COMT Val^{158}Met genotype influences neurodegeneration within dopamine-innervated brain structures

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ABSTRACT

Objective: We sought to determine whether the Val^{158}Met polymorphism in the catechol-*O*-methyltransferase (COMT) gene influences neurodegeneration within dopamine-innervated brain regions.

Methods: A total of 252 subjects, including healthy controls and patients with Alzheimer disease, behavioral variant frontotemporal dementia, and semantic dementia, underwent COMT genotyping and structural MRI.

Results: Whole-brain voxel-wise regression analyses revealed that COMT Val^{158}Met Val allele dosage, known to produce a dose-dependent decrease in synaptic dopamine (DA) availability, correlated with decreased gray matter in the region of the ventral tegmental area (VTA), ventromedial prefrontal cortex, bilateral dorsal midinsula, left dorsolateral prefrontal cortex, and right ventral striatum. Unexpectedly, patients carrying a Met allele showed greater VTA volumes than age-matched controls. Gray matter intensities within COMT-related brain regions correlated with cognitive and behavioral deficits.

Conclusions: The results are consistent with the hypothesis that increased synaptic DA catabolism promotes neurodegeneration within DA-innervated brain regions. *Neurology*® 2012;78:1663–1669

GLOSSARY

ABI = Applied Biosystems Inc.; **AD** = Alzheimer disease; **bvFTD** = behavioral variant frontotemporal dementia; **CDR** = Clinical Dementia Rating; **COMT** = catechol-*O*-methyltransferase; **DA** = dopamine; **dlPFC** = dorsolateral prefrontal cortex; **dMI/FO** = dorsal midinsula/frontal operculum; **MAC** = Memory and Aging Center; **MPRAGE** = magnetization-prepared rapid gradient echo; **SemD** = semantic dementia; **TIV** = total intracranial volume; **UCSF** = University of California, San Francisco; **VBM** = voxel-based morphometry; **vmPFC** = ventromedial prefrontal cortex; **VStr** = ventral striatum; **VTA** = ventral tegmental area.

Each neurodegenerative disease is characterized by a prototypical regional distribution[1] but also by significant anatomical heterogeneity. Autosomal dominant genes cause dementia in a minority of patients, while in sporadic disease genetic background may confer increased risk or earlier age at onset.[2] Little attention has been paid, however, to genes that produce clinical heterogeneity by modifying the injury pattern or severity.

COMT Val^{158}Met, a common functional single nucleotide polymorphism (exon 4 G/A; rs4680), influences synaptic dopamine (DA) concentration. The Val allele confers increased enzymatic activity compared to the Met allele at body temperature, resulting in a dose-dependent decrease in synaptic DA availability.[3] Studies of healthy volunteers suggest that COMT genotype influences cognitive, reward-related, and emotion processing.[4–7]

Here, we questioned whether the COMT Val^{158}Met polymorphism might influence neurodegeneration within brain structures reliant upon dopaminergic neurotransmission. We considered 2 competing hypotheses. Increased DA catabolism might prove deleterious to DA-reliant regions;

Supplemental data at www.neurology.org

Supplemental Data

From the Memory and Aging Center (E.D.G., J.A.C., J.Z., R.K.C., D.A.S., A.K., A.L.B., K.P.R., M.L.G.-T., H.J.R., J.H.K., B.L.M., W.W.S.), Department of Neurology, University of California, San Francisco; Division of Geriatrics (S.J.B.), Department of Internal Medicine, University of Nebraska Medical Center, Omaha; and Center for Imaging of Neurodegenerative Disease (M.W.), San Francisco Veteran's Administration Medical Center, San Francisco, CA.

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Table 1 Subject characteristics[a]

	Normal controls	Alzheimer disease	Behavioral variant frontotemporal dementia	Semantic dementia
Total (M/M, M/V, V/V)	83 (25, 41, 17)	77 (19, 36, 22)	53 (12, 23, 18)	39 (7, 22, 10)
Age at scan, y	66.9 (8.7)	65.7 (9.8)	61.6 (9.2)	64.5 (7.5)
Sex, M:F	33:50	46:31	34:19	21:18
Illness duration, y	N/A	5.1 (4.5)	5.1 (3.2)	5.3 (3.3)
CDR, total	0.0 (0.0)	1.0 (0.5)	1.2 (0.7)	0.8 (0.5)
CDR, sum of boxes	0.0 (0.0)	5.4 (2.8)	6.7 (3.3)	4.0 (2.9)
MMSE (max = 30)	29.6 (0.6)	21.2 (5.9)	22.1 (7.8)	21.4 (7.7)

Abbreviations: CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination.
[a] Values are expressed as mean (SD). See also tables e-1 and e-2.

conversely, reduced synaptic DA availability might protect vulnerable tissues by reducing metabolic demand or by inducing long-term compensatory enhancement of DA-innervated regions. We conducted a whole-brain voxel-wise structural MRI analysis on a large subject pool (n = 252, table 1, tables e-1 and e-2 on the *Neurology*® Web site at www.neurology.org) composed of healthy controls and 3 clinical dementia syndromes: Alzheimer disease (AD), behavioral variant frontotemporal dementia (bvFTD), and semantic dementia (SemD). Our findings link COMT genotype to the integrity of DA-innervated regions in patients with neurodegenerative disease.

METHODS

Subjects. We searched the University of California, San Francisco (UCSF) Memory and Aging Center (MAC) database for subjects who had undergone COMT genotyping and had a usable 1.5-T MRI scan. Of those, subjects with a clinical diagnosis of AD, bvFTD, or SemD as well as recruited normal controls were included. Patients were required to meet consensus research criteria[8,9] within 180 days of MRI scanning. Medications were not used as exclusion criteria. All controls were free of neuropsychiatric medications, except 1 on escitalopram and trazodone and 1 on paroxetine, and lacked significant structural abnormalities on MRI. Patients were not on DA-modifying drugs except 1 patient with bvFTD, who took pramipexole. Demographic information is provided in table 1 and tables e-1 and e-2.

Standard protocol approvals, registrations, and patient consents. Procedures were approved by the UCSF Committee on Human Research. All subjects provided informed consent prior to study participation.

Cognitive and neuropsychiatric testing. All subjects underwent a comprehensive neurologic assessment, and the majority underwent additional neuropsychological and functional assessment at the UCSF MAC as described[10] (tables e-1 and e-2). Test scores nearest to the MRI date were included in the analyses, provided that they were obtained within 180 days of scanning. Clinical severity was assessed using the Clinical Dementia Rating (CDR) scale. The Neuropsychiatric Inventory[11] was used to assess 12 domains of behavioral impairment, as well as a total score and an index of caregiver distress.

COMT genotyping. The COMT1 rs4680 SNP was assayed by a TaqMan 5′ nuclease SNP genotyping assay using 0.125 mL premade Drug Metabolism Assay Mix (C-25746809-50, Applied Biosystems Inc. [ABI], Carlsbad, CA), 2.5 mL TaqMan master mix (ABI), and 10 ng DNA in a 5 mL total reaction volume. Forward primer: tcaccatcgagatcaacccc; reverse primer: acaacgggtcaggcatgca. Reactions were cycled using the ABI recommended protocol (5 minutes 95°C, 40 cycles of 95°C for 15 seconds followed by 60°C for 1 minute in an ABI 9700 thermal cycler). The plates were post read on an ABI 7900HT DNA analyzer and analyzed with SDS v2.1 analysis software. Deviations from the Hardy-Weinberg principle were tested using Pearson χ^2 test on the observed genotype frequencies in our sample and the expected frequencies obtained from the Hardy-Weinberg equation (table e-3). Genotype distributions were in Hardy-Weinberg equilibrium in all diagnostic groups. Population stratification was not assessed.

Image acquisition. Structural MRI scans were acquired at the San Francisco Veterans Affairs Medical Center's 1.5-T Magnetom Vision system (Siemens Inc., Iselin, NJ) using a standard quadrature head coil. A volumetric magnetization-prepared rapid gradient echo (MPRAGE) MRI (repetition time/echo time/inversion time = 0/4/300 msec) sequence was used to obtain a T1-weighted image of the entire brain (15° flip angle, coronal orientation perpendicular to the double spin echo sequence, 1.0-mm^2 in-plane resolution of 1.5-mm slab thickness).

Image analysis: Voxel-based morphometry. Images were preprocessed using the VBM5 toolbox (Christian Gaser; http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/) within SPM5 (Wellcome Trust Centre for Neuroimaging, London; http://www.fil.ion.ucl.ac.uk/spm/). First, MRI volumes were inspected for quality visually and using the VBM5 toolbox's check sample homogeneity function. Images were then segmented, normalized to Montreal Neurological Institute space, and modulated. Segmented gray matter volumes were smoothed using a 10-mm^3 Gaussian kernel. At this point, each voxel is represented by a gray matter intensity value, reflecting the local signal intensity after preprocessing. The resulting MRI were entered into a general linear model with diagnosis as a factor, Val dose (Met/Met = 0, Met/Val = 1, Val/Val = 2) as the covariate of interest, and age at scan, sex, and total intracranial volume (TIV) as nuisance covariates. The make majority mask function of SPM5 was used to create an explicit whole-brain gray matter mask[12] to ensure that all gray matter is included in the analysis, including atrophic areas of atrophy that can be omitted by default masking procedures.

Statistical analyses. Group differences in demographic and clinical variables were assessed using parametric testing after normality of the relevant distributions was confirmed. For the whole-brain voxel-based morphometry (VBM) analyses described above, regions identified at a statistical threshold of $p < 0.001$, uncorrected, extent threshold = 10 voxels, were considered significant if they fell within a priori hypothesized (DA-innervated) regions of interest in the frontal, temporal, insular, striatal, and midbrain gray matter. Following the VBM analysis, we used the Marsbar toolbox for SPM (http://marsbar.sourceforge.net/) to extract mean gray matter intensities from the original smoothed, segmented T1-weighted images corresponding to each cluster identified in the all-subjects linear Val dose contrast. We then, as a confirmatory analysis, performed stepwise linear

regression to assess whether the effect of COMT genotype on the extracted regional gray matter intensities persisted after accounting for additional potential confounders, including those not modeled in the initial VBM analysis due to concerns regarding the statistical power of the whole-brain assessment. Separate models were created for each cluster, with that cluster's mean gray matter intensity as the dependent variable. The first step of each regression included age at scan, sex, years of education, CDR sum of boxes score, and TIV as the predictors. The second step added diagnosis (modeled as 3 dummy variables to represent the 4 groups), and the third step added Val dose. This approach allowed us to assess the significance of the R^2 change associated with each block of predictor variables. p Values <0.05 were considered significant; correction for the 7 statistical tests was not applied due to the few tests and the confirmatory nature of these analyses.

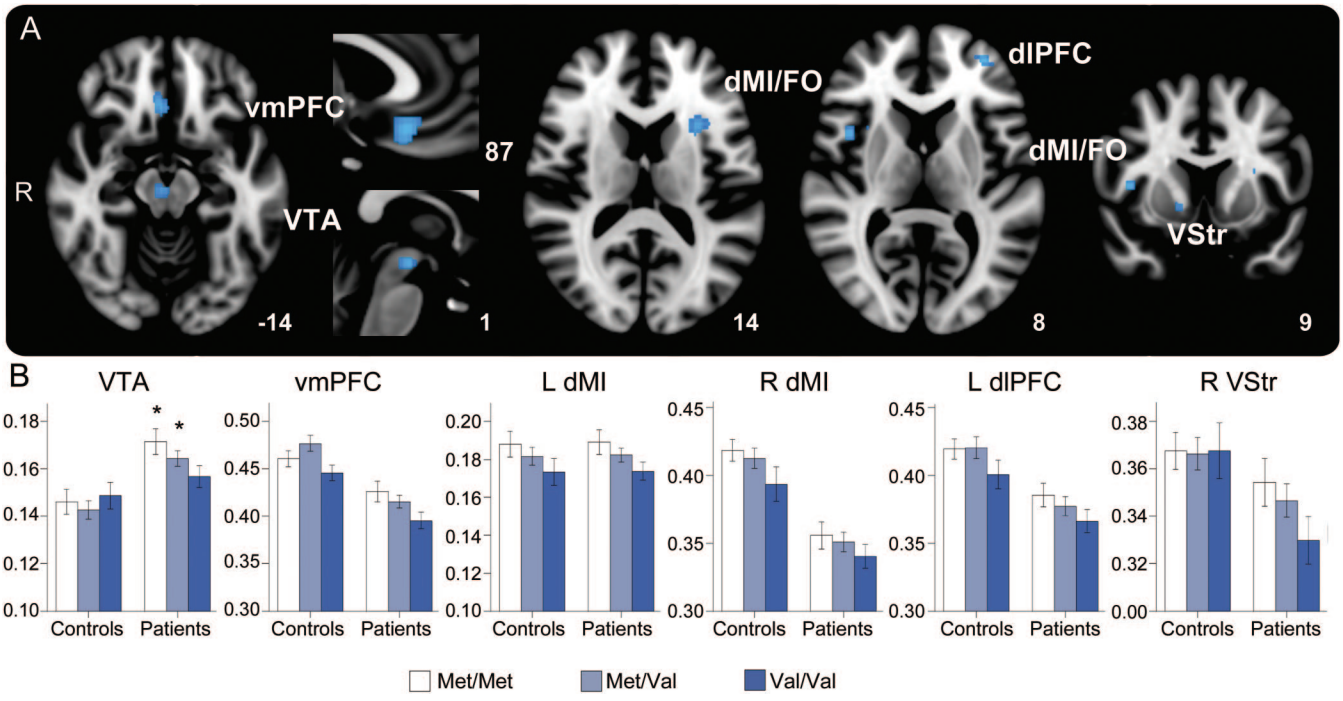
Multivariate general linear models were used to evaluate relationships between COMT genotype and cognitive and NPI scores. These analyses were performed on patients only because controls were not routinely administered the NPI. Among the 14 NPI scores, we analyzed the 2 overall scores and the 9 subdomains for which at least 30% of the patients across all diagnostic groups had scores greater than zero (table e-2). Cognitive and NPI scores served as dependent variables in 2 separate models (1 for cognitive scores, 1 for NPI; cases with missing data were excluded listwise). In each model, diagnosis and COMT genotype were entered as fixed factors, and age at scan, sex, education, TIV, and CDR sum of boxes score were entered as covariates. p Values <0.05 were considered significant.

Relationships between the VBM-identified regions' gray matter intensities and cognitive and NPI scores were assessed in patients using stepwise linear regression. The first step included age at scan, sex, years of education, and TIV as predictors, the second step added diagnosis (modeled as 2 dummy variables to represent the 3 diagnoses), and the third step added all cluster mean gray matter intensities. Cognitive and NPI variables served as the dependent measures in separate models, 1 for each measure. Alpha was set to 0.05, adjusted for 9 cognitive and 11 NPI measures using the Bonferroni method to yield significance thresholds of $p = 0.006$ (cognitive) and $p = 0.005$ (NPI).

All analyses were performed in SPSS 19 (IBM, Armonk, NY).

RESULTS COMT Val^{158}Met Val allele dosage predicts greater atrophy within dopamine-innervated brain structures. First, we explored whether the COMT Val^{158}Met Val allele exerts dose-dependent linear effects on brain structure. In a whole brain analysis across all subjects, increasing Val allele dosage was associated with decreasing gray matter intensity in only 6 regions ($p < 0.001$, uncorrected; extent threshold = 10 voxels; figure, A, table 2), including clusters in midline ventral midbrain in the vicinity of the VTA, ventromedial prefrontal cortex (vmPFC), bilateral dorsal midinsula/frontal operculum (dMI/FO), left dorsolateral prefrontal cortex (dlPFC), and right ventral striatum (VStr). The identified forebrain structures receive robust dopaminergic innervation via the mesostriatal and mesocortical pathways.[13,14] Mean gray matter intensities extracted from these clusters for each subject were grouped by

Figure Effect of catechol-*O*-methyltransferase (COMT) Val^{158}Met genotype on regional brain structure in patients with dementia



(A) Increasing Val dose correlated with decreasing gray matter intensity in the ventral midbrain (in the vicinity of the ventral tegmental area [VTA]), ventromedial prefrontal cortex (vmPFC), left and right dorsal midinsula/frontal operculum (dMI/FO), left dorsolateral prefrontal cortex (dlPFC), and right ventral striatum (VStr) (n = 252, $p < 0.001$, uncorrected). See also table e-4. (B) Bar graphs show total intracranial volume (TIV)–adjusted gray matter (GM) intensities by genotype in controls and patients. TIV-adjusted GM intensity = extracted GM intensity × (all subjects' mean TIV/subject's TIV). Error bars indicate SEM. *$p < 0.05$ vs COMT genotype-matched healthy controls.

Table 2 Regions showing a linear relationship to COMT Val[158]Met Val dose across all groups[a]

	MNI coordinates			Cluster size	z Score
	x	y	z		
Negative correlations with Val dose					
VTA	4	−20	−12	62	3.51
vmPFC	4	26	−16	102	3.45
L dorsal midinsula	−30	16	16	49	3.53
R dorsal midinsula	42	8	8	29	3.41
L dlPFC	−34	50	6	37	3.52
R ventral striatum	16	8	−4	11	3.22
Positive correlations with Val dose					
L hippocampus	−24	−10	−22	14	3.25

Abbreviations: COMT = catechol-*O*-methyltransferase; dlPFC = dorsolateral prefrontal cortex; MNI = Montreal Neurological Institute; vmPFC = ventromedial prefrontal cortex; VTA = ventral tegmental area.
[a] $\alpha = 0.001$, n = 252.

Table 3 Effects of COMT Val[158]Met Val dose on VBM-identified clusters after controlling for potential confounders[a]

	Change statistics		
	R^2 change	F change	Sig. F change
VTA			
1	0.322	20.262	1.600E-16
2	0.040	4.434	0.005
3	0.037	12.974	3.947E-04
L dorsal midinsula			
1	0.081	3.738	0.003
2	0.049	3.900	0.010
3	0.034	8.495	0.004
R dorsal midinsula			
1	0.424	31.401	6.804E-24
2	0.071	9.866	4.087E-06
3	0.014	5.931	0.016
L dlPFC			
1	0.354	23.347	1.115E-18
2	0.016	1.726	0.163
3	0.016	5.361	0.022
R ventral striatum			
1	0.139	6.875	5.706E-06
2	0.068	6.020	0.001
3	0.018	4.773	0.030
vmPFC			
1	0.341	22.010	9.341E-18
2	0.081	9.839	4.234E-06
3	0.024	9.240	0.003
L hippocampus			
1	0.233	12.963	5.121E-11
2	0.344	56.819	6.220E-27
3	0.017	8.732	0.003[b]

Abbreviations: CDR = Clinical Dementia Rating; TIV = total intracranial volume; vmPFC = ventromedial prefrontal cortex; VTA = ventral tegmental area.
[a] $\alpha = 0.05$, n = 219. First step of regression: predictors include age, sex, education, CDR sum of boxes score, and TIV. Second step adds diagnosis, and third step adds Val dose.
[b] Increasing Val dose correlated with increasing gray matter intensity in the L hippocampus only.

genotype and disease status (controls vs patients) and graphed (figure, B). Inspection of these data suggested that the detected linear relationships between Val dose and gray matter intensity were driven primarily by the patients, although the linear trend was also observed in bilateral dMI/FO in controls. In the opposite direction, increasing Val dose correlated with increasing gray matter intensity in only the left hippocampus (table 2). Follow-up stepwise linear regression analyses (table 3) confirmed that COMT genotype exerted an effect on VBM-identified clusters' mean gray matter intensities, even after accounting for additional potential confounders, including age, sex, education, clinical severity, TIV, and diagnosis.

Unexpectedly, patients carrying at least 1 Met allele showed higher gray matter intensity in the region of the VTA compared to controls (figure, B), in contrast to all other COMT-related regions, which exhibited Val dose-dependent reductions in the setting of disease. Unplanned comparisons confirmed that patients with at least 1 Met allele had higher VTA volumes compared to controls of the same COMT genotype ($\alpha = 0.05$; Met/Met: 25 controls vs 38 patients: $t = 3.19$, $p = 0.02$; Met/Val: 41 controls vs 81 patients: $t = 4.1$, $p = 8.4\text{E-}5$), whereas this increase was not detected in Val/Val carriers (17 controls vs 50 patients; $t = 0.9$, $p = 0.35$).

COMT Val[158]Met genotype exerts no direct effect on cognition or behavior after controlling for diagnosis. Next, we sought to determine whether COMT genotype exerted a direct effect on patient cognition (table e-1) or behavior (table e-2) irrespective of diagnosis and other potential confounders. Such an effect might indicate a direct neurochemical influence of COMT genotype. Multivariate analyses, however, revealed no effect of COMT genotype on cognition (patients only, n = 111; $\alpha = 0.05$, $p = 0.175$ to 0.960 across cognitive measures) or behavior (patients only, n = 103; $\alpha = 0.05$, $p = 0.381$ to 0.981 across NPI scores).

Brain regions influenced by COMT Val[158]Met genotype correlate with cognitive and behavioral function. Having detected no direct effect of COMT Val[158]Met genotype on cognition or behavior, we examined the

Table 4 Relationships between VBM-identified regional volumes and cognitive scores[a]

	CVLT, 10-min recall (n = 144)		Modified Rey-Osterrieth, 10-min recall (n = 140)		Modified Rey-Osterrieth figure copy (n = 145)		BNT total (n = 150)		Semantic fluency (n = 146)		Modified trails test, lines/min (n = 132)		Modified trails test, errors (n = 133)		Digit span backward (n = 142)		Letter fluency (n = 142)	
	β	Sig.	β	Sig.	β	Sig.	β	Sig.	β	Sig.	β	Sig.	β	Sig.	β	Sig.	β	Sig.
VTA	−0.021	0.827	−0.171	0.078	−0.206	0.031	0.061	0.403	−0.109	0.239	−0.023	0.824	−0.140	0.179	0.081	0.396	−0.010	0.922
L dMI	0.076	0.373	0.213	0.012	0.163	0.053	0.094	0.138	0.178	0.032	0.141	0.105	−0.110	0.217	0.278	0.001[b]	0.210	0.014
R dMI	0.042	0.671	0.228	0.022	0.145	0.141	0.038	0.604	0.233	0.016	0.221	0.029	−0.219	0.033	0.175	0.074	0.279	0.005[b]
L dlPFC	0.172	0.078	0.252	0.008	0.186	0.050	0.135	0.058	0.328	0.001[b]	0.206	0.037	−0.323	0.001[b]	0.382	80.37E-05[b]	0.285	0.005[b]
R VStr	−0.134	0.124	0.048	0.587	0.024	0.784	0.039	0.558	−0.022	0.801	0.130	0.153	−0.071	0.438	−0.042	0.635	0.129	0.149
vmPFC	0.134	0.169	0.130	0.190	−0.020	0.840	0.241	0.001[b]	0.134	0.159	0.091	0.357	−0.075	0.455	−0.057	0.558	0.132	0.190
L Hipp	0.344	0.001[b]	0.321	0.003[b]	−0.177	0.089	0.355	30.10E-06[b]	0.175	0.091	−0.121	0.252	0.056	0.606	0.048	0.642	0.129	0.223

Abbreviations: BNT = Boston Naming Test; CVLT = California Verbal Learning Test; dlPFC = dorsolateral prefrontal cortex; dMI = dorsal midinsula; VBM = voxel-based morphometry; vmPFC = ventromedial prefrontal cortex; VStr = ventral striatum; VTA = ventral tegmental area.

[a] Patients only; $\alpha = 0.05$, yielding a Bonferroni-corrected significance threshold of $p = 0.006$ after adjusting for 9 tests; n indicated for each measure.

[b] Regions related to the cognitive measure (after Bonferroni correction). First step predictors include age, sex, education, and total intracranial volume. Second step adds diagnosis and third step adds the 7 identified clusters' mean gray matter intensities.

influence of COMT-related regions' gray matter intensities on these functional domains in patients. Stepwise linear regression models demonstrated predictable relationships between cognitive (table 4) and behavioral (table e-4) scores and gray matter intensity in COMT-related structures. For example, atrophy within the COMT-related dlPFC cluster predicted greater cognitive impairment in several domains known to rely on lateral frontal integrity (table 4). The vmPFC cluster, in contrast, predicted more severe behavioral disinhibition (table e-4). The VTA exhibited an unanticipated relationship to behavior, wherein higher gray matter intensity was associated with more severe eating dysregulation and overall behavioral impairment.

DISCUSSION Applying whole-brain magnetic resonance VBM to patients with 3 dementia syndromes and healthy age-matched control subjects, we found that the COMT Val^{158}Met Val allele is associated with reduced gray matter within a network of DA-innervated cortical and subcortical regions, following a dose-dependent function. These results, driven primarily by the patient groups, favor the hypothesis that increased synaptic DA catabolism proves harmful to degenerating DA-innervated brain regions. To our surprise, patients with 1 or 2 Met alleles had significantly increased gray matter in the region of the VTA when compared to controls of the same COMT Val^{158}Met genotype. COMT Val^{158}Met was not found to exert a direct effect on cognition or behavior, although this negative finding should be viewed with caution until assessed in a larger sample. Finally, atrophy within COMT Val^{158}Met-related brain structures correlated with cognitive and behavioral impairment. Collectively, these findings suggest that the COMT Val^{158}Met Val allele acts as a neurodegenerative disease-modifying gene by accentuating gray matter loss within cortical and striatal DA projection targets.

Anatomical heterogeneity within clinical dementia syndromes can be substantial and provides a major source of diagnostic uncertainty.[15,16] Identifying sources of this individual variation may clarify disease mechanisms and suggest potential disease-modifying therapies. Building on previous work, our findings suggest that a patient's genetic background may skew or exacerbate the anatomical injury pattern. Possession of an *APOE* ϵ4 allele, for example, worsens atrophy in patients with AD or bvFTD but exerts this effect within regions known for their vulnerability to each disorder.[2] Functional polymorphisms in *FOXP2,* a gene which when mutated causes a developmental language disorder, are associated with language system hypoperfusion in FTLD.[17] Our data

suggest that COMT Val^{158}Met Val allele dosage exerts an effect across dementia syndromes by exacerbating neurodegeneration within regions that receive robust dopaminergic input from the VTA. Although we identified significant genotype effects at an uncorrected statistical threshold within a priori hypothesized (DA-innervated) brain regions, significant regional associations with Val allele dosage did not emerge at the whole-brain level after correcting for multiple comparisons. Compared to disease-related gray matter effects, we anticipated relatively small effects of COMT genotype, and our findings fit with this prediction. The circumscribed pattern of COMT Val^{158}Met genotype-associated regions, as well as the paucity of regions detected by the reverse contrast (more atrophy with increasing Met allele dosage), suggest that the findings are unlikely to reflect Type 1 error.

How synaptic DA availability modulates neurodegeneration merits further study. Healthy Val allele carriers show executive function deficits and inefficient frontal activation during working memory tasks.[18–23] More recent studies have forged links between COMT Val^{158}Met genotype and normative reward and emotion processing.[5–7] Lifelong possession of a Val allele could therefore predispose individuals to greater damage to the DA system once a neurodegenerative disease takes hold. Alternatively, reduced DA catabolism, as produced by the Met allele, may increase DA availability and confer resistance to the progressive synaptic transmission deficits that arise in AD, bvFTD, and SemD.

We found increased gray matter in the vicinity of the VTA in patients with at least 1 Met allele compared to genotype- and age-matched healthy controls. Although this unexpected finding requires confirmation in a larger dataset, it challenges conventional views of how neural systems respond to degenerative injury. One potential account of these data is that emerging disease within VTA projection targets disrupts cortical and striatal DA signaling and feeds back on VTA neurons to increase VTA output. Increased VTA activity, in turn, could induce proximal neuronal hypertrophy or increased dendritic arborization, resulting in the increased VTA gray matter intensity observed here. This response, however, appears unattainable by Val allele carriers, suggesting that the compensatory response, whatever its mechanism, may require greater synaptic DA availability.

Previous work in healthy elders and patients with Parkinson disease found no interaction between disease status, COMT Val^{158}Met genotype, and regional brain volume.[24] Val allele carriers, however, showed greater age-related atrophy in bilateral dorsal insulae, regions which showed age- and disease-independent volume reduction in Val carriers in the present study. Another study in AD showed that the Val allele was associated with more severe psychotic symptoms, such as hallucinations and agitation.[25] Hallucinations were too infrequent in our patient sample to analyze COMT genotype effects, and no significant effects of COMT genotype or COMT-related clusters' gray matter intensities were found with regard to agitation. Nonetheless, our results and these previous findings support the view that COMT Val^{158}Met influences clinico-anatomic features in patients with dementia and that, in the future, knowing a patient's genotype might help predict prognosis and choose treatments. In particular, patients with the diagnoses studied here may benefit from pharmacologic strategies, such as COMT inhibition, which increase synaptic DA availability, thereby mimicking the effect of possessing a COMT Val^{158}Met Met allele.

Regions showing Val allele dose-dependent atrophy participate in cognitive, emotional, and reward-related processing. Not surprisingly, we found that higher functioning in these domains was associated with structural integrity within COMT Val^{158}Met genotype-related brain regions. These findings highlight the behavioral relevance of COMT-related brain regions but do not imply a specific relationship between COMT-related regions and behavior. Perhaps the most striking finding from these analyses, however, was that increasing VTA volume predicted more prominent eating disturbance and overall behavioral impairment. With regard to eating, greater VTA volume could predispose patients to heightened limbic striatal DA release in response to rewarding food stimuli; this hypothesis could be addressed in future studies.

Despite the large clinical cohorts available, this study was limited by smaller sample sizes once each clinical syndrome was divided by genotype. This constraint prevented us from exploring potentially relevant interactions, such as sex-specific influences of COMT genotype on brain volume. Future larger studies may help address this issue and add security to our major findings. The present findings suggest that genetic background exerts a predictable influence on patterns of regional neurodegeneration. The results have potential treatment implications, suggesting that patients harboring a Val allele may benefit from COMT inhibition and justifying exploration of COMT inhibitors as neuroprotective agents for patients with the disorders studied here. Despite the increasing feasibility of more exhaustive genotyping and gene–imaging correlations, this work provides a model for exploring how single gene polymorphisms influence system-specific brain structures. Future studies could explore effects of other neuromodulatory gene poly-

morphisms, with the goal of clarifying disease mechanisms and identifying potential new symptomatic or neuroprotective therapies.

AUTHOR CONTRIBUTIONS

W.W.S. designed the study. E.D.G., J.A.C., J.Z., R.K.C., D.S., A.L.B., S.J.B., and J.H.K. collected data and performed analyses. S.J.B. performed COMT genotyping. J.H.K. and B.L.M. provided material and funding support and assisted with study design. E.D.G. and W.W.S. wrote the paper. All authors critically reviewed the manuscript.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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