^{158}Met polymorphism, while the Val allele increases phasic DA transmission and is expected to improve cognitive flexibility, the Met^{158} allele increases tonic DA transmission, and is therefore expected to improve working memory and executive functions that require cognitive stability.[145] Furthermore, since some neuropsychological tests require both cognitive stability and cognitive flexibility,[145] the DA hypothesis may help explain the inconsistency in findings regarding the association between the COMT Val^{158}Met polymorphism and neuropsychological performance.

With respect to brain structure, the evidence reviewed points to an association between smaller temporal areas (e.g., hippocampus, amygdala, middle temporal gyrus) and the Val/Val and Val/Met genotypes in patients with schizophrenia. Smaller frontal areas also seem to be associated with the Val/Val genotype in patients with schizophrenia and in people at high risk for psychosis. This is interesting since CPT performance is associated with prefrontal cortex volume in patients with schizophrenia. Although, to our knowledge, no study has been conducted to date using the n-back task and structural MRI, we speculate that this test may be associated with both prefrontal and medial temporal volumes in view of evidence of prefrontal activation during the task[88,95,126–129] and of an association between worse working memory performance and smaller frontal, prefrontal and temporal lobe volumes.[131,132] Moreover, both neuropsychological tasks (n-back task and CPT) and brain regional volumes (medial temporal and prefrontal cortex), which have been reported to be associated with the COMT Val^{158}Met polymorphism, met most of the criteria for an endophenotype.

Taken together, these results suggest that the COMT Val^{158}Met polymorphism may contribute to 2 neuropsychological and 2 brain structural endophenotypes that characterize schizophrenia, with the prefrontal cortex representing a common neural substrate underlying both n-back task and CPT performance. It is interesting to note that the association between the COMT Val^{158}Met polymorphism and the endophenotypes detected (with the exception of the hippocampus) is more evident in patients with schizophrenia than in healthy controls. This suggests that this polymorphism alone is not sufficient to produce a variation at the neuropsychological and brain structural levels. The presence of these endophenotypes (e.g., working memory impairment, prefrontal cortex grey matter volume reduction) seems to result from an interaction between the COMT Val^{158}Met polymorphism and other genetic and nongenetic (e.g., environmental) factors (possibly present in excess in affected individuals), which together contribute to shape the neuropsychological and brain structural alterations that characterize schizophrenia.[47,80,146] We speculate that alterations in the fine-tuning of cortical DA may be responsible for worse neuropsychological performance and for brain volume reductions. More specifically, the COMT Val carriers may have reduced DA levels in the prefrontal cortex, leading to a decrease in D_1 receptor activation with subsequent impairment in cognitive tasks, such as working memory.[147] In fact, working memory seems to be related to the activity of both D_1 and D_2 receptors: the D_1 receptors would signal to prefrontal pyramidal neurons via *N*-methyl-D-aspartate postsynaptic receptors, maintaining and stabilizing task-relevant signals while reducing signal-to-noise ratio in the prefrontal cortex via GABAergic inhibitory effect on nonrelevant "noisy" signals. The D_2 receptors would in turn allow the development of new informative signals.[147] In addition, the presence of the COMT Val allele may indirectly influence the neurodevelopment and neuroplasticity processes, ultimately leading to changes in the volume of brain areas such as the prefrontal cortex. Since *COMT* is

responsible for DA cortical availability,[67] it may also be implicated in key neuronal processes that ultimately lead to brain morphogenesis and development. How this actually occurs remains to be established. Interestingly, a recent review has proposed that *COMT* influences neurodevelopment and neuroplasticity via an epistatic interaction with other genes, such as *AKT1*.[148] *AKT1* and dopaminergic pathways have already been shown to be synergistically responsible for neuronal atrophy after chronic opiate exposure.[148,149] Also, genetic variation in *AKT1* has been linked to DA-associated prefrontal cortical structure and function in humans.[148] It is possible that the combination of different risk alleles results in impaired prefrontal activity during challenging cognitive tasks and in changes in key neurodevelopmental pathways affecting neuronal morphology and development.[150]

Limitations

The main limitation to our interpretation of the literature is that the association between a single genetic variant and an endophenotype does not necessarily imply a causal relationship between them. In other words, we hypothesized that the COMT Val^{158}Met polymorphism, which affects prefrontal DA levels, may contribute to both CPT and n-back impairment and reduced prefrontal and medial temporal volume. However, schizophrenia is characterized by a complex genetic architecture, with an intricate interplay among several genes. As mentioned previously, the COMT Val^{158}Met polymorphism can interact with other genes in shaping the neuropsychological profile and the brain structural alterations that characterize schizophrenia (for example, see the studies by Caldú and colleagues,[47] Zinkstok and colleagues,[80] and Dickinson and colleagues[146]).

Moreover, variables such as sex and age need to be taken into account. For example, estrogen reduces COMT enzymatic activity, and the production of estrogen varies across age.[146] Finally, the COMT Val^{158}Met polymorphism interacts with environmental factors like stress. This has been suggested by a recent study reporting that individuals homozygous for Met performed significantly worse than those homozygous for Val on the n-back task under stress.[151] This highlights the importance of considering the complex interaction between genes and environment when evaluating neurocognitive performance.[151]

In view of this complexity, it is possible that the endophenotypes we found to be associated with the COMT Val^{158}Met polymorphism are also related to other polymorphisms. Furthermore, there is little evidence on the association between neuropsychological tasks and brain structure in patients with schizophrenia, and the link we suggest in this review needs further investigation. With these caveats in mind, this may explain, at least in part, the biological substrate of 4 important endophenotypes that characterize schizophrenia.

Conclusion

Our review comprehensively evaluated evidence on the link between the COMT Val^{158}Met polymorphism and both neuropsychological performance and brain structure in patients with schizophrenia and their relatives, and in healthy controls. The review also summarized this evidence within a biological framework that may be used to advance our knowledge on the molecular mechanisms that underlie the pathophysiology of schizophrenia.

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