

RESEARCH ARTICLE

The impact of pimavanserin on psychotic phenotypes and tau phosphorylation in the P301L/COMT- and rTg(P301L)4510 mouse models of Alzheimer's disease

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Abstract

Introduction: Psychosis in Alzheimer's disease (AD) is associated with grave clinical consequences including a precipitous cognitive decline and a hastened demise. These outcomes are aggravated by use of existing antipsychotic medications, which are also associated with cognitive decline and increased mortality; preclinical models that would develop new therapeutic approaches are desperately needed. The current report evaluates the ability of the neoteric antipsychotic, pimavanserin, to normalize hyperkinesia and sensorimotor gating in the novel catechol-O-methyltransferase (COMT) deleted P301L/COMT- and rTg(P301L)4510 models of psychotic AD, and the impact of pimavanserin on tau pathology.

Methods: Female P301L/COMT- mice were behaviorally characterized for abnormalities of locomotion and sensorimotor gating, and biochemically characterized for patterns of tau phosphorylation relative to relevant controls utilizing high-sensitivity tau enzyme-linked immunosorbent assay (ELISA). Female P301L/COMT- and rTg(P301L)4510 mice were randomized to pimavanserin or vehicle treatment to study the ability of pimavanserin to normalize locomotion and rescue sensorimotor gating. Additionally, high-sensitivity tau ELISA was used to investigate the impact of treatment on tau phosphorylation.

Results: P301L/COMT- mice evidenced a hyperlocomotive phenotype and deficits of sensorimotor gating relative to wild-type mice on the same background, and increased tau phosphorylation relative to COMT-competent P301L mice. Pimavanserin normalized the hyperkinetic phenotype in both the P301L/COMT- and rTg(P301L)4510 mice but had no impact on sensorimotor gating in either model. Pimavanserin treatment had little impact on tau phosphorylation patterns.

Discussion: These data suggest that pimavanserin ameliorates tau-driven excessive locomotion. Given the morbidity associated with aberrant motor behaviors such as

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ancing in AD and lack of effective treatments, future studies of the impact of pimavanserin on actigraphy in patients with this syndrome may be warranted.

KEYWORDS

Alzheimer's disease, antipsychotic, dopamine, locomotion, prepulse inhibition, psychosis, sensorimotor gating, tau

1 | INTRODUCTION

Psychosis often complicates the course of Alzheimer's disease (AD) and its association with aggression renders it a significant cause of caregiver distress with higher rates of institutionalization.¹ Of the two canonical pathogenic proteins implicated in AD, a concatenation of evidence points to abnormally phosphorylated tau rather than other protein pathologies such as amyloid beta ($A\beta$) in the pathophysiology of psychosis in AD.²⁻⁴ Although evidence supports the efficacy of atypical antipsychotics in treating AD psychosis,⁵ they have been associated with an increased rate of cognitive decline and mortality;^{6,7} currently there are no Food and Drug Administration-approved treatments for AD psychosis. There is evidence that pimavanserin, a medication approved for the treatment of Parkinson's disease (PD) psychosis, may be effective in treating psychosis in AD and other dementias.⁸⁻¹⁰ Pimavanserin is novel among antipsychotics as it does not antagonize dopamine receptors as all other available antipsychotics do, rather it acts as an inverse agonist primarily at neuronal 5-HT_{2A} and, to a lesser extent, 5-HT_{2C}, receptors with no appreciable activity at other targets, including dopamine receptors.^{8,11,12} This unique binding profile avoids the extra-pyramidal side effects such as dystonia, tremor, and akathisia associated with dopamine blocking antipsychotics.¹³

Although the phenomenology of psychosis is a strictly human construct, a common strategy in the development of novel antipsychotic medications involves screening candidate compounds in preclinical models using behavioral outcomes established in human psychosis that can be observed in animal models. The two most commonly used preclinical behavioral approaches in the evaluation of antipsychotics are the quantification of locomotive behavior (hyperkinesia being an analogue of behavioral disorganization in psychosis) and sensorimotor gating integrity with prepulse inhibition (PPI) of acoustic startle, deficits of which have been reported in psychotic conditions.^{14,15} Currently approved typical and atypical D₂-receptor-blocking medications used in the treatment of psychosis have been extensively studied in mice, and consistently inhibit locomotive velocity, rescue PPI deficits driven by psychotomimetic compounds, and even increase sensorimotor gating integrity in otherwise untreated wild-type mice.^{15,16} Though there is evidence that pimavanserin, which does not antagonize dopamine receptors, can rescue PPI deficits and increase locomotion driven by psychotomimetics,^{17,18} its ability to impact these behaviors has not been previously reported in transgenic models of AD.

Transgenic animal models of tauopathy have been proposed as potentially preclinically relevant to treatment studies of AD psychosis.¹⁴ As some evidence points toward focal frontal neurode-

generation in AD psychosis¹⁹ driven by an increase in focal tau phosphorylation,^{3,20} the existing rTg(tauP301L)4510 model of human mutant tau with an early burden of frontal pathology models the distribution of pathology.²¹ In support of this, we have previously studied these mice for deficits of sensorimotor gating and reported that rTg(P301L)4510 mice develop deficits of PPI over time;²² these deficits were driven by tau phosphorylated at epitopes in similar patterns to what we have previously observed in a *post mortem* study of the frontal cortex of patients who suffered from AD psychosis.³ Additionally, in separate studies the rTg(P301L)4510 mouse evidenced robust hyperactivity in locomotor assays relative to non-transgenic controls, which is reversed with tau reduction, suggesting that the tauopathy itself drives the hyperkinetic phenotype.²³

We have developed a newer candidate specifically to model outcomes relevant to AD psychosis comprising a P301L tau mutation together with a deleted dopamine-degrading catechol-O-methyltransferase (COMT) gene (COMTKO).²⁴ We developed the model predicated on the well-established relationship between dopamine, either endogenous or exogenous, and psychosis across the diagnostic spectrum from bipolar disorder and schizophrenia to Parkinson's disease to AD, in which D1/D3 dopamine receptor genetic variations and D2/D3 receptor density in the striatum have been directly correlated with psychotic symptoms in AD patients.²⁵⁻³⁰ Previously, we reported that the P301L/COMT- model evidences increased extracellular dopamine and surges in frontal tau phosphorylation from extracellular dopamine in response to catecholamine reuptake inhibition.²⁴ Tau phosphorylation patterns in the absence of absence of pharmacologic treatment and behavioral deficits with relevance to psychosis in the P301L/COMT- model such as sensorimotor gating abnormalities in the form of PPI and locomotive phenotypes have not been previously reported.

In the current report, we first conducted experiments to determine whether there are relative deficits in the P301L/COMT- model in the psychosis-relevant phenotypes of locomotion and sensorimotor gating compared to sex- and age-matched strain-specific COMT-competent P301L, COMTKO, and wild-type (WT) mice. Subsequently, as a pathological correlate to the behavioral investigation, we compared tau phosphorylation patterns in the P301L/COMT- and COMT-competent P301L tau models. Next, having identified sensorimotor gating abnormalities and increased locomotion in the P301L/COMT- mice, we investigated the ability of acute administration of pimavanserin to normalize velocity and increase PPI in two transgenic models of AD: the P301L/COMT- mouse and the hyperlocomotive,²³ PPI-impaired,²² rTg(P301L)4510 mouse. Finally, as serotonin

promoting medications have been shown to reduce tau phosphorylation in P301L mice,³¹ and as pimavanserin has very recently been shown to suppress A β and improve cognitive function in APP/PS1 mice,³² we quantified tau phosphorylation in the P301L/COMT⁻ and rTg(P301L)4510 mice after treatment with pimavanserin to determine whether there is an impact on tau phosphorylation.

2 | METHODS

2.1 | Animals

All experiments were performed with the approval of the Institutional Animal Care and Use Committee at the Feinstein Institutes for Medical Research (FIMR) and complied with the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978). Mice were housed in the Center for Comparative Physiology (CCP) at the FIMR. The P301L/COMT⁻, P301L/COMT⁺⁺, COMT⁻, and WT mice sharing background strain were generated from a cross of COMT-deleted mice (COMT^{-/-}) on a C57BL/6 background (generously donated from Joseph Gogos at Columbia University) with JNPL3 mice (Prmp-MAPT*P301L; Taconic Biosciences, stock #1638) on a C57BL/6*DBA/2 background. Mice were bred over many generations to produce cohorts of P301L/COMT⁻(DM); P301L/COMT⁺⁺; COMT⁻; and WT on the same C57BL/6*DBA/2 background at the FIMR as described previously.²⁴ The deleted degradative COMT gene renders the mice hyperdopaminergic, while the expression of the human mutant P301L autosomal dominant tau mutation associated with FTDP-17 produces a tauopathy in the forebrain and in the hindbrain that eventually involves the spinal cord.^{24,33} The rTg(P301L)4510 mouse, used in treatment experiments for comparison to the P301L/COMT⁻, is a bigenic mouse model of tauopathy comprising the human P301L mutation downstream of a tetracycline-operon-responder construct that requires co-expression of an activator construct itself set downstream in the rTg(P301L)4510 of a Ca⁺/calmodulin kinase II (CaMKII) promoter, limiting tau expression to the forebrain, and resulting in severe tau pathology.²¹ rTg(P301L)4510 (Camk2a-tTA/TetO-MAPT*P301L) mice were procured from Jackson Laboratories (stock # 024854).

Mice were housed in the CCP four to a cage, with access to food and water ad libitum, and maintained on a reverse 12-hour light/dark cycle with lights out at 8:30 AM. Behavioral experiments were conducted during the dark cycle under dim red lighting. Female mice were used exclusively for all experiments owing to the higher expression of tau in the P301L models.³⁴ Genotyping of mice for COMT deletion and presence of P301L mutation was performed from tail samples sent to Transnetyx, using quantitative polymerase chain reaction-based system.

2.2 | Open field

The open field test was performed to quantify locomotion by placing animals in the center of an open acrylic box (17" X 17") with 12-inch

RESEARCH IN CONTEXT

- 1. Systematic Review:** The authors reviewed the literature (e.g., via PubMed) on the nascent preclinical modeling of the psychotic syndrome of Alzheimer's disease (AD). Recent work on candidate models including the novel P301L/COMT mouse is cited, together with previous work on the impact of antipsychotic medications on tau neuropathology.
- 2. Interpretation:** Our findings suggest that the P301L/COMT⁻tau mouse has a novel psychosis-relevant behavioral phenotype that can be used in preclinical studies of psychotic AD. The hyperkinetic component of this phenotype is rescued by a novel serotonin-blocking antipsychotic, pimavanserin.
- 3. Future Directions:** Studies of the P301L/COMT⁻ mouse should be extended to other mechanistically distinct antipsychotics, such as dopamine-blocking typical and atypical compounds. Pimavanserin may have utility in the treatment of aberrant motor behaviors in AD including restlessness and pacing.

walls and allowing them to freely explore the environment for 10 minutes while being recorded by video tracking software (EthoVision XT 14 with Automatic Mouse Behavioral Recognition, Noldus, via a Gigabit Ethernet [Gig-E] high-resolution camera as previously described.³⁵ Ethovision XT 14 tracks the location and movement of mice from the live video feed and reports these for each trial as total distance traveled and then calculates mean velocity (distance/second) over the 10-minute interval from the distance traveled. For behavioral characterization of P301L/COMT⁻; P301L/COMT⁺⁺; COMT⁻; and WT mice, assays were conducted at one time point to calculate total distance traveled. As P301L mice develop hindbrain and spinal cord pathology with motor consequence, open field testing was conducted on young mice.³³ For pimavanserin studies, to control for impact of treatment on field exploration as a motor function versus a novelty seeking behavior and to control for baseline differences in the individual mice,¹⁴ mice were assayed at baseline (2 weeks prior to injection of pimavanserin or saline to acclimate the mice and reduce the novelty of the paradigm) and then again 60 minutes after injection to calculate both distance traveled at outcome and a within-mouse percent reduction in open field $\frac{\Delta \text{ in velocity}}{\text{baseline velocity}} \times 100$.

2.3 | PPI

For interrogation of sensorimotor gating, an SR-LAB system acoustic startle box with digitized electronic output comprising a piezoelectric accelerometer mounted under a Plexiglass cylinder and integrated with San Diego Instruments' startle response software was used to generate startle and measure PPI. As in our previously reported

methodology,²² PPI assessment began with each animal being acclimated to the startle box 2 weeks prior to the PPI sessions for 10-minute acclimation sessions at a background noise intensity of 65 dB. For PPI sessions, The SR-LAB machine was programmed to deliver acoustic startle stimuli over a 65 dB background with a variable inter-trial interval. The startle stimulus was presented as a fast-rise noise burst lasting 40 milliseconds at an intensity of 120 dB. The animal's whole-body flinch response to each stimulus was recorded as 65 consecutive 1-millisecond recordings at stimulus onset. For prepulse trials, a prepulse of 6 or 12 dB over background (72 or 77 dB) of 20 millisecond duration preceded the primary pulse by 100 milliseconds. Acoustic startle reactivity in millivolts was calculated from the average startle magnitude for the initial six pulse alone (120 dB) trials. The PPI—the percent inhibition of the acoustic startle amplitude when preceded by a prepulse—was calculated for each prepulse intensity (6 or 12 dB) as $100 \times \frac{\text{pulse alone amplitude}}{\text{prepulse with pulse amplitude}}$ where scores were averaged across a pseudorandom admixture of trials as in previously published methodology.²² As in our previous work with rTg(P301L)4510 mice we found that in that model PPI diminishes over time out to 5.5 months as pathology accrued,²² we measured PPI in P301L/COMT-; P301L/COMT++; COMT-; and WT mice at 3, 6, and extended to 10 months to test the hypothesis that P301L/COMT- mice would exhibit a relative impairment of PPI over time. To test the hypothesis that antipsychotic treatment would augment PPI in mice with locomotive and sensorimotor gating abnormalities, for pimavanserin treatment studies P301L/COMT- and rTg(P301L)4510 mice were evaluated with baseline PPI sessions 2 weeks prior to treatment, then outcome PPI 70 minutes after injection.

2.4 | Pimavanserin injections

Pimavanserin tartrate was synthesized by ACADIA Pharmaceuticals. P301L/COMT- and rTg(P301L)4510 mice were randomized to pimavanserin or saline treatment and injected with either pimavanserin at a dose of 3 mg/kg³⁶ dissolved in saline and delivered intraperitoneally (IP) at a volume of 100 ul or saline vehicle at a volume of 100 ul. Behavioral raters were blinded to treatment condition. Sixty minutes after injections, mice were assessed first with Open Field (10 minutes) followed by PPI sessions (30 minutes), followed by sacrifice and preparation for tau assays.

2.5 | Euthanasia/sample preparation/phosphorylated tau quantification

P301L/COMT- and rTg(P301L)4510 mice in the pimavanserin treatment study were euthanized approximately 90 minutes after injection via isoflurane overdose and blood was collected for serum quantification of pimavanserin. Serum was frozen at -80°C. The brain was removed in all mice and hemisected sagittally. The forebrain was dissected and the cortex, striatum, and hippocampus were separated and prepared for quantitative tau biochemistry as published previously.³⁷

Briefly, after dissection, the brain was homogenized using an appropriate volume of homogenizing buffer comprising a solution of Tris-buffered saline, pH 7.4 containing: 10 mM NaF; 1 mM NaVO₃; and 2 mM EGTA, with a complete Mini protease inhibitor cocktail (Roche Molecular Biochemicals, catalogue #11836153001). The prepared samples were stored at -80°C. Heat-stable preparations were used to obtain soluble tau levels by first adding 5% β mercaptoethanol and 200 mM NaCl to brain homogenate. Samples were then heated at 100°C for 10 minutes, cooled at 4°C for 15 minutes on ice, and then centrifuged at 1300 g at 4°C for 15 minutes followed by supernatant collection. Total tau was measured with DA31,³⁸ phosphorylation at Ser202 was measured with CP13,³⁹ and tau phosphorylated at Thr231 was measured with RZ3.⁴⁰ For the enzyme-linked immunosorbent assays (ELISAs), 96-well plates were coated with either DA31, CP13, or RZ3 at a concentration of 6 hg/ml in coating buffer, for at least 48 hours at 4°C. Plates were washed 3 × in wash buffer, and blocked for 1 hour at 20°C using Starting Block to prevent non-specific binding. Each plate was then washed 5 × and 50 ul of sample was added to the wells of the plate, with 50 ul of DA9 detection antibody. Plates were then incubated overnight at 4°C and washed 9 × in wash buffer. 1-Step Ultra TMB-ELISA was added for 30 minutes at 20°C before stopping the reaction with 2 MH₂SO₄. Plates were read with an infinite m200 plate reader at 450 nm.

2.6 | Statistics

Difference in locomotion among the four groups of mice (P301L/COMT-, P301L/COMT++, COMT-, and WT) at 3 months of age was assessed using ordinary one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test for pairwise comparisons. Longitudinal PPI was assessed using mixed model repeated measures ANOVA (MMRA) as previously used in the characterization of sensorimotor gating in Tg4510 mice²² to explore main effects and interactions among mouse type (P301L/COMT-, P301L/COMT++, COMT-, and WT), age (3, 6 and 10 months of age), and PPI (6 and 12 dB above background). The outcome variable was the PPI of acoustic startle. The analytic strategy was to investigate mouse type effects on PPI and pairwise comparisons between genotypes of mice. Statistical significance was built in to model with an alpha risk of 0.05. Effects of pimavanserin treatment on cross-sectional PPI, open field, and tau phosphorylation was assessed with unpaired *t* test with an alpha risk of 0.05. Statistical analyses were carried out using SAS 9.4. Software (SAS Institute) and GraphPad Prism version 9.1.2 for Windows (GraphPad Software).

3 | RESULTS

3.1 | Locomotion in the P301L/COMT- mouse

Locomotion was assessed in the dopamine-driven P301L/COMT- tau mouse relative to littermate P301L/COMT++, COMT-, and WT mice

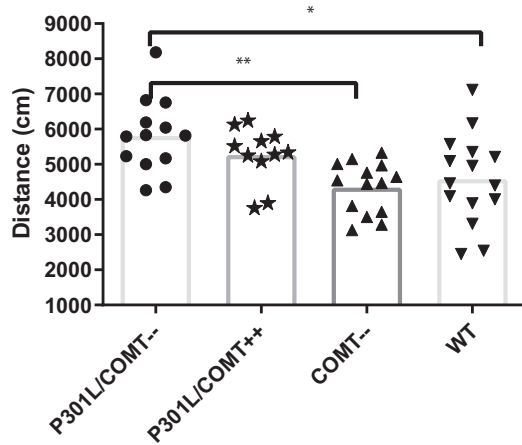


FIGURE 1 Distance traveled (cm) in open field over 10 minutes: 3-month-old female P301L/COMT⁻ ($N = 13$), P301L^{+/+} ($N = 11$), COMT⁻ ($N = 14$), and wild-type (WT; $N = 15$) mice. Analysis of variance $F(3,49) = 5.913$, $P = .002$, followed by Tukey's multiple comparisons test, * $P < .05$, ** $P < .01$

to evaluate whether the admixture of dopamine and tau would result in hyperkinesia. Locomotion, the distance traveled by each mouse over a 10-minute interval, was quantified in cohorts of 3-month-old female P301L/COMTKO ($N = 13$), P301L/COMT^{+/+} ($N = 11$), COMT⁻ ($N = 14$), and WT ($N = 15$) mice from colonies bred on the same background over many generations²⁴ with open field using EthoVision XT14 Automatic Mouse Behavioral Recognition. Young mice were used to study the central impact of tau on kinetics as the tau transgene in the P301L/COMT⁻ and P301L/COMT^{+/+} is also expressed in the hindbrain, and as pathology progresses in older mice it eventually affects the spinal cord, gradually leading to hindleg weakness and inhibiting locomotion.³³ Across all groups, there were differences in mean distance traveled between genotypes (ANOVA, $F[3,49] = 5.913$, $P = .002$; Figure 1). After controlling for multiple comparisons, the P301L/COMT⁻ had increased locomotion relative to both COMT⁻ and WT mice (Figure 1). There were no significant differences in direct comparisons among P301L/COMT^{+/+}, COMT⁻, and WT mice (Figure 1). The data suggest that while excess extracellular dopamine alone in the COMT⁻ model does not enhance locomotion relative to COMT-competent mice, the admixture of tau and dopamine in P301L/COMT⁻ drives a hyperkinetic phenotype in young mice.

3.2 | PPI in the P301L/COMT⁻ mouse

Sensorimotor gating integrity was assessed longitudinally in cohorts of female mice as our previous work in the rTg(P301L)4510 has shown that tau mice aged to 5.5 months develop relative deficits of PPI of acoustic startle over time as pathology accrues.²² PPI was measured in P301L/COMT⁻, P301L/COMT^{+/+} ($N = 11$), COMT⁻ ($N = 15$), and WT ($N = 15$) mice all on the C57BL/6*DBA/2 background starting at 3 months of age, then at 6 months, and finally out to 10 months, to evaluate whether the P301L/COMT⁻ mouse evidences relative impairments

of PPI. Two prepulse intensities, 6 and 12 dB above background (72 or 77 dB, respectively), were used as these were shown in our previous work with P301L-expressing mice to have robust impacts on acoustic startle and to diminish over time with the development of tau pathology.²² In a MMRA, there were significant effects of genotype on PPI. Controlling for covariates, over the course of the three time points the P301L/COMT⁻ mouse evidenced significantly impaired PPI relative to COMT-competent WT and COMT⁻ mice (Figure 2A), and approached significance of deficit compared to P301L mice ($P = .08$, Supplemental Table 3). Differences between P301L/COMT⁻ mice and comparators peaked at 6 months diminishing over time to the 10-month time point (Figure 2B). Consistent with these data, longitudinal studies of C57BL/6 mice suggest that PPI of acoustic startle increases over time and then diminishes in these mice with aging,⁴¹ peaking at 6 to 7 months and then declining.⁴² The P301L/COMT^{+/+} mouse did not evidence significantly impaired PPI relative to WT, suggesting tau pathology alone in the model is not sufficient to drive relative deficits (Figure 2A, 2B). This is in distinction to the rTg(P301L)4510 mice in which the P301L transgene drove relative deficits of PPI at 5.5 months of age, perhaps a reflection of the increased expression of P301L tau pathology driven by the CaMKII promoter in the forebrain.²² Surprisingly (as the COMT⁻ was developed as an animal model of dopamine-driven psychosis,⁴³ and exogenous dopamine has been shown to be PPI-disruptive, specifically via D2 receptor stimulation),⁴⁴ in the current report, COMT⁻ mice evidenced significantly elevated PPI compared to each of P301L/COMT⁻, P301L/COMT^{+/+}, and WT mice, peaking at 6 months and then declining (Figure 2A, and Supplemental) to the 10-month time point (Figure 2B). The diminished PPI integrity of the P301L/COMT⁻ model containing both a COMT deletion and a tau transgene suggests that while in isolation excess dopamine in the frontal cortex in the COMT⁻²⁴ is PPI enhancing, the combination of tau and dopamine are PPI-disrupting, an effect beyond the contribution of either dopamine or tau in isolation.

3.3 | Tau phosphorylation in the P301L/COMT⁻ and P301L/COMT^{+/+} mice

To determine whether the locomotive and sensorimotor gating abnormalities found in the P301L/COMT⁻ model relative to comparators might be related to differences in phosphorylation states of tau, we investigated tau phosphorylation with high-sensitivity assays in female P301L/COMT⁻ ($N = 12$) and P301L/COMT^{+/+} ($N = 12$) mice utilizing CP13 and RZ3 monoclonal phosphotau antibodies (Figure 3). In these young mice, to detect increased phosphorylation associated with very early neuritic neuropathology, phosphorylation at Ser202 was measured with CP13;³⁹ to quantify tau phosphorylation associated with a more mature pre-neurofibrillary tangle pathology, phosphorylation at Thr231 was measured with RZ3.⁴⁰ In 3-month-old mice, tau phosphorylation was increased in P301L/COMT⁻ mice relative to P301L/COMT^{+/+} mice in the frontal cortex as quantified with both antibodies (Figure 3A, 3B, RZ3, $P = .005$; CP13, $P = .04$); in the hippocampus with only RZ3 (Figures 3C, 3D, RZ3, $P = .03$); and in the

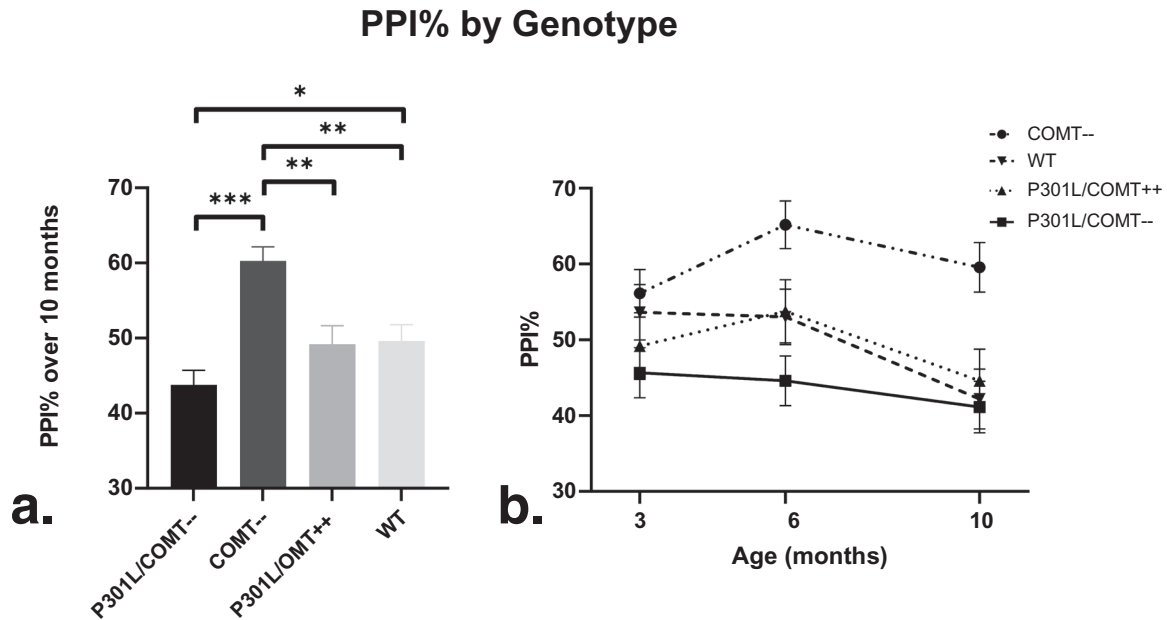


FIGURE 2 Mean prepulse inhibition (PPI%) of acoustic startle (6 dB and 12 dB prepulse above 65 dB background) was measured in P301L/COMT- ($N = 15$), P301L/COMT++ ($N = 11$), COMT- ($N = 15$), and wild-type (WT; $N = 15$) mice at 3 months of age, 6 months, and 10 months. In a mixed model repeated measures analysis of variance over the three time points, there were significant effects of genotype on mean PPI%. A, Least square mean estimates of PPI% of acoustic startle shown for each genotype with 6 and 12 dB intensities combined, with standard error of the mean (SEM). B, Least square estimates of PPI% at each time point for each genotype with SEM. Pairwise comparisons shown, * $P < .05$, ** $P < .01$, *** $P < .001$

striatum with both antibodies (Figures 3E-3F, RZ3, $P = .007$; CP13, $P = .03$). In general, RZ3 phosphotau quantification distinguished the P301L/COMT- from the P301L/COMT++ more robustly than CP13, an observation that may be a consequence of the developmental stage of tau neuropathology in the mice of this age, or may reflect a unique pattern of tau phosphorylation at Thr231 that is associated with dopamine neurotransmission.²⁴

3.4 | The impact of pimavanserin on locomotion and PPI in the rTg(P301L)4510 and P301L/COMT- mouse

Cohorts of female rTg(P301L)4510 ($N = 40$) and P301L/COMT- mice ($N = 40$) at 4 months of age were each randomized to pimavanserin ($N = 20$) at 3 mg/kg IP or saline vehicle ($N = 20$). Two weeks after baseline assessment mice were treated and assessed in open field 60 minutes after injection, followed by PPI, to calculate the change with treatment on mean velocity and sensorimotor gating in each of the mice, and compare the difference in the change between pimavanserin- and saline-treated mice. In rTg(P301L)4510 mice, pimavanserin-treated mice covered less distance (cm) in open field after injection (Figure 4A), and had a 70.0% (+/-7.2) reduction in mean velocity, measured in cm/second over the 10 minute interval, from baseline compared to saline treated mice (Figure 4B). In P301L/COMT- mice, while pimavanserin treatment also reduced distance traveled in open field (Figure 4C), the reduction in mean velocity from baseline in pimavanserin-

treated mice was only 19.9% (+/- 6.2) compared to saline treated mice (Figure 4D). The more robust effect in the rTg(P301L)4510 mice may have been secondary to the increased serum levels achieved in that model relative to the P301L/COMT- model (Figure 5). There were no differences between pimavanserin and saline in mean change of PPI from baseline in either the rTg(P301L)4510 or P301L/COMT- mice, at either 72 (6 dB above background) or 77 (12 dB above background) dB prepulse intensity (Figure 6).

3.5 | The impact of pimavanserin on tau phosphorylation in the P301L/COMT- and rTg(P301L)4510 mouse

The cohorts of rTg(P301L)4510 and P301L/COMT- mice randomized to either pimavanserin or saline were sacrificed after PPI assessments to quantify the impact of treatment on tau phosphorylation in the frontal cortex, hippocampus, and striatum. In the P301L/COMT- mice, although tau phosphorylation as measured with CP13 was mildly increased with pimavanserin in the frontal cortex relative to vehicle, this difference did not achieve statistical significance, and treatment did not appreciably alter patterns in either the hippocampus or striatum (Supplemental Figure 1). In the rTg(P301L)4510 mice, with CP13 and RZ3 there were non-significant reductions in phosphorylation in the frontal cortex with pimavanserin treatment relative to vehicle, and no effect in the hippocampus. Treatment was associated with an increase in tau phosphorylation in the striatum that was not

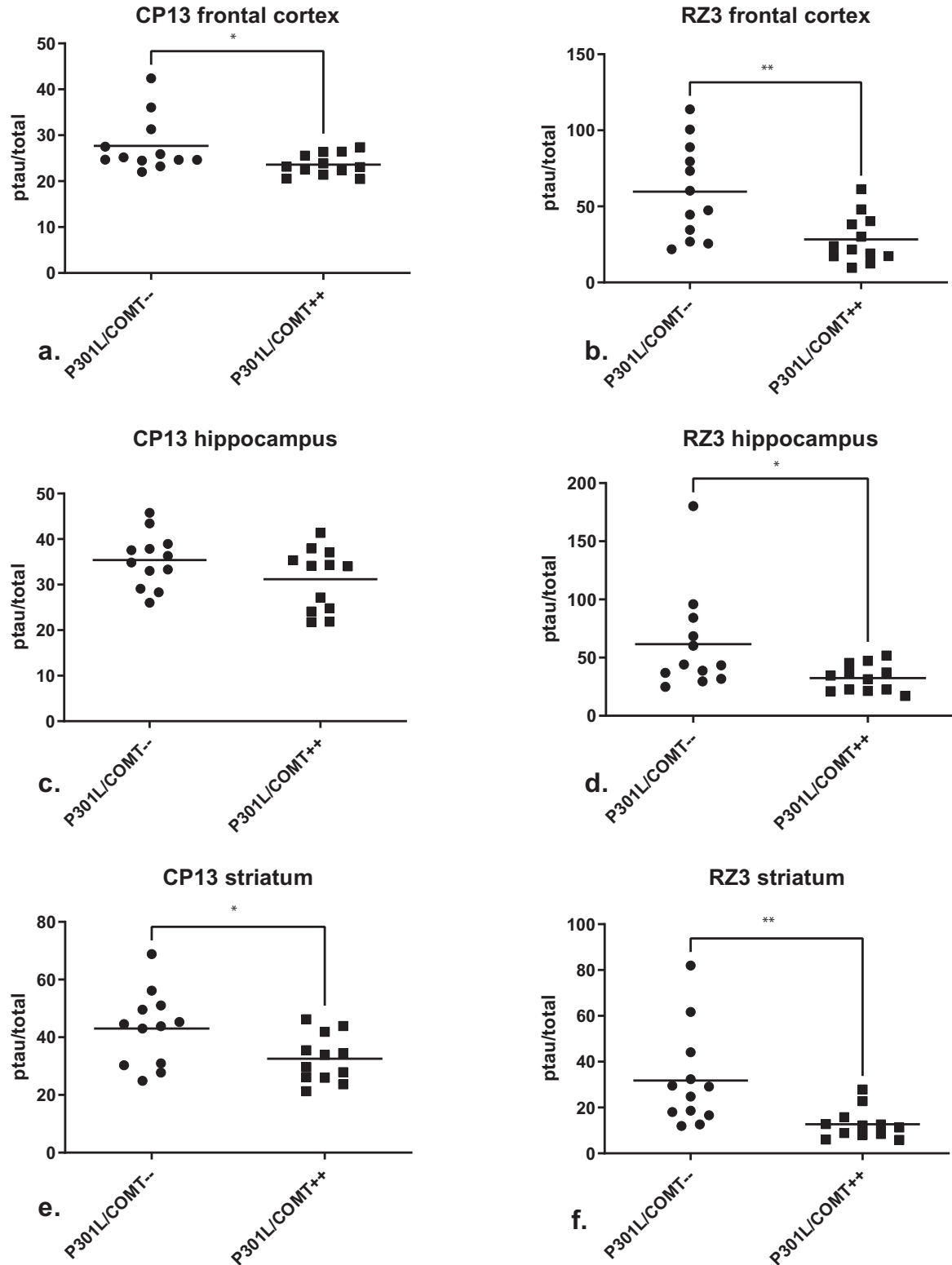


FIGURE 3 High sensitivity enzyme-linked immunosorbent assay was utilized to quantify tau phosphorylation in 3-month-old female P301L/COMT^{-/-} (N = 12) compared to female P301L/COMT^{+/+} (N = 12) mice utilizing CP13 and RZ3 monoclonal tau antibodies in the frontal cortex, hippocampus, and striatum (A–F). Fractions of phosphotau/total tau (as measured with DA31) shown, *P < .05, **P < .01

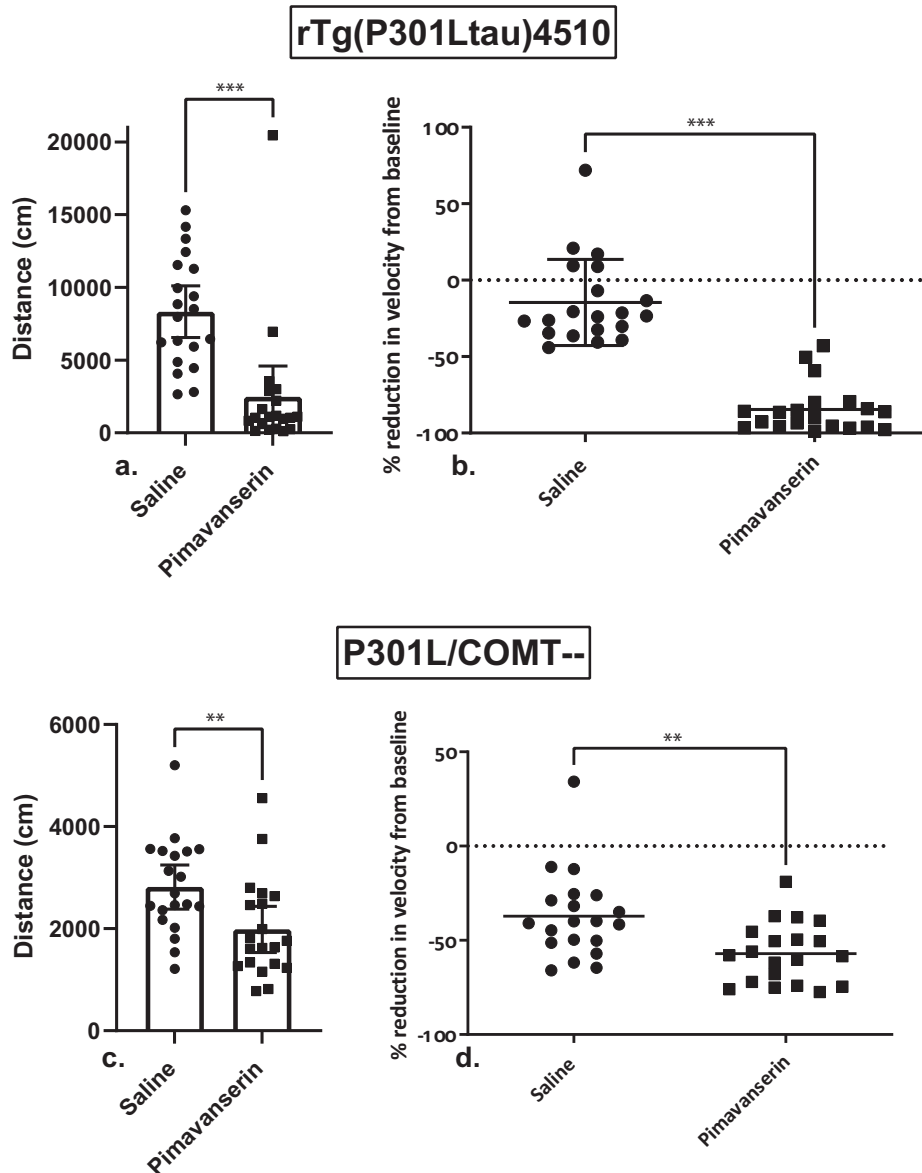


FIGURE 4 Pimavanserin or saline vehicle was administered to two tau mouse models at 4 months of age (A–B, rTg[P301L]4510, $N = 40$ and C–D, P301L/COMT $^{-/-}$, $N = 40$) after baseline assessment of velocity in each mouse with open field. Open field velocity was again assayed 60 minutes after injection, and distance traveled after injection (A and C) and % reduction from baseline in velocity (B and D) was calculated for each mouse and compared between treatment groups. ** $P < .01$, *** $P < .001$

significant, with differences that approached significance only with CP13 that did not survive correction for multiple comparisons (Supplemental Figure 2).

4 | DISCUSSION

Pimavanserin treatment of the P301L/COMT $^{-/-}$ and rTg(P301L)4510 models normalized locomotion in these hyperkinetic models but did not discernably impact sensorimotor gating in these experiments and had little impact on tau phosphorylation. Other preclinical studies of pimavanserin in lesion-based animal models of PD and AD have investigated its ability to impact these two psychosis-relevant behavioral phe-

notypes with positive results. In a 6-hydroxydopamine lesion model of PD in rats that induces substantia nigra pars compacta insufficiency to mimic the motor phenotype of PD, pimavanserin treated animals evidenced a mitigation of amphetamine-induced hyperkinesia and a normalization of lesion-induced sensorimotor gating deficits.¹⁷ Similarly, in a mouse model of AD comprising the intracerebroventricular infusion of the A β peptide, pimavanserin reversed amphetamine-induced hyperkinesia and rescued PPI deficits.¹⁸ The failure of pimavanserin to impact PPI in the current report in contradistinction to other models may reflect the hyperphosphorylated tau-driven PPI deficits of the P301L/COMT $^{-/-}$ and rTg(P301L)4510 models, and the lack of robust effect of pimavanserin on phosphorylation states of tau. The recent report of the significant impact of pimavanserin on A β in APP/PS1

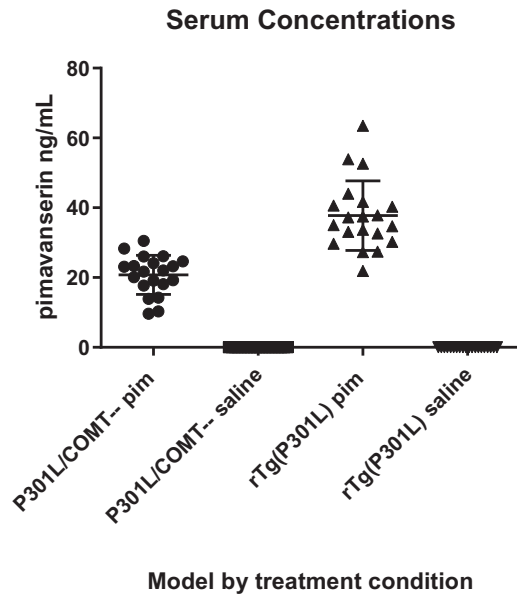


FIGURE 5 Serum quantification of pimavanserin in P301L/COMT⁻ ($N = 40$) and rTg(P301L)4510 ($N = 40$) mice treated with either pimavanserin or saline in treatment groups of $N = 20$ and assayed with open field and prepulse inhibition

mice may explain its ability to rescue PPI in amyloid models.³² By contrast, we have previously reported that the D₂-blocking typical antipsychotic haloperidol robustly and consistently reduces phosphorylation states of tau across brain regions.³⁷ In that study, Tg4510 mice treated with haloperidol had reductions in phosphorylation of tau quantified with CP13 and RZ3 in the frontal cortex and striatum compared to vehicle-treated controls, driven by inactivation of the tau kinase AMPK.³⁷ Further studies of haloperidol in tau models such as the P301L/COMT⁻ and rTg(P301L)4510 would be necessary to determine whether haloperidol treatment can rescue hyperphosphorylated tau-driven PPI deficits.

In the current report, female P301L/COMT⁻ mice exhibited a relative hyperactivity together with increased tau phosphorylation in the frontal cortex, hippocampus, and striatum relative to P301L/COMT^{+/+} mice. One construal of these findings is that it is the dopamine-driven increase in tau phosphorylation in the DM that may be responsible for this locomotive abnormality. The association of increased activity with phosphorylation states of tau has been previously suggested in a study in which the tau-driven hyperactivity of rTg(P301L)4510 mice was ameliorated by doxycycline administration (effectively inhibiting transgene expression), and found to be specifically associated with phosphorylated tau species.²³ Mice expressing the P301L mutation even in the absence of conditional forebrain expression have also been previously reported to have increased locomotion.^{45,46}

Longitudinal assessments of sensorimotor gating in the P301L/COMT⁻ model suggest a relative impairment of PPI of acoustic startle responsiveness, a difference that appears to diminish compared to aging WT mice that themselves manifested a declining PPI of acoustic startle that is known to occur after 6 months,⁴² perhaps secondary to hearing impairment or changes in dopamine D₂ receptor

expression with age.^{41,47} The impairment observed is significant as the loss of PPI integrity has been associated with a variety of chronic human psychotic conditions in addition to those induced by dopaminergic drugs of abuse.^{48–50} Sensorimotor gating deficits have been most extensively documented in schizophrenic psychosis.⁵¹ The COMT-model was developed as a candidate model of the 22q11 microdeletion syndrome associated with schizophrenic psychosis.^{43,52} In the current report, relative to each of the three other genotypes (P301L/COMT⁻, P301L/COMT^{+/+}, WT) bred on the same C57BL/6*DBA/2 background, COMT deficiency was associated with significantly increased rather than decreased PPI integrity as might be expected from a pre-clinical psychosis model of excess dopamine. This suggests that while in conditions of large non-focal surges in dopamine, for example, after cocaine administration, PPI is consistently diminished,⁵⁰ small tonic augmentation of dopamine in the frontal cortex in the COMT-deleted mice may enhance sensorimotor gating as in the current report. Alternatively, it may be that PPI disruption associated with increased dopamine signaling is an effect observed only when increases occur in regions of densely expressed D₂ receptors such as the striatum.⁵³ Interestingly, the increased dopamine in the COMT-deficient mice²⁴ that augments PPI integrity in the absence of tau, in the context of P301L tau expression has an inhibitory effect, as the P301L/COMT⁻ evidenced significantly impaired PPI relative to WT mice, a diminution that also approached significance relative to P301L mice (MMRA, $t = -1.73$, $Pr > [t] = 0.08$, supplemental). This suggests that dopamine-driven tau hyperphosphorylation observed in the P301L/COMT⁻ may drive deficits of PPI in the model, as was reported previously in the rTg(P301L)4510.²²

In P301L/COMT⁻ and rTg(P301L)4510 mice, the magnitude of the impact of pimavanserin on reduction in locomotion diverged, perhaps secondary to the higher serum levels achieved in the rTg(P301L)4510 mice (Supplemental), or perhaps secondary to the relative hyperkinesis of the untreated rTg(P301L)4510 mice (Figure 4). As the pharmacodynamic activity of pimavanserin has been well established,^{8,11} the impact on locomotion is presumed to be a consequence of 5-HT₂ blockade. Serotonergic neurons in the brainstem provide descending inputs to the spinal cord that facilitate the initiation of locomotion, an effect that is believed to be mediated in part by 5-HT_{2A} receptors.⁵⁴ In addition, tau pathology may contribute to disinhibition of cortical pyramidal cells (especially in the forebrain expressed rTg(P301L)4510, further facilitating hyperactivity through increased descending glutamatergic stimulation of striatal output, another pathway that is modulated by 5-HT_{2A} receptors.⁵⁴ In this pathway pimavanserin-induced locomotive attenuation may be a consequence of descending serotonergic blockade suppressing hyperexcited pyramidal cell activity in the cortex.

In treatment studies, pimavanserin does not have the deleterious effects on motor function the D₂-blocking antipsychotics do.^{55,56} Interestingly, results of a meta-analysis of genetic studies of behavioral symptoms of AD has found that those with psychosis or aberrant motor behavior (AMB) of AD—a morbid late-stage syndrome affecting those with later stage disease in which people rummage, pace, and attempt to wander making supervision difficult and creating safety concerns—have a reduction in risk from a polymorphism in the 5-HT_{2A}

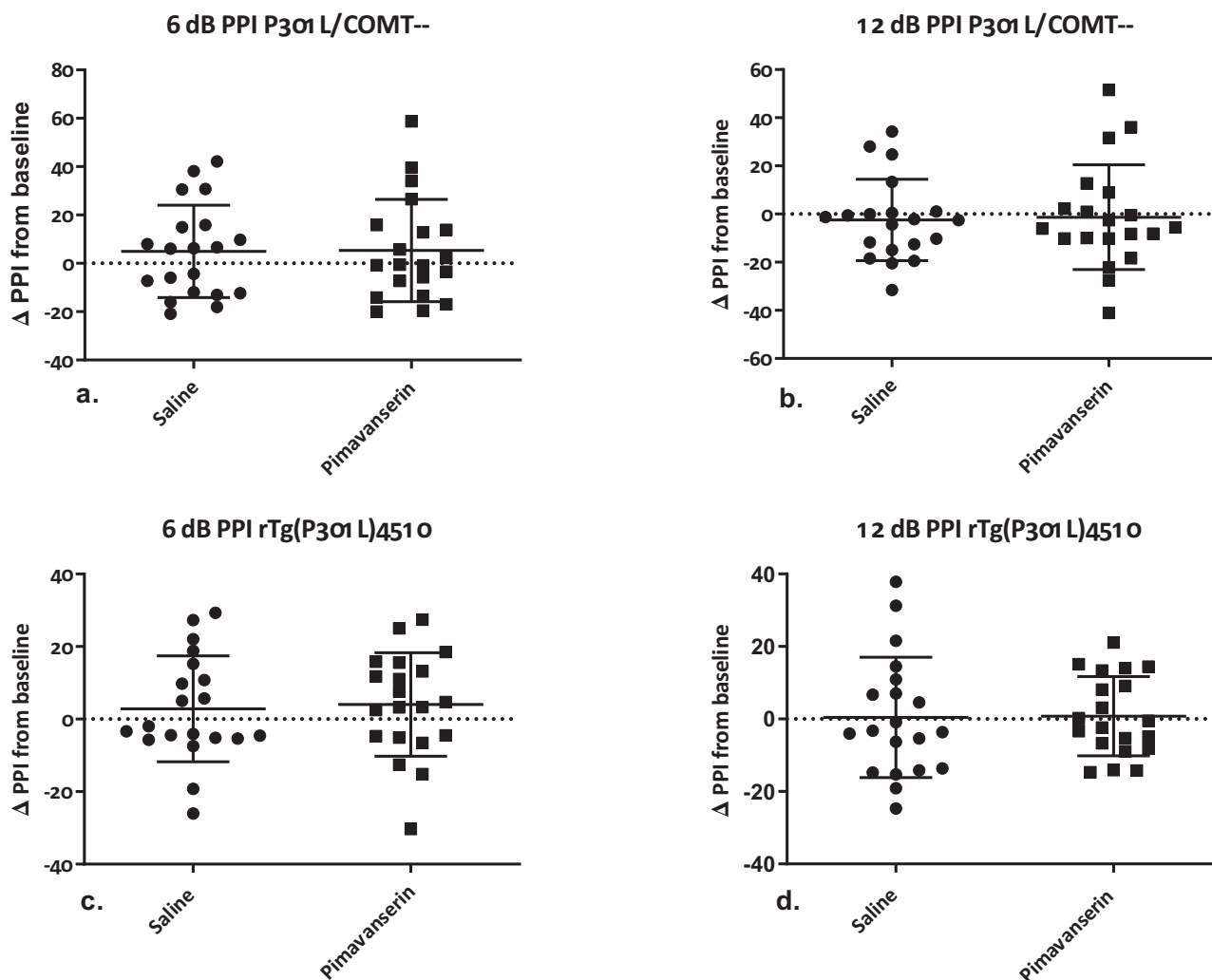


FIGURE 6 Pimavanserin or saline vehicle was administered to P301L/COMT- ($N = 40$, A and B) and rTg(P301L)4510 ($N = 40$, C and D) 2 weeks after baseline assessment of prepulse inhibition (PPI) of acoustic startle at 6 and 12 dB over background prepulse. PPI was again assayed 60 minutes after injection, and % reduction in PPI was calculated for each mouse and compared among treatment groups

gene (T102C; TT genotype AMB, odds ratio [OR] = 0.58 [95% confidence interval (CI) = 0.35–0.95], psychosis, OR = 0.34 [95% CI = 0.17–0.67]).⁵⁷ It is possible that those with AMB may benefit from modulation of this receptor from pimavanserin in a similar fashion to what has been reported with psychosis, while avoiding the akathisia that the D_2 -blocking antipsychotics induce, which could worsen AMB.¹³

Animal modeling of psychiatric symptomatology faces the ineluctable obstacle that experiential states in non-humans are by definition beyond all potential human experience and so are beyond the reach of science. Nonetheless, development of candidate molecules in the preclinical pipeline has been aided by neurobehavioral paradigms that capture surrogate phenotypic or relevant endophenotypic aberrancies in organisms that share neurobiological homology with humans. In the development of antipsychotic medications, effects on locomotor activity and sensorimotor gating have been standard approaches to screening candidate molecules and validating candidate

preclinical models of psychotic disease.¹⁴ In critiquing this approach, it has been cautioned that these impairments are non-specific in their association with human disease and so must be interpreted with caution when drawing conclusions about the candidacy of any model or treatment solely based on these outcomes.⁵⁸ However, the behavioral catalogue of mice is limited, and while more specific analogues of human behavior with relevance to psychiatric illness would be very useful in preclinical testing and are desperately needed, locomotion and sensorimotor gating remain mainstays.

In summary, PPI was not altered by acute pimavanserin treatment in either the P301L/COMT- or rTg(P301L)4510 mouse models of psychotic AD, but the hyperkinetic phenotype was rescued by pimavanserin treatment in both models. Given the lack of available treatments for AMB, the effect of pimavanserin on locomotion in these models together with evidence of an association with the 5-HT_{2A} gene support future clinical studies targeting AMB with pimavanserin.

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CONFLICTS OF INTEREST

Ethan S. Burstein is an employee of ACADIA Pharmaceuticals and has received stock options. Jesus Gomar has received funding from the Alzheimer's Association. All other authors have nothing to disclose.

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