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The catechol-O-methyltransferase (*COMT*) Val158Met genotype modulates working memory-related dorsolateral prefrontal response and performance in bipolar disorder

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Objectives: Cognitive dysfunction affects a substantial proportion of patients with bipolar disorder (BD), and genetic-imaging paradigms may aid in the elucidation of mechanisms implicated in this symptomatic domain. The Val allele of the functional Val158Met polymorphism of the catechol-O-methyltransferase (*COMT*) gene is associated with reduced prefrontal cortex dopamine and exaggerated working memory-related prefrontal activity. This functional magnetic resonance imaging (fMRI) study investigated for the first time whether the *COMT* Val158Met genotype modulates prefrontal activity during spatial working memory in BD.

Methods: Sixty-four outpatients with BD in full or partial remission were stratified according to *COMT* Val158Met genotype (ValVal [n=13], ValMet [n=34], and MetMet [n=17]). The patients completed a spatial n-back working memory task during fMRI and the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory test outside the scanner.

Results: During high working memory load (2-back vs 1-back), Val homozygotes displayed decreased activity relative to ValMet individuals, with Met homozygotes displaying intermediate levels of activity in the right dorsolateral prefrontal cortex (dlPFC) (*P*=.016). Exploratory whole-brain analysis revealed a bilateral decrease in working

memory-related dlPFC activity in the ValVal group vs the ValMet group which was not associated with differences in working memory performance during fMRI. Outside the MRI scanner, Val carriers performed worse in the CANTAB Spatial Working Memory task than Met homozygotes ($P \leq .006$), with deficits being most pronounced in Val homozygotes.

Conclusions: The association between Val allelic load, dlPFC activity and WM impairment points to a putative role of aberrant PFC dopamine tonus in the cognitive impairments in BD.

KEYWORDS

bipolar disorder, catechol-O-methyltransferase (*COMT*) Val158Met, functional magnetic resonance imaging (fMRI), working memory

1 | INTRODUCTION

Cognitive dysfunction across attention, memory, and executive function is a core feature of bipolar disorder (BD), which persists after clinical remission from mood episodes and impedes patients' functional recovery.[1,2] Unaffected first-degree relatives of patients with BD display similar non-specific, albeit generally milder, cognitive deficits,[3] indicating that cognitive dysfunction is associated with genetic liability for BD. Functional magnetic resonance imaging (fMRI) studies of BD patients and high-risk groups show consistently that the cognitive deficits are accompanied by aberrant (hypo- and hyper-) activity in the dorsolateral and medial prefrontal cortex (dlPFC and mPFC) during working memory (WM) performance.[4-11] Nevertheless, there is little understanding of the association between cognitive deficits, abnormal neural activity, and genetic liability for BD.

A risk gene encoding the enzyme catechol-O-methyltransferase (*COMT*) has attracted attention as a common candidate gene for both neuropsychiatric illness and cognitive dysfunction.[12] The functional Val158Met polymorphism (rs4680) of the *COMT* gene mediates the degradation of dopamine (DA) in the synaptic cleft, and its Val allele seems to be associated with lower levels of synaptic DA in the PFC, while the Met allele is related to higher PFC DA levels.[13] Evidence from animal and human studies suggests that hyper- and hypo-dopaminergic states contribute to mania and depression, respectively (eg, 14,15). Thus, an increase of synaptic DA levels can create manic phenotypes (eg, 16). Conversely, psychotropics that cause DA depletion can induce a depressed state (eg, 17,18), whereas the DA agonist pramipexole attenuates depressive symptoms in depressed BD patients.[19-21] The relationship between DA activity in the PFC and cognitive performance has been described as an inverted U-shape, in which both high and low cortical DA tonus is associated with cognitive impairments.[22] Indeed, there is relatively consistent evidence from studies on schizophrenia and healthy samples for poorer cognitive function in Val homozygotes (with low PFC DA tonus) relative to Met carriers, particularly within the executive function domain,[12,23-26] although some studies found no such association.[27-29] At the neural level, the Val allele (particularly Val homozygosity) is associated with

exaggerated dlPFC activity during n-back WM across patients with schizophrenia and healthy individuals where no behavioral impairments are observed.[13,30-35] This evidence has led to the hypothesis of inefficient prefrontal processing in Val homozygotes, as reflected by a need to recruit greater dlPFC resources to maintain normal task performance.[36,37]

Despite evidence linking the *COMT* Val158Met genotype to neural and cognitive impairments, its influence on neurocognitive function in BD is unclear. One study found that cognitive dysfunction in patients with BD type I is modulated by the presence of a Val allele, with Val carriers (n=54) exhibiting lower deficits in executive function and verbal fluency relative to Met homozygotes (n=18) during manic and mixed episodes.[38] Another study found no effect of the Val allele on attention, verbal memory, or executive function in 52 clinically stable patients with BD type I,[39] although a second functional polymorphism within *COMT* (rs165599) was found to influence verbal memory. However, no neuroimaging study has investigated the association between *COMT* Val158Met and WM-related neural response in BD, which could provide a more sensitive assay of abnormal brain function than behavioral measures.[40,41] The present fMRI study therefore aimed to investigate whether the *COMT* Val158Met polymorphism modulates dlPFC activity during the spatial n-back WM task and WM performance in remitted patients with BD. We hypothesized that Val homozygous remitted BD patients would exhibit (i) greater dlPFC activity during high-load n-back WM and (ii) impaired performance on a spatial WM test relative to Met carriers.

2 | METHODS

2.1 | Study design and participants

The study included baseline data from patients with BD recruited for two randomized intervention studies targeting cognitive dysfunction.[42,43] Patients, 18–65 years of age, were screened with Schedules for Clinical Assessment in Neuropsychiatry to confirm ICD-10 diagnosis of BD and were rated with the Hamilton Depression Rating Scale (HDRS-17; REF) and Young Mania Rating Scale (YMRS) to confirm

partial or full remission (HDRS-17 and YMRS scores <14). Participants reported moderate to severe cognitive difficulties according to the Cognitive and Physical Functioning Questionnaire (CPFQ)[44] (score ≥4 on at least two domains). The original studies were approved by the local ethics committee, Danish Medicines Agency, and Danish Data Agency, and registered at clinicaltrials.gov (numbers NCT00916552 and NCT01457235, respectively). After complete description of the study, written informed consent was obtained from all participants. For further details on the recruitment and screening procedures, please refer to previous work.[42,43]

2.2 | Genotyping

Genomic DNA was extracted from blood samples using the Maxwell Blood DNA purification kit (Promega, Madison, WI, USA) in accordance with the manufacturer's protocol and genotyped using the Illumina Infinium PsychArrayBeadChip (Illumina, San Diego, CA, USA).

2.3 | Neurocognitive tests

N-back WM tasks were employed as they are widely used to probe memory aspects of executive function.[45] During fMRI, participants performed a spatial n-back WM task.[46] The task consisted of blocks of three types of conditions that differed in terms of WM load (0-back, 1-back and 2-back). In each condition, a yellow circle appeared in a sequence of 14 appearances at random locations in a 5 by 5 grid. The circle was displayed for 300 ms followed by an empty grid for 1200 ms. In 1-back and 2-back conditions, patients indicated with a button press when the circle appeared at the same location as one trial and two trials back, respectively. During the 0-back condition, patients pressed a button when the circle appeared in one of the four grid corners. The blocks had an average of three target trials and were presented successively five times (15 blocks in total) interleaved with 8-second fixation crosses. The total task length was 7 minutes 35 seconds.

Within the week of the fMRI scan [mean ± standard deviation (SD) 3.3±2.5 days], participants were also given a spatial working memory (SWM) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) on a laptop computer as part of a larger neurocognitive test battery (for details see Demant et al.[47]). This task was selected for the present study because it probes similar aspects of WM to the spatial n-back WM paradigm administered inside the scanner, thus providing a sensitive behavioral read-out of spatial WM. Moreover, we were interested in the domain of WM more specifically due to prior reported effects of COMT on this domain. Behavioral outcome measures of interest were the 'between errors' score, as indicated by the number of errors made (i.e., on 4–8 boxes), and the 'strategy' score, specifying the number of times inefficient search strategies were used.

2.4 | Magnetic resonance imaging

Whole-brain MRI data were collected at the Danish Research Centre for Magnetic Resonance with a 3 Tesla Siemens Trio MR scanner (Siemens, Erlangen, Germany) using an eight-channel head array coil.

Blood-oxygen-level-dependent (BOLD)-sensitive fMRI used a T2*-weighted echo-planar imaging (EPI) sequence with an echo time (TE) of 30 ms, a repetition time (TR) of 2.49 ms and a low flip angle of 20° to minimize physiological noise.[48] For the WM task, a total of 184 brain volumes were acquired in a single fMRI session, each consisting of 42 slices with a slice thickness of 3 mm and a field of view (FOV) of 192 × 192 mm using a 64 × 64 grid. High-resolution 3D structural T1-weighted spin echo images were obtained after the first session of BOLD fMRI (TI=800, TE=3.93, TR=1540 ms, flip angle 9°; 256 × 256 FOV; 192 slices).

2.5 | fMRI data analysis

Functional MRI data processing was performed with the FMRI Expert Analysis Tool (FEAT; version 6.00), part of FMRIB's Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Pre-processing included image realignment, non-brain removal, spatial normalization to a Montreal Neurologic Institute (MNI) template and spatially smoothing (Gaussian kernel, 5 mm full-width-half-maximum). The time series in each session were high pass-filtered (to max 0.008 Hz). Three conditions, '1-back', '2-back' and '0-back', were modeled as blocks convolved with a canonical hemodynamic response function.

To investigate the hypothesis that the COMT Val158Met genotype would modulate spatial WM-relevant activity in the PFC, we defined a spherical region of interest (ROI) with a 10 mm radius around the peak of the right dlPFC (x=40, y=34, z=29) involved in spatial WM processes as reported in a meta-analysis.[45] The ROI was constructed on the MNI template using the WFU PickAtlas toolbox.[49] We extracted the mean percent BOLD signal change in the dlPFC ROI during 1-, 2- and 0-back and computed the differential signal change for the 2-back>0-back and 2-back>1-back contrasts to assess the effects of COMT genotype on neural response during general WM and high-load specific WM, respectively. Analysis of the extracted mean percent signal change in the dlPFC ROI was performed in Statistical Package for Social Sciences (SPSS; version 22; IBM Corporation, Armonk, NY, USA) using two one-way ANOVA models with COMT genotype (ValVal, ValMet and MetMet) as an independent factor and high-load specific WM (2-back>1-back) and general WM (2-back>0-back) as dependent factors, respectively. Bonferroni correction was applied to adjust for the number of comparisons of signal change from the dlPFC ROI (adjusted threshold for significance: P=.05/2=.025).

We also carried out a whole-brain exploratory analysis. Individual subject data were computed using the general linear model with local autocorrelation correction.[50] The individual contrasts of interest (2-back>1-back or 2-back>0-back) were included in separate general linear models with nonparametric permutation inference (n=5000) using the 'randomize' algorithm implemented in FSL.[51] The main effect of COMT genotype was assessed using an F test. Significant clusters were identified using the threshold-free cluster enhancement method at corrected P<.05. The mean percent BOLD signal change in clusters showing significant differences between groups was extracted for visualization purposes. A standard anatomical atlas[52] was used to localize peak cluster activations.

2.6 | Statistical analyses of behavioral and mood data

For the spatial n-back WM task, signal detection theory was applied to obtain a measure of spatial n-back WM accuracy corrected for participants' response tendency (d').[53] Outliers, defined as WM accuracy of ≥2 SD below the sample's mean, were excluded. The influence of COMT genotype on spatial n-back WM performance (accuracy and speed) during scanning was examined with WM load[1,2] as the within-subject factor and genotype (ValVal, ValMet or MetMet) as the between-subject factor (all tests were two-tailed). Significant interactions were followed up by independent-samples t tests. For the SWM task, the effect of genotype on spatial WM performance (strategy and errors, respectively) was examined using one-way ANOVA with genotype as the between-subjects factor. Effects of COMT Val158Met genotype on these behavioral measures were subjected to Bonferroni corrections for multiple comparisons (adjusted thresholds for significance: n-back WM: P=.05/4=0.0125; SWM: P=.05/2=.025). For any statistically significant interactions between genotype and cognitive performance/brain activity, we (i) conducted post hoc analysis of covariance (ANCOVA) with adjustment for any potential differences in demographic variables to explore their possible influence on the findings and (ii) explored the potential interacting effects of COMT genotype and gender on cognitive performance and dlPFC activity, given emerging evidence for influence of COMT genotype on gender differences in brain function.[54] Exploratory correlational analyses were conducted between clusters showing differential effects of COMT

Val158Met genotype on WM-related activity and WM performance, mood symptoms and medication status. These post hoc analyses were not adjusted for multiple comparisons due to their exploratory nature. Finally, medication status across the genotype groups was examined with Pearson's chi square. Statistical analyses were performed in SPSS (version 22; IBM Corporation, Armonk, NY, USA).

3 | RESULTS

3.1 | Patient characteristics

Four individuals with WM accuracy of ≥2 SD below the mean were excluded from the fMRI and behavioral analyses, resulting in a total sample of 64 participants. Genotype groups (ValVal: N=13; ValMet: N=34; MetMet: N=17) were comparable for age, gender, education level, mood, and medication (P>.05; see Table 1). ValVal individuals were characterized by numerically older age and longer illness duration than Met carriers, although this was not statistically significant (Table 1). The allelic frequencies for the total sample were 0.47 for the Val allele and 0.53 for the Met allele. Genotype frequencies were confirmed to be in Hardy–Weinberg equilibrium (P=.59).

3.2 | Behavioral results

The WM accuracy (d') score data showed a negative skew due to near-ceiling accuracy rates. As d' scores are in the range of 0−1, we arcsine transformed the data to approach a normal distribution prior

TABLE 1 Demographic and clinical data according to catechol-O-methyltransferase (COMT) Val158Met genotype

	COMT Val158Met genotype			
	ValVal (N=13)	ValMet (N=34)	MetMet (N=17)	P-value
Age, mean (SD)	42 (10)	35 (11)	36 (9)	0.12
Gender, female, n (%)	9 (69)	19 (56)	10 (59)	0.71
Education, mean (SD)	15 (2)	15 (3)	14 (5)	0.62
HDRS-17, mean (SD)	9 (5)	7 (5)	8 (4)	0.62
YMRS, mean (SD)	3 (3)	2 (2)	2 (2)	0.87
No. prior depressions, mean (SD)	8 (11)	5 (3)	9 (9)	0.10
No. prior (hypo)manias, mean (SD)	10 (14)	6 (7)	11 (10)	0.16
Age at debut (years)	22 (12)	20 (8)	20 (10)	0.82
Illness duration (years)	21 (10)	15 (9)	16 (11)	0.19
Bipolar disorder type II subtype, n (%)	5 (39)	15 (44)	8 (47)	0.90
Current medication				
Lithium, n (%)	5 (39)	15 (44)	8 (47)	0.66
Anticonvulsants, n (%)	9 (69)	20 (59)	8 (47)	0.57
Antidepressants, n (%)	5 (39)	14 (41)	6 (35)	0.99
Antipsychotics, n (%)	7 (54)	9 (27)	5 (29)	0.14
Benzodiazepines, n (%)	4 (31)	9 (27)	2 (12)	0.51
Melatonin, n (%)	1 (8)	2 (6)	0 (0)	0.59
No medications, mean (SD)	0 (0)	0 (0)	0 (0)	1.00
No. of medications, mean (SD)	2.5 (0.9)	2.0 (0.9)	2.1 (0.5)	0.21

HDRS-17, Hamilton Depression Rating Scale; standard deviation; YMRS, Young Mania Rating Scale.

TABLE 2 n-Back working memory (WM) performance according to catechol-O-methyltransferase (*COMT*) Val158Met genotype

N-back WM performance in the scanner				
	Mean (SD)	F	df	P-value
Accuracy (arcsine transformed *d'* values)				
WM across 1- and 2-back				
COMT ValVal	1.09 (0.17)	1.44	2,61	.25
COMT ValMet	1.12 (0.17)			
COMT MetMet	1.18 (0.09)			
1-back WM				
COMT ValVal	1.22 (0.15)	0.56	2,61	.58
COMT ValMet	1.25 (0.19)			
COMT MetMet	1.29 (0.12)			
2-back				
COMT ValVal	0.98 (0.26)	1.42	2,61	.25
COMT ValMet	1.02 (0.22)			
COMT MetMet	1.09 (0.10)			
Response times (for correct detection)				
0-back control				
COMT ValVal	592 (65)	0.86	2,61	.43
COMT ValMet	554 (98)			
COMT MetMet	559 (92)			
1-back WM				
COMT ValVal	638 (113)	1.48	2,61	.24
COMT ValMet	575 (102)			
COMT MetMet	588 (115)			
2-back WM				
COMT ValVal	636 (136)	0.81	2,61	.45
COMT ValMet	595 (125)			
COMT MetMet	576 (129)			
SWM outside scanner				
SWM strategy				
COMT ValVal	35.3 (6.7)	5.65	2,56	.006
COMT ValMet	34.1 (6.5)			
COMT MetMet	28.1 (5.6)			
SWM errors				
COMT ValVal	37.8 (17.4)	8.36	2,56	.001
COMT ValMet	27.2 (20.7)			
COMT MetMet	10.1 (11.2)			

SD, standard deviation; SWM, spatial working memory.

to statistical analysis.[55] There were no differences between the three genotype groups in n-back WM accuracy ($P \geq .26$) or speed ($P \geq .31$) (Table 2). In contrast, performance on the CANTAB SWM test outside the scanner showed statistically significant differences between groups on SWM 'strategy' ($F_{2,56} = 5.65$, $P = .006$) and SWM 'errors' ($F_{2,56} = 8.36$, $P = .001$) (Figure 1), which remained statistically significant after post hoc adjustment for age ($P \leq .009$) and illness duration ($P \leq .006$). These interactions were driven by less efficient strategies
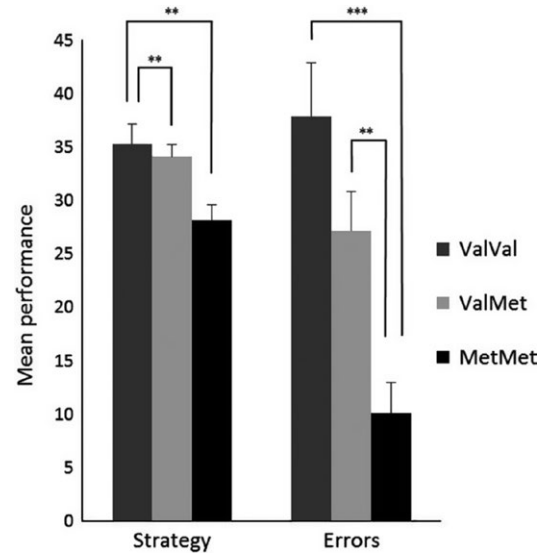

FIGURE 1 Mean performance (strategy and errors) during the Cambridge Neuropsychological Test Automated Battery (CANTAB) spatial working memory task outside the scanner stratified for catechol-O-methyltransferase (*COMT*) Val158Met genotype. Higher values indicate more inefficient strategies and more errors, respectively. Error bars represent the standard error. There were significant differences between groups on SWM 'strategy' ($F_{2,56} = 5.65$, $P = .006$) and SWM 'errors' ($F_{2,56} = 8.36$, $P = .001$). The interactions were driven by less efficient strategies and more errors in the Val carriers than Met homozygotes (strategy: ValVal vs MetMet: $t = 3.03$, $df = 25$, $P = .006$; Cohen's $d = 1.16$; ValMet vs MetMet: $t = 3.05$, $df = 45$, $P = .004$; Cohen's $d = 0.98$; errors: ValVal vs MetMet: $t = 5.03$, $df = 25$, $P < .001$; Cohen's $d = 1.90$; ValMet vs MetMet: $t = 2.99$, $df = 45$, $P = .005$; Cohen's $d = 1.03$). **corresponds to a significance level of $P < 0.01$; ***corresponds to a significance level of $P < 0.001$.

and more errors in the Val carriers compared with Met homozygotes (strategy: ValVal vs MetMet: $t = 3.03$, $df = 25$, $P = .006$; Cohen's $d = 1.16$; ValMet vs MetMet: $t = 3.05$, $df = 45$, $P = .004$; Cohen's $d = 0.98$; whereas ValVal vs ValMet: $P > .61$; errors: ValVal vs MetMet: $t = 5.03$, $df = 25$, $P < .001$; Cohen's $d = 1.90$; ValMet vs MetMet: $t = 2.99$, $df = 45$, $P = .005$; Cohen's $d = 1.03$; whereas ValVal vs ValMet: $P > .12$). These findings are consistent with a linear trend based upon Val allelic load. No interacting effects of *COMT* genotype and gender were found on SWM strategy and errors, respectively ($P \geq .80$).

3.3 | fMRI results

3.3.1 | A priori dorsolateral prefrontal cortex region of interest

The right dlPFC ROI was significantly activated during the WM task (2-back>0-back) ($t = 12.71$, $df = 63$, $P < .001$) and showed greater response under high than low WM loads (2-back>1-back) ($t = 6.19$, $df = 63$, $P < .001$). Dorsolateral PFC response showed no differences between genotype groups during general WM (2-back>0-back) ($P > .54$), but was differentially activated between the groups during high-load specific WM (2-back>1-back) ($F_{2,61} = 4.45$, $P = .016$). This interaction was driven
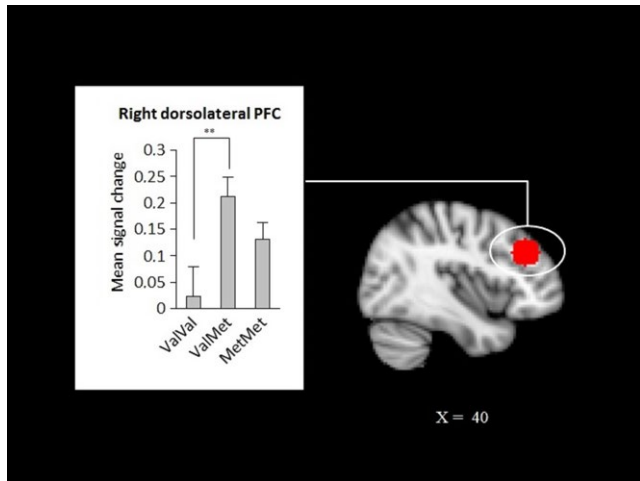
FIGURE 2 A priori region of interest (ROI) in the right dorsolateral prefrontal cortex (dlPFC) (red) and plot of mean blood-oxygen-level-dependent (BOLD) signal change during high working memory (WM) load (2-back>1-back) across the catechol-O-methyltransferase (*COMT*) Val158Met genotype groups. Bars show the mean; error bars show the standard error. The dlPFC showed differential response between the groups during high-load specific WM ($F_{2,61}$=4.45, *P*=.016), which was driven by lower activity in ValVal compared to ValMet individuals (*t*=2.73, *df*=45, *P*=.009; Cohen's *d*=0.90) and a strong trend towards lower response in ValVal than MetMet individuals (*t*=2.03, *df*=19.32, *P*=.06). **corresponds to a significance level of *P*<0.01. [Colour figure can be viewed at wileyonlinelibrary.com]

by lower activity in ValVal compared to ValMet individuals (*t*=2.73, *df*=45, *P*=.009; Cohen's *d*=0.90) and a strong trend towards lower response in ValVal than MetMet individuals (*t*=2.03, *df*=19.32, *P*=.06), whereas no difference was observed between ValMet and MetMet individuals (*P*>.31) (see Figure 2). This interaction remained statistically significant after adjustment for age (*P*=.032) and was reduced to a strong trend after adjustment for illness duration (*P*=.051). Notably, the lower dlPFC activity in ValVal individuals during high-load specific WM was also observed in post hoc comparison of ValVal individuals with all Met carriers (MetMet and ValMet) (*t*=2.81, *df*= 62, *P*=.007). No significant effects of *COMT* genotype and gender were found on high-load specific dlPFC activity (*P*>.99).

3.3.2 | Whole-brain exploratory analyses

High-load specific (2-back>1-back) WM activated a widespread fronto-parietal network of overlapping regions, including the right and left dlPFC (for peak cluster activations, see Table 3), consistent with the literature.[45] Exploratory whole-brain analyses revealed no effect of genotype for either high-load specific or general WM (*F* tests assessing possible differences between genotype groups). Prompted by our ROI finding, we also tested whether the differential right dlPFC activity in ValVal vs ValMet individuals during high-load specific WM extended to additional brain regions. This whole-brain analysis revealed four clusters within the left and right dlPFC showing reduced high-load specific activity in ValVal compared with ValMet individuals in all clusters (with MetMet individuals consistently showing intermediate responses; see Figure 3).

3.4 | Associations between mood, medication, BOLD response and behavior

Across the entire sample, subsyndromal mania and depression symptoms showed no correlation with high-load specific dlPFC activity (*P*≥.28) or performance on the n-back WM task during the scan (*P*≥.35). There was also no association between mood symptoms and SWM strategy (*P*≥.14), although more subsyndromal depressive symptoms correlated weakly with more SWM errors (*r*=.26, *P*=.04). The use of lithium, anticonvulsants, antidepressants, antipsychotics or benzodiazepines was not associated with high-load specific dlPFC activity (*P*≥.14) or with performance on the n-back and SWM tests across the entire cohort (*P*≥.21 and *P*≥.06, respectively).

There were no interactions between *COMT* Val158Met genotype and the total number of medications for n-back WM performance (*P*≥.38) or WM-related dlPFC activity (*P*≥.53). There were also no interactive effects of genotype and the number of medications on SWM performance (strategy: *P*≥.33; errors: *P*≥.46). There was a trend towards correlation between more high-load specific dlPFC activity and better n-back WM performance across the entire sample (*r*=.21, *df*=64, *P*=.10) as well as within the Valval group (*r*=.54, *df*=13, *P*=.058). Post hoc analysis showed that better SWM performance (reflected by lower strategy scores and fewer errors) correlated weakly with better n-back WM accuracy across the entire sample (SWM strategy: *r*=−.27, *df*=59, *P*=.002; SWM errors: *r*=−.40, *df*=59, *P*=.002).

4 | DISCUSSION

The present fMRI study examined the effects of the functional *COMT* Val158Met polymorphism on WM-related neural activity in partially or fully remitted BD patients. Based on previous studies of schizophrenia and healthy groups,[37] we had hypothesized that Val homozygous BD patients would exhibit increased activity in the dlPFC during high-load WM relative to Met carriers. Contrary to our predictions, Val homozygous patients showed decreased dlPFC activity during high-load WM compared with Met carriers. We observed no effect of genotype on n-back WM performance during the scan. However, as hypothesized, Val carriers displayed poorer performance than Met homozygotes on the CANTAB SWM task outside the scanner, as reflected by less efficient strategies and more errors (effect sizes: Cohen's *d*=0.98−1.90). The observed effects of genotype on WM-related neural activity and spatial WM performance in our BD cohort occurred in the absence of differences between genotypes in demographic characteristics, subsyndromal mood symptoms or medications.

The relatively reduced dlPFC activity during high-load specific WM in Val homozygous patients was unexpected given evidence pointing to hyperactivity and purported inefficient dlPFC function in Val carriers.[13,30-35] However, it is conceivable that Val homozygous patients' lower dlPFC activity reflects failure to recruit task-relevant dlPFC resources, given their impaired performance on the CANTAB SWM task. Indeed, decreased right dlPFC activity during high WM loads in Val homozygous patients with BD is consistent with the literature on

Regional response	Cluster size (no. voxels)	Cluster P-value	Coordinates		
			x	y	z
High-load specific WM (2-back>1-back) across the entire cohort (main effect of task)					
Frontal cortex	21675	.001			
Left superior frontal gyrus (BA6)			−20	0	74
Right middle frontal gyrus (BA6)			46	20	46
Left middle frontal cortex (BA32)			−2	38	25
Right thalamus			18	−22	18
Left middle frontal gyrus (BA9)			−50	26	32
Parietal cortex	18079	.001			
Left precuneus (BA7)			−4	−62	56
Right supramarginal gyrus (BA40)			56	−36	42
Left supramarginal gyrus (BA40)			−48	−40	38
Right lateral occipital cortex (BA18)			−34	−86	0
Left lateral occipital cortex (BA19)			38	−76	0
Right cerebellum	521	.004	32	−64	−26
Left cerebellum	505	.005	−32	−60	−26
Right inferior temporal gyrus (BA20)	44	.036	58	−42	−14
ValMet>ValVal (2-back>1-back)					
Right superior frontal gyrus (BA6)	63	.035	22	10	50
Left middle frontal gyrus (BA8)	47	.043	−46	10	50
Left middle frontal gyrus (BA6)	10	.044	−36	−4	60
Right superior frontal gyrus (BA8)	2	.048	36	28	52

TABLE 3 Peak cluster activation in regions identified in whole-brain analysis as showing decreased response during high-load specific working memory (WM) (2-back>1-back) in catechol-O-methyltransferase (*COMT*) 158Val homozygotes relative to ValMet individuals

BA, Brodmann area. MNI coordinates (*x, y, z*) refer to the point of peak activation within each cluster.

the neural underpinnings of cognitive deficits in BD, where the most consistent finding is dlPFC hypoactivity during high-load WM conditions.[56,57] These findings point to a distinct effect of the *COMT* genotype on neural activity and cognitive function in patients with BD as compared to healthy individuals and patients with schizophrenia. Notably, this association between *COMT* genotype and dlPFC activity was rendered non-significant in a post hoc analysis adjusted for illness duration (P=.051). While the sample size is small, this could suggest that presumed progressive cognitive decline with more chronic illness weakens the association between *COMT* genotype and dlPFC function in BD.

The demonstration of no behavioral difference between *COMT* genotype groups on the n-back WM task is in line with previous research utilizing this test in psychiatric and healthy populations.[27-29] This finding is likely to reflect a ceiling effect attributable to high n-back WM accuracy in all participants (i.e., 89% accuracy across all genotype groups) given (i) the significant correlation between performance on the n-back WM and SWM tests, indicating that the two tests measure the same construct (i.e., spatial WM) and (ii) the separation between groups on performance on the (more difficult) CANTAB SWM test outside the scanner. Indeed, prior evidence suggests that accuracy is generally high in the n-back paradigm and that WM loads — even when including three items — fail to yield differences in performance between the *COMT* Val158Met genotypes.[27] Nevertheless, the n-back task is arguably the most commonly used fMRI paradigm in the

assessment of neural underpinnings of executive function and is optimized for delineating task-relevant neural activity precisely because it ensures high performance accuracy (i.e., neural activity subserving correct performance). The task should thus be combined with more demanding WM tasks devoid of ceiling effects outside the scanner to optimize sensitivity for differences in behavioral read-outs.

Previous research in patients with schizophrenia and healthy individuals has shown that Val homozygotes exhibit exaggerated WM-related activity in the dlPFC in the absence of behavioral differences. Increased PFC activity has therefore been hypothesized to indicate reduced neural efficiency.[27] However, the decreased dlPFC activity in Val homozygous BD patients may also be indicative of less efficient recruitment of WM-related neural resources, which could explain these individuals' poorer performance on the SWM test outside the scanner. Indeed, task-related dlPFC *hypo*activity in BD has been hypothesized to play a key role in patients' common deficits in attention control and decision making.[58] Accordingly, both dlPFC hypo- and hyperactivity as observed in ValVal and ValMet individuals, respectively, may reflect PFC dysfunction (deficient recruitment of PFC resources and inefficient processing, respectively), whereas the medium levels of WM-related dlPFC activity in the cognitively superior Met homozygotes may reflect optimal PFC function (see illustration in Figure 4). The reduced PFC function and WM performance in Val carriers (which was most pronounced in Val homozygotes) could be explained by differences in dlPFC cellular pathology in BD relative to
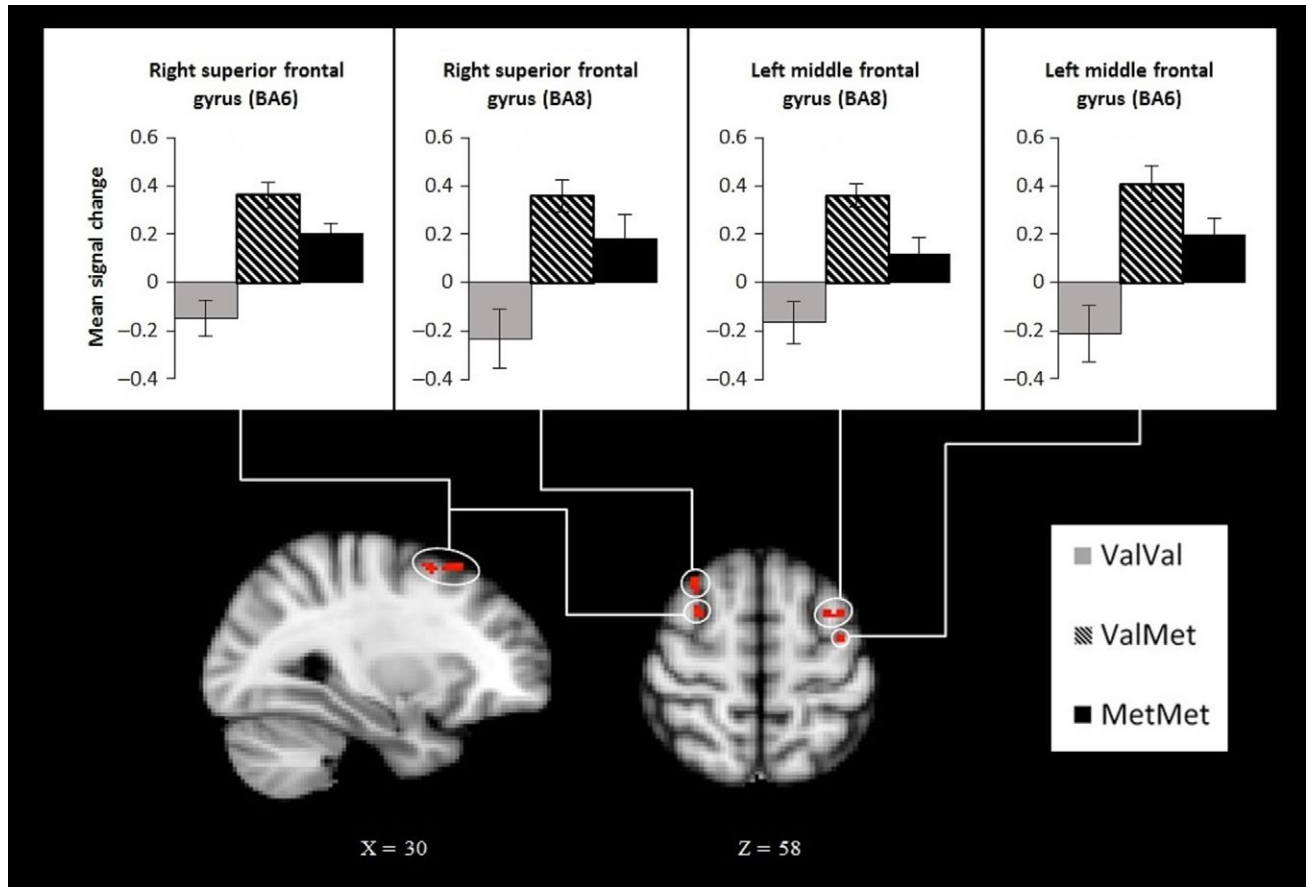
FIGURE 3 *Lower part:* Neural networks activated during high-load specific working memory (WM) (2-back>1-back) across all patients stratified for the catechol-O-methyltransferase (*COMT*) Val158Met genotype. Clusters show decreased response in ValVal vs ValMet subjects in the right and left dorsolateral prefrontal cortex in the exploratory whole-brain analysis. Data were modeled using a general linear model with nonparametric permutation inference (n=5000), and significant clusters were identified using the threshold-free cluster enhancement method at corrected *P*<.05. *Upper part:* Bar charts represent mean blood-oxygen-level-dependent (BOLD) signal change during n-back high-load specific WM. Bars show the mean; error bars represent the standard error of the mean. [Colour figure can be viewed at wileyonlinelibrary.com]
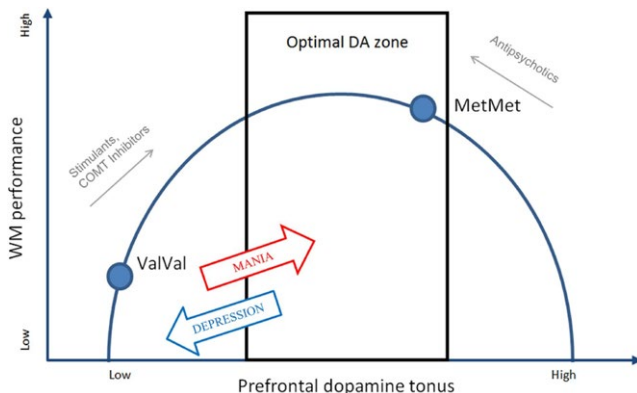
FIGURE 4 Hypothetical inverted-U-shaped interaction between catechol-O-methyltransferase (*COMT*) Val158Met genotype and the effects of dopaminergic drugs on prefrontal cortex (PFC)-dependent working memory (WM) function in remitted patients with bipolar disorder (BD) (adapted from 22) [Colour figure can be viewed at wileyonlinelibrary.com]

healthy individuals and patients with schizophrenia.[59] In particular, it is possible that a shift in DA tonus would lead to suboptimal prefrontal DA and greater cognitive impairment in Val homozygotes and (albeit to a lesser degree) in ValMet individuals than in Met homozygous BD patients during remission. Consistent with this, one study has shown that Val carriers exhibit better cognitive performance during manic episodes, presumably due to increased prefrontal DA.[38] Interestingly, a study investigating the effect of DA agonism on cognitive impairment in clinically stable BD patients found a phase effect of pramipexole, in which only euthymic BD patients showed improvements on a WM task.[60] It is therefore conceivable that cognitive benefits of increasing prefrontal DA tonus with pramipexole could be specific for patients with relatively low baseline DA, such as patients who are euthymic. Hence, future studies should investigate whether pramipexole treatment may be associated with particularly beneficial cognitive effects in euthymic patients with BD and further investigate the effect of *COMT* Val158Met genotype on treatment efficacy on cognition.

There is emerging evidence for Val158Met genotype moderation of antipsychotic effects on WM function. Specifically, preclinical evidence suggests that stimulants and other agents that increase prefrontal DA (e.g., methylphenidate and tolcapone) improve WM abilities only in conditions where PFC DA levels are challenged (such as in Val carriers).[61-63] In contrast, antipsychotics that decrease DA levels (e.g.,

olanzapine) have particularly negative effects on cognition in Val homozygotes[64] and may be beneficial for Met homozygotes. In keeping with this, it was concluded in a recent systematic review that *COMT* inhibitors (which lead to DA increase) have the greatest cognitive benefits in Val homozygotes, and that antipsychotics are generally associated with better cognitive outcome among Met homozygotes.[22] However, this seems to be caused by state-related changes in DA since Val carriers in hyper-dopaminergic manic states exhibit superior cognitive abilities relative to Met carriers.[38] Hence, in manic states, stimulating DA would theoretically be counterproductive, leading to excessive prefrontal DA and thus cognitive decline. Taken together, the findings suggest that future treatment strategies targeting cognition are likely to benefit from taking patients' *COMT* Val158Met genotype into consideration. This could provide a basis for studies investigating personalized medicine strategies in BD, in which pharmacological interventions that increase cortical dopaminergic activity (e.g., *COMT* inhibitors) may be targeted to Val carriers and antipsychotic medications preferentially used in Met homozygotes.[22]

The moderate sample size of the present study may have influenced the validity of the findings, limits generalization of results and impedes further analysis of the effects of medication status on WM abilities by *COMT* genotype group. The findings therefore require replication in a larger sample. It was also a limitation that we had not recorded information about patients' particular antipsychotic drugs or doses or whether they had experienced psychotic episodes in the course of their illness, as these variables may differ between the *COMT* Val158Met genotypes and thus potentially confound the findings. Indeed, numerically (but not statistically significantly) more Val homozygotes were treated with antipsychotic drugs. Nevertheless, post hoc analyses revealed no association between antipsychotic treatment and high-load specific dlPFC activity or WM performance across the entire cohort. In addition, the lack of a healthy control group hampered direct assessment of whether the dlPFC in BD Val homozygotes was hypoactive during high-load WM. Another limitation was that the SWM was not administered on the same day as the fMRI scan but merely within the same week and that daily variations in mood were therefore not controlled for. Although other single nucleotide polymorphisms (SNPs) have been shown to have an effect on DA availability, cognition, and risk for BD (e.g., rs165599), participants in the present study were stratified only for *COMT* Val158Met genotype. Nevertheless, the present study is the first to demonstrate the moderating effect of *COMT* Val158Met genotype on WM-related dlPFC activity and WM performance in a well-characterized partially or fully remitted sample of BD patients.

In conclusion, this is the first study to demonstrate a moderating effect of *COMT* Val158Met genotype on WM-related dlPFC activity and WM performance in remitted patients with BD. Specifically, Val homozygotes showed less recruitment of task-relevant dlPFC resources during high-load WM and impaired WM performance relative to Met carriers. This is consistent with an association between Val allelic load and WM impairment in BD and points to a putative role of aberrant PFC dopamine tonus in the cognitive impairments in BD.

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