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Epistatic interaction between COMT and DTNBP1 modulates prefrontal function in mice and in humans

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Abstract

Cognitive functions are highly heritable and the impact of complex genetic interactions, though undoubtedly important, has received little investigation. Here we show in an animal model and in a human neuroimaging experiment a consistent non-linear interaction between two genes—catechol-O-methyl transferase (COMT) and dysbindin (dys; dystrobrevin-binding protein 1 (DTNBP1))—implicated through different mechanisms in cortical dopamine signaling and prefrontal cognitive function. In mice, we found that a single genetic mutation reducing expression of either COMT or DTNBP1 alone produced working memory advantages, while, in dramatic contrast, genetic reduction of both in the same mouse produced working memory deficits. We found evidence of the same non-linear genetic interaction in prefrontal cortical function in humans. In healthy volunteers (N = 176) studied with functional magnetic resonance imaging during a working memory paradigm, individuals homozygous for the COMT rs4680 Met allele that reduces COMT enzyme activity showed a relatively more efficient prefrontal engagement. In contrast, we found that the same genotype was less efficient on the background of a dys haplotype associated with decreased DTNBP1 expression. These results illustrate that epistasis can be functionally multi-directional and non-linear and that a putatively beneficial allele in one epistastic context is a relatively deleterious one in another. These data also have important implications for single-locus association analyses of complex traits.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Keywords

cognition; fMRI; genes; translational research; working memory

INTRODUCTION

Cognition is highly dependent on genetic variation and the complex interactions between genes.[1–3] Higher order cognitive functions such as working memory are critically dependent on dopaminergic neural transmission in prefrontal cortex (PFC).[4,5] In particular, dopamine signaling and cognitive functions dependent on PFC follow an inverted U-shaped relationship where too little or too much dopamine signaling have analogously detrimental effects, presumably because optimum function depends on an optimum relative level of D1/D2 receptor activation.[6–10] In other words, too little D1 activation or too much D2 activation can have similarly deleterious effects on cortical function; despite the fact that different biological effectors are involved. Although the pharmacology and physiology of the dopamine signaling inverted U response in PFC has been extensively studied in experimental models[5] and to some degree in humans,[11] epistatic genetic interactions that might underlie this non-linear relationship have received little attention. We conducted a hypothesis-driven translational investigation of genetic interaction between two genes implicated in cortical dopamine function, catechol-O-methyl transferase (COMT) and dysbindin (dys; dystrobrevin-binding protein 1 (DTNBP1)), in a mouse model of PFC cognition and an analysis of human imaging of PFC function based upon this mouse model.

COMT regulates cortical synaptic dopamine via enzymatic methylation and inactivation of dopamine. It has been recently estimated that in mice > 50% of PFC dopamine flux is accounted by COMT.[12] In previous studies of cortical function based on COMT genetic variation in both mouse and humans,[13–16] variations producing increased COMT enzyme activity and by inference decreased dopamine induce relatively impaired PFC-related cognition and physiology. This effect is presumably due to a leftward shift to the downslope of the dopamine–PFC function inverted U relationship. Conversely, genetic variations associated with decreased enzyme activity in mouse and humans have the relatively opposite effects.[13–16] Thus, viewed from the perspective of one gene (COMT) and its effect on PFC-dependent working memory, there is an advantageous variation (decreased enzyme activity and increased dopamine) and a disadvantageous variation (increased activity and decreased dopamine). Of course, COMT has a much more complex role in cortical function (for example, potentially opposite effects of COMT genotype on emotional processing), but in this report we will retain the specific context noted above.

Dys or DTNBP1 emerged as a candidate gene for schizophrenia based on linkage data.[17] Genetic variations in dys also influence cognitive abilities in humans as well as in mice.[18–21] Dys has been implicated in various aspects of synaptic biology, including in excitatory transmission and presynaptic plasticity.[22,23] More central to the hypothesis of this study, as a component of the biogenesis of lysosome-related organelles complex-1, dys participates in lysosomal trafficking of D2 receptors, and downregulation of dys expression in cell culture leads to upregulation of D2 receptors on the surface of the cell and increased D2 signaling.[24]

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Similarly, a genetic mutation that reduces dys expression in mice leads to upregulation of D2 receptors on the neuronal surface, a D2-dominated functional state in the PFC, and a pattern of abnormal excitability in PFC circuits.[20,21,25]

Based on these previous results, we predicted that the relatively advantageous effects of reduced COMT (that is, more dopamine in PFC) on prefrontally mediated working memory could be paradoxically modulated by genetic variation in dys. Specifically, based on the individual biological effects of each of these genes on cortical dopamine signaling and the inverted U function, we predicted an epistatic interaction where genetically reduced COMT activity combined in the same individual with genetically reduced dys would result in D2 signaling overdrive in the PFC and paradoxically abnormal cortical function (Figure 1). We believe our results represents a watershed example of biological epistasis related to cognition and brain function by demonstrating that the effect of an allele in one gene implicated in a complex, non-linear biological function is critically dependent on alleles in other genes that impact on the same non-linear function.

MATERIALS AND METHODS

Mice subjects

All procedures were approved by the NIMH Animal Care and Use Committee and followed the NIH Guidelines ‘Using Animals in Intramural Research’. All mice used were littermates and bred by double heterozygous mating (♀COMT+/− dys+/− × ♂COMT+/− dys+/−). We developed these new double knockout (ko) mice by intercrossing single COMT and dys ko mice previously described.[14,21,26] The COMT and dys single ko animals are the same single gene ko mice previously shown to have increased prefrontal dopamine function and increased prefrontal D2 receptor expression and function, respectively. Mice were identified by PCR analysis of tail DNA. Mice were group-housed (2–4/cage) in a climate-controlled animal facility (22 ± 2 °C), maintained on a 12-h light/dark cycle and given free access to food and water, unless during the T-maze testing. Testing was conducted in male mice, 3–7-months old, during the light phase. Experimenters were blind to the genotype during behavioral testing. Mice were handled by the experimenter on alternate days during the week preceding the test. At least 1 h before any test manipulation, mice were habituated in a room adjacent to the testing room.

Physical health

Measures of general health and neurological reflexes were assessed in the mice as described previously.[14,21]

Discrete paired-trial variable-delay T-maze task

Naive mice were presented with a sequence of randomly chosen forced runs, each followed by a choice run thus requiring the integration of information held online (the forced run) with the learned rule (non-match to sample) as previously described[14,21] (see also Supplementary Materials and Methods for more details). Owing to the large number of mice used in this experiment, it was not possible to run them all at the same time. However, in each different batch run, all seven genotypes were always present.

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Statistical analysis in mice experiments

Two-tailed Fisher's exact analyses were used to compare genotypes for some general health parameters and for the number of mice reaching the learning criteria of the T-maze task. Two-way analysis of variance (ANOVA) with genotype (COMT+/+ dys+/+, COMT+/− dys +/+, COMT−/− dys+/+, COMT+/+ dys+/−, COMT+/+ dys−/−, COMT+/− dys+/− and COMT−/− dys−/−) as a between-subjects factor and days of habituation (days 1 and 2) as a within-subject factor were used to examine the latency to retrieve the first hidden food pellet from the end of the T-maze alleys. One-way ANOVA was used to compare genotypes (COMT+/+ dys+/+, COMT+/− dys+/+, COMT−/− dys+/+, COMT+/+ dys+/−, COMT+/+ dys−/−, COMT+/− dys+/− and COMT−/− dys−/−) on the days needed to reach the criteria in the T-maze task. To directly compare the current results with previously published results,[14,21] we also performed separate one-way ANOVAs to examine the days needed to reach criteria in the T-maze task considering only COMT single ko mice (COMT+/+, +/−, −/−) and dys single ko mice (dys+/+, +/−, −/−). *Post-hoc* analyses for individual group comparisons used Newman–Keuls analyses. The accepted value for significance was $P < 0.05$.

Human subjects and functional magnetic resonance imaging (fMRI) protocol

We analyzed 176 healthy Caucasian volunteers who provided written consent for and participated in the Clinical Brain Disorders Branch/NIMH Genetic Study of Schizophrenia (CBDB Sibling Study; NCT00001486, DRW PI) with high-quality fMRI data plus COMT and DTNBP1 genotypes (see supporting online Supplementary Tables S1 and S2 for demographic data). In particular, for the genotypes we assessed the rs4680 functional genetic variation in COMT (that is, the Val-Met single-nucleotide polymorphism) and a DTNBP1 haplotype previously associated with reduced DTNBP1 mRNA expression in the human brain, the three-marker rs2619538-rs3213207-rs1047631 or here, the 'Bray haplotype'. Subjects were tested on the N-back working memory task as previously described.[13,27,28] The fMRI data underwent a rigorous protocol for quality control for all individual data sets.[27] We measured fMRI activation differences using whole-brain blood oxygenation level-dependent (BOLD) fMRI data collected at 3T (General Electric Systems, Milwaukee, WI, USA) using a GE-EPI pulse sequence (24 axial slices (echo time = 30 msec, repetition time = 2 s, flip angle = 90°, field of view = 24 cm, matrix = 64 × 64, voxel dimensions = 3.75 × 3.75 × 6 mm). We used SPM5 software (Wellcome Department of Cognitive Neurology, London, UK http://www.fil.ion.ucl.ac.uk/spm) to pre-process and then spatially normalize these fMRI data to the MNI common stereotaxic space (Montreal Neurological Institute template).

Demographic variables and 2-back performance measures across genotype groupings were analyzed using ANOVAs within SPSS (IBM, Chicago, IL, USA). fMRI data were analyzed in SPM5. For each individual, first-level contrasts were created by contrasting the working memory 2-back with the control 0-back. These individual contrast images were examined for genetic interaction via multiple regressions that modeled main effects of COMT, the dys 'Bray haplotype' and their interaction. Specifically, we had nine groups based on three-COMT-by-three-Bray-haplotype (Supplementary Tables S1 and S2): (1) COMT Val/Val without the Bray haplotype (−/−), (2) COMT Val/Met without the Bray haplotype (−/−), (3)

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COMT Met/Met without the Bray haplotype (−/−), (4) COMT Val/Val and heterozygous for Bray (+/−), (5) COMT Val/Met and heterozygous for Bray (+/−), (6) COMT Met/Met and heterozygous for Bray (+/−), (7) COMT Val/Val and homozygous for Bray haplotype (+/+), (8) COMT Val/Met and homozygous for Bray haplotype (+/+), and (9) COMT Met/Met and homozygous for Bray haplotype (+/+). As we have done in other imaging genetics reports, we included age and sex as nuisance variables in the multiple regression. Statistical significance was determined using two-tailed *t*-tests within SPM5 at an uncorrected whole-brain threshold of $P \leq 0.001$ and small volume correction as reported previously.[29]

RESULTS AND DISCUSSION

Generation of COMT*dys double ko mice

Genetically altered mice provide a level of molecular specificity that is not possible in human studies, where potential interactions between functional loci within the gene and with genetic background are difficult to control. To investigate the genetic interaction between COMT and dys, we generated COMT*dys double ko mice. In particular, the single COMT and dys mutations in our mice were transferred to the C57BL/6J genetic background by 11 generations of backcrossing for each single mutant line. Furthermore, following the intercrossing of these two single mutant lines, we backcrossed the resulting double mutants with C57BL/6J for two more generations. Thus, creation of a more homogenous C57BL/6J genetic background eliminates a series of behavioral/genetic-related problems present in the original COMT mutation on a mixed 129/JxC57BL/6J background and in the original dys mutation on the DBA/2J background.[21,26,30,31] This extensive series of back crosses also diminishes the potential for systematic differences in flanking genomic regions between individual knockout strains and the combined knockout strain. Genetic modifications can also change maternal behavior, and in turn, influence the cognitive functions and behavior of the offspring. To avoid these gene–environment uncontrolled interactions and to properly identify the specific role played by COMT*dys genetic modifications, we adopted a COMT*dys double heterozygote breeding scheme (♀COMT+/− dys+/− × ♂COMT+/− dys +/−). This approach allowed us to contrast in littermates life-long effects of genetic variations resulting in relatively low COMT activity (COMT single ko mice), relatively low dys (dys single ko mice), the combination of decreased COMT and dys in the same individual (COMT*dys double ko mice) and normal endogenously expressing COMT and dys (wild-type COMT+/+ dys+/+ mice). Concurrent genetic reductions of both COMT and dys did not affect the general health or physical abilities of COMT*dys double genetically modified mice (supporting online Supplementary Table S3); as was found for genetic modification resulting in decrease of only COMT[14] or only dys.[21]

Working memory deficits in COMT*dys double ko mice

Working memory functions are closely related to PFC dopamine signaling.[10,32] We tested single COMT, single dys and double COMT*dys mutant littermates in a well validated version of a working memory T-maze task in which acquisition of correct responses to criteria depends on the medial PFC in mice.[14,21,33] During the habituation phase of the task, all mice readily learned to run through the maze to retrieve the food reward ($F_{1,83} = 236.78$, $P < 0.0001$), independently of their COMT and/or dys genotype ($F_{6,83} = 1.96$, $P = 0.09$;

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Figure 2a). Habituation performance is considered a reference memory component of this T-maze task.[14,21,33] Mice carrying a single mutation of either COMT or dys acquired this task faster than wild-type, COMT+/+ dys+/+ littermates (COMT ko: $F_{2,38} = 3.44$, $P < 0.05$; dys ko: $F_{2,36} = 5.99$, $P < 0.006$; Figure 2b). These data in the dys ko mice are also consistent with evidence that stimulation of D2 receptors improves working memory in both monkeys and humans.[34–37] However, both COMT*dys double heterozygote (that is, COMT+/− dys+/−) and double homozygote null mutant mice (that is, COMT−/− dys−/−) required more days to learn this working memory task ($F_{6,80} = 6.96$, $P < 0.0001$; Figure 2b; see also supplementary Figure 1). A similar proportion of the 16 COMT+/+ dys+/+, 13 COMT+/− dys+/+, 13 COMT−/− dys+/+, 10 COMT+/+ dys+/−, 15 COMT+/+ dys−/−, 12 COMT+/− dys+/− and 11 COMT−/− dys−/− mice tested reached the criteria (100, 92.3, 100, 90, 93, 100 and 100%, respectively; $P \geq 0.4$). Thus, as we previously found,[14,21] a single disruption of either the COMT or dys gene on this genetic background strain resulted in faster acquisition of this working memory task while, in dramatic contrast, the combined reduction of both the COMT and the dys genes in the same subject results in marked cognitive disadvantages. These results point to a COMT*dys genetic interaction in the modulation of cognitive functions dependent on the medial PFC. Consistent with the basic science data showing non-linear effects of increasing D2 signaling in PFC, our genetic interaction was also non-linear at the phenotypic level, in that single ko s might showed advantageous effects under certain conditions but combined ko s were deleterious.

Prefrontal physiology related to working memory is impaired by COMT*dys genetic interaction in humans

Based on the COMT*dys double ko mice results (Figure 2), we questioned whether these non-linear epistatic interactions would be observable in humans in an analogous working memory task related to PFC functions. We investigated the interaction between the COMT Val-Met functional genetic variation (that is, COMT enzyme activity: COMT Val/Val > COMT Val/Met > COMT Met/Met)[38] and the DTNBP1 Bray haplotype (that is, DTNBP1 mRNA expression: Bray −/− >Bray +/− >Bray +/+).[39,40] We compared the modulation of these functional COMT and DTNBP1 genetic variants on the BOLD fMRI signal during the N-back working memory task in healthy human volunteers. This paradigm of statistical association has been previously used and validated for the identification of subtle effects of many genetic variants on brain function.[13,28,41] The cognitive task used here is an explicit test of information processing efficiency within the PFC.[13,27,28] As reported in several studies in healthy volunteers,[13,28,42] COMT Val carriers show relatively less PFC physiological efficiency during working memory tasks as indicated by greater BOLD fMRI activation for equivalent task accuracy.[43] This physiological effect is thought to reflect dopaminergic modulation of intrinsic inhibitory activity, which is critical for focusing cortical activity during working memory.[44,45] Our selection criteria were valid COMT × DTNBP1 genotypes and high-quality BOLD fMRI data from the 2-back working memory task.

We analyzed 176 healthy Caucasian volunteers meeting these inclusion criteria (supporting online Supplementary Tables S1 and S2). We included only those individuals for whom diplotype identity was unambiguous using the program *PHASE*. No significant differences

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were found across genotype groupings for age, sex, years of education, 2-back accuracy or WAIS IQ ($P > 0.3$; supporting online Supplementary Table S2). This lack of performance differences was expected considering that the genetic effects in humans are relative (that is, quantitative traits and not absolute null alleles), the task itself is relatively easy and that the variance in working memory accuracy in these healthy subjects was low. However, controlling for performance across genotype groups during the N-back task allowed the physiological data to be interpreted in terms of how the information is processed in brain circuits independent of the potentially confounding effects of performance. As predicted, we found epistatic effects within dorsolateral PFC analogous to those in mice. Specifically, the effect of the COMT Val-Met genotype depended on the DTNBP1 Bray haplotype background (Supplementary Table S4). Individuals homozygous for COMT Met alleles having no Bray DTNBP1 haplotypes were more efficient than other COMT genotypes, consistent with many earlier studies[42] (Figure 3). In contrast, the relatively increased inefficiency associated with COMT Val-Val genotype was not apparent in individuals heterozygous for the dys Bray haplotype (Figure 3). Finally, individuals with COMT Met/Met genotypes who were also homozygous for the Bray low dys expression-associated haplotype were now the most inefficient compared with other COMT genotypes (Figure 3). In other words, reduced dys rescues the relatively inefficient physiological state of Val/Val genotypes (that have relative increased COMT and reduced dopamine) and depreciates the efficient Met/Met state (that has relative reduced COMT and increased dopamine). This is strikingly analogous to the non-linear interaction of both lower dys and lower COMT activity in the COMT*dys double ko mice.

CONCLUSIONS

These data confirm at the level of mouse working memory and human working memory-associated physiology a genetic interaction between COMT and DTNBP1 that is consistent with predictions from basic model systems about the non-linear relationship between cortical dopamine signaling and cortical function and the effects of these genotypes on the biology of their respective proteins. The key finding of this direct translational study is that a relatively ‘advantageous’ genotype in one context becomes disadvantageous in another depending on the biology of the interaction. Thus, because decreased dys upregulates D2 signaling, this effect is presumably biologically compensated by relatively less synaptic dopamine in individuals with relative increased COMT activity (the human COMT Val or the mice COMT+/+). In contrast, this effect is exacerbated by relative decreased COMT enzyme activity and increased synaptic dopamine. Although we have not directly confirmed at the molecular level the mechanism of the cognitive effect in the double ko mice, the previous molecular data from the single ko animals and the well-characterized inverted U function describing dopamine signaling and prefrontal function suggest that the COMT × dys interaction is based on their convergence in dopamine/D2 pathways in the PFC. Specifically, this genetic interaction seems to fit well into the inverted U curve correlating working memory with dopamine levels and the D2/D1 ratio signaling in the PFC (Figure 1).

Finally, our data highlight the complexity of genetic association with complex brain functional traits. Analogous results have recently been described in the role of ion channel mutations causing genetic epilepsy syndromes, in which allelic effects are critically

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dependent on genetic background interactions.[46] It is apparent that relatively advantageous individual genotypes might become risk associated in the context of other genes that impact in the same molecular pathways. These results also have implications for understanding variation in genetic association of individual genes across different populations and may explain some of the inconsistencies in the clinical association literature related to psychiatric disorders and other complex behavioral conditions, because genetic background in relevant pathways is not generally considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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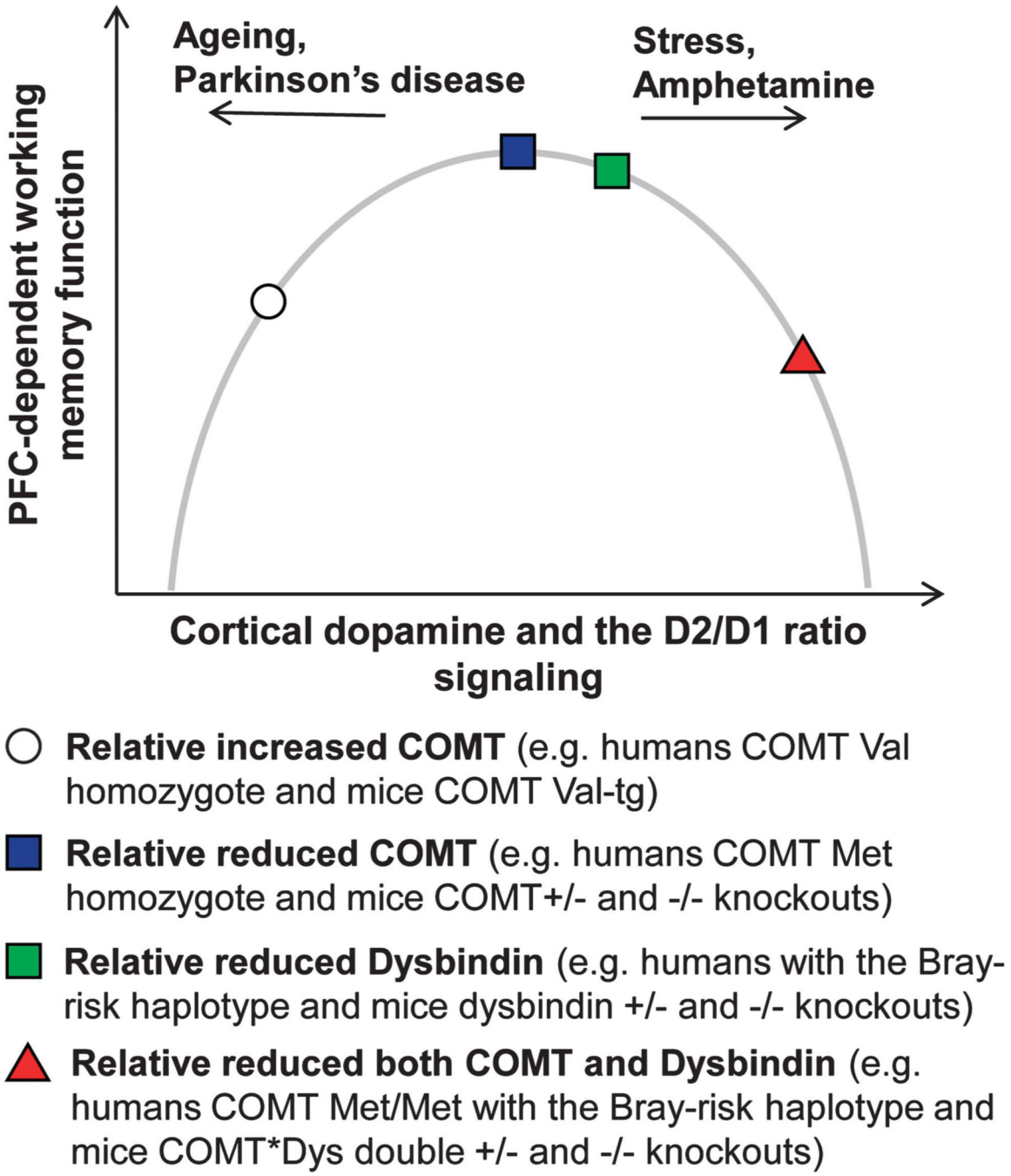

Figure 1.

Theoretical inverted U model describing the predicted epistatic effects of catechol-O-methyl transferase (COMT) and dys genotypes on prefrontal cortex (PFC)-dependent working memory function in relationship to cortical dopamine levels and D2/D1 activation. Healthy adults (both humans and mice) with relative increased COMT enzyme activity and less synaptic dopamine (that is, human COMT Val homozygote and mice COMT Val-tg: white circle in the figure) are displaced relatively leftwards on the×axis resulting in relatively less efficient PFC functions and/or working memory deficits.[13–16,28] Conversely, healthy adults

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(both humans and mice) with relative decreased COMT enzyme activity (that is, human COMT Met homozygote and mice COMT+/− and −/− knockouts: blue square in the figure) show a rightward shift resulting in more optimal PFC functions and/or working memory improvements.[13–16,28] Healthy adults (both humans and mice) with relative decreased dys levels (that is, humans carrying the Bray-risk haplotype and mice dys+/− and −/− knockouts and relatively enhanced D2 signaling: green square in the figure) should show, at least at baseline, a relative rightward shift resulting in a more efficient PFC function and/or working memory improvements.[21] However, healthy adults (both humans and mice) with relative decreases of both COMT enzyme activity (that is, human COMT Met homozygote and mice COMT+/− and −/− knockouts) and dys levels (that is, humans carrying the Bray-risk haplotype and mice dys+/− and −/− knockouts) would be expected to show an exaggerated rightward shift resulting in less efficient PFC function and/or working memory deficits, possibly due to potential dopamine/D2 signaling overdrive (red triangle in the figure).

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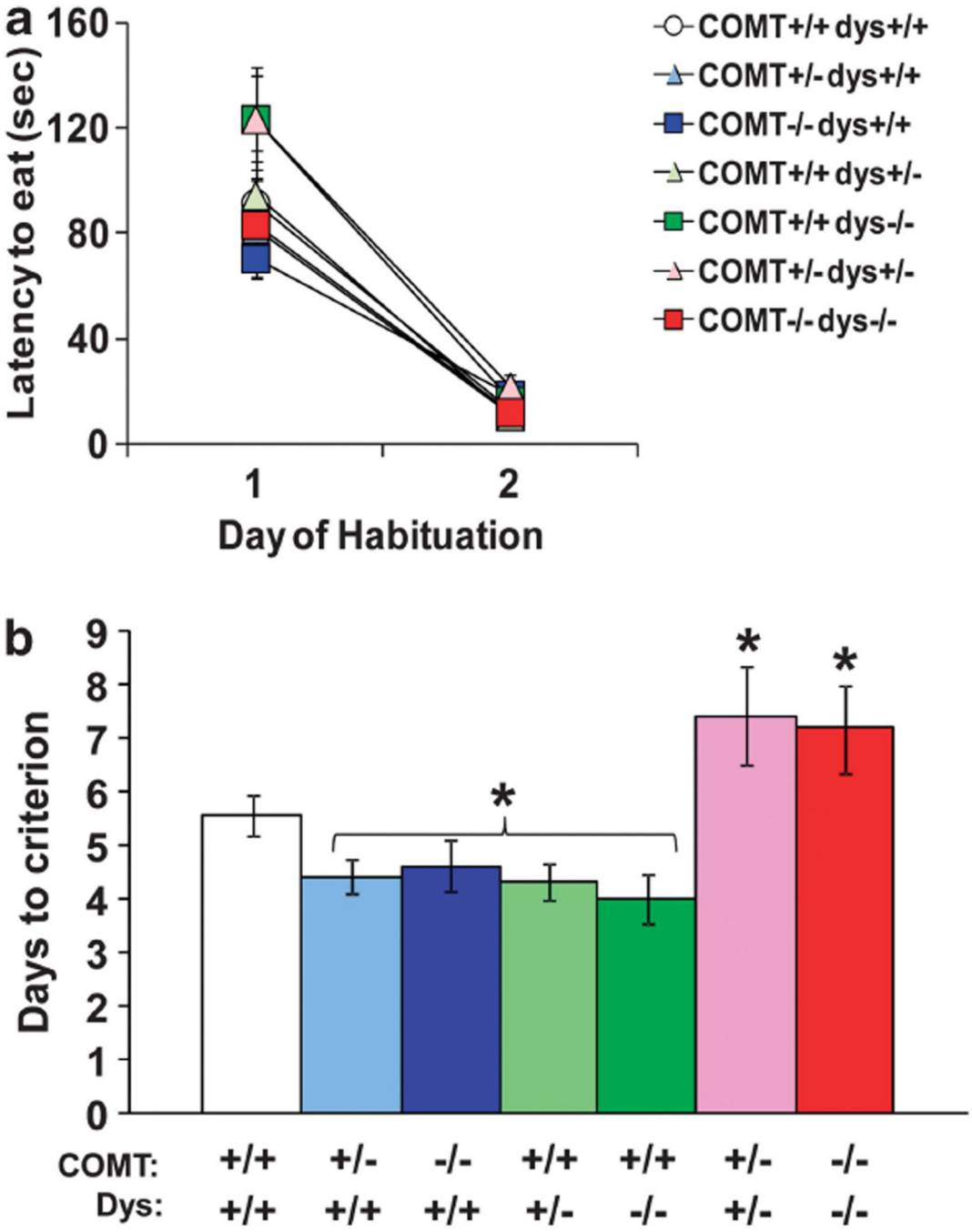

Figure 2.

Working memory deficits in COMT*dys double knockout mice. (**a**) Latency to retrieve the hidden food pellet displayed by catechol-O-methyl transferase (COMT) single ko mice, dys single ko mice and COMT*dys double ko mice during the discrete paired-trial T-maze task. N = 11–16/group. All mice readily learned to run through the maze to retrieve the food reward independently of their COMT and/or dys genotype indicating that COMT, dys and their interaction did not alter reference memory components of this T-maze task. (**b**) Days needed to reach criteria displayed by wild-type (COMT+/+ dys+/+), COMT knockouts

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(COMT+/− dys+/+; COMT−/− dys+/+), dys knockouts (COMT+/+ dys+/−; COMT+/+ dys −/−) and COMT*dys double knockout (COMT+/− dys+/−; COMT−/− dys−/−) littermates during the discrete paired-trial T-maze task. Values represent mean±s.e.m. $N = 9–16$/group; $*P < 0.05$ versus wild-type (COMT+/+ dys+/+) littermates.

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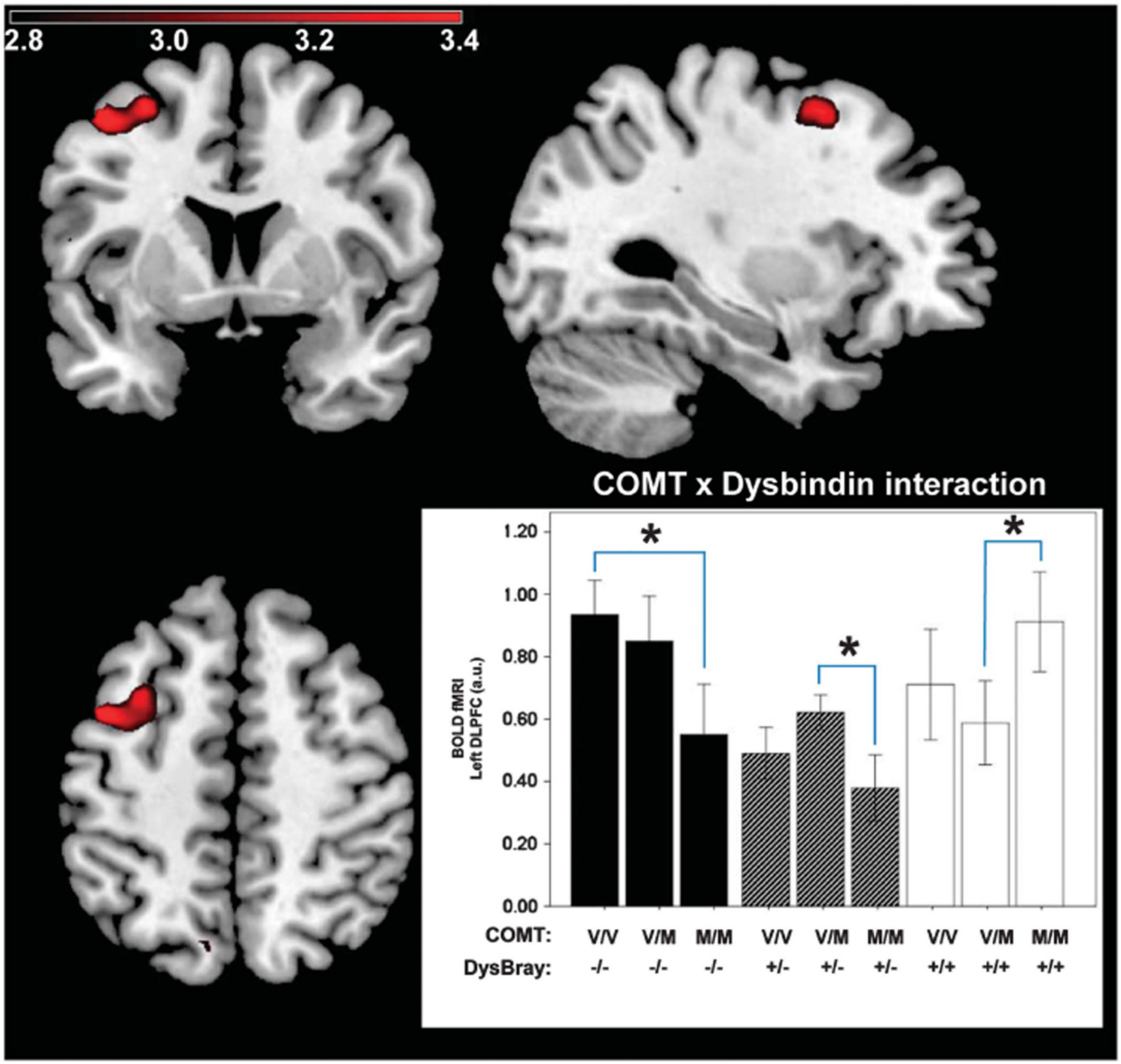

Figure 3.

The relationship between prefrontal cortex (PFC) efficiency and catechol-O-methyl transferase (COMT) Val/Met genotype depends upon dystrobrevin-binding protein 1 (DTNBP1) genotype during a working memory task. In the context of reduced DTNBP1 expression given by the presence of the Bray haplotype (DysBray +/+), COMT Met/Met subjects (COMT M/M) no longer show a PFC efficiency advantage during working memory —instead becoming among the least efficient. Blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging signal was extracted from an area of COMT × dysbidnin Bray haplotype interaction within left dorsolateral PFC ((−47, 27, 29), SPMT = 3.22, $P = 0.001$, $k = 228$, family-wise error small volume correction $P = 0.03$). BOLD signal

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is presented as mean (arbitrary units (a.u.)) ± s.e. *$P < 0.05$ versus COMT Met/Met subjects. SPMT, statistical parametric mapping t.