

Systemic Trace Amine-Associated Receptor 1 (TAAR1) Activation Reduced Mania-Relevant Hyperexploration and Risky Decision-Making in Dopamine Transporter Knockdown Mice

Benjamin Z. Roberts¹, Tarannum Y. Munir¹, & Jared W. Young^{1,2}

1. Dept. Psychiatry, University of California San Diego, 9500 Gilman Dr., La Jolla, California, 92093, U.S.A.
2. Research Service, VA San Diego Healthcare System, San Diego, CA, USA

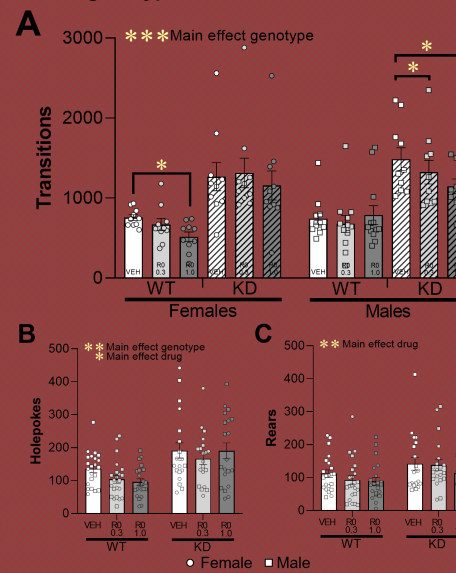


jaredyoung@ucsd.edu
bzroberts@ucsd.edu

BACKGROUND

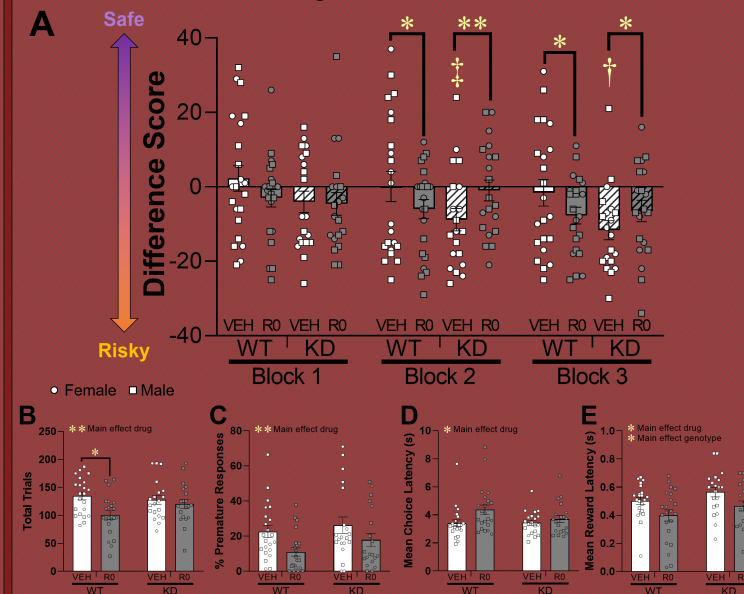
- Elevated risky decision-making is a cardinal feature of bipolar disorder (BD) that is observed across manic, depressed, and euthymic states¹.
- Laboratory measures of risk preference are associated with suicidal behaviors² and future drug use³ in this population, yet no pharmacotherapies exist that target this deficit.
- The **lowa Gambling Task (IGT)** is a cross-species translatable test of risk preference that consistently identifies decision-making deficits (increased risk preference) in people with BD¹, which we have reproduced in **dopamine transporter knockdown (DAT KD) mice**⁴⁻⁶.
- DAT KD mice** reproduce BD-related DAT hypoexpression^{7,8} (*construct validity*), as well as a BD-consistent behavioral profile in the cross-species **Behavioral Pattern Monitor (BPM)**⁹ (*face validity*) that is sensitive to mood stabilizers¹⁰ (*predictive validity*).
- The trace amine-associated receptor 1 (**TAAR1**) reduces presynaptic dopamine release¹¹ and attenuates behaviors induced by acute¹² and chronic¹³ hyperdopaminergia.
- We administered a **TAAR1 agonist (R05256390)** to male and female DAT KD (n=20) and wildtype (WT; n=23) mice before BPM (VEH, 0.3, & 1 mg/kg, i.p., within-subjects) and IGT (VEH & 1 mg/kg i.p., within-subjects) testing to assess the therapeutic potential of TAAR1 activation for treatment of BD-related behavioral deficits.

Fig. 3. TAAR1 activation reduced exploration across genotypes.



DAT KD mice demonstrated elevated locomotion (A) and specific exploration (B) [$F_{(1,38)} > 12.0, p < .01$]. Both 0.3 and 1 mg/kg R05256390 reduced locomotion in DAT KD males, while 1 mg/kg reduced locomotion in WT females [interactions: $F_{(2,76)} > 3.1, p < .05$; post hoc: $p < .05$] (A). 0.3 mg/kg R05256390 reduced specific exploration across genotypes (B), while 1 mg/kg reduced diverse exploration [$F_{(2,76)} > 3.8, p < .05$] (C). TAAR1 activation did not affect path trajectories. * $p < .05$, ** $p < .01$, *** $p < .001$. Data presented as mean \pm S.E.M.

Fig. 4. TAAR1 activation remediated DAT KD IGT risky decision making, worsened WT decision making.



(A) DAT KD mice demonstrated elevated risky decision making [blocks 2 ($p = .060$) & 3 ($p < .05$), block \times genotype \times drug interaction: $F_{(2,76)} = 3.1, p < .05$]. TAAR1 activation attenuated this deficit (i.e., increased safe decision making; $p < .05$), but drove risky decision making in WTs ($p < .05$). TAAR1 activation reduced trial completion in WT mice [interaction: $F_{(1,38)} = 5.0, p < .05$; post hoc: $p < .001$] (B), and reduced motoric impulsivity [$F_{(1,38)} = 10.0, p < .01$] (C), increased decision-making time [$F_{(1,38)} = 5.3, p < .05$] (D), and sped reward collection overall [$F_{(1,38)} = 7.0, p < .05$] (E). †, ‡ $p < .05$ and $p < .10$ vs corresponding WT groups, respectively, * $p < .05$, ** $p < .01$, *** $p < .001$. Data presented as mean \pm S.E.M.

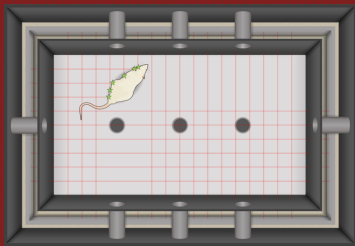
Fig. 1. The Behavioral Pattern Monitor (BPM). An enclosed arena with two arrays of photobeams that quantify animals' movement (transitions across the nine regions of the field) and rearing. Eleven apertures distributed across the walls and floor of the chamber quantify exploratory holepoking (specific exploration).

Fig. 2. The Iowa Gambling Task (IGT). The IGT operates on similar contingencies across species. Human and rodent participants are presented with 4 stimuli of variably risky and safe reward/punishment contingencies. Task contingencies differ only in terms of the nature of stimuli, rewards, and punishments. The IGT is conducted in a single session across species. Primary outcome variable:

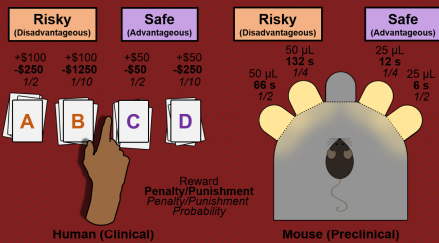
Difference Score:
(# safe choices - # risky choices)

CONCLUSIONS

- As previously reported¹⁴, the DAT KD mouse model of mania demonstrated an array of BD-consistent behaviors in the BPM (hyperlocomotion, hyperexploration, straight-line path trajectories) and IGT (reduced difference score).
- Acute pharmacological TAAR1 activation attenuated the hyperlocomotion and hyperexploratory profile of DAT KD males and general activity of WT females.
- TAAR1 activation attenuated risky decision making in DAT KD mice, but increased risky decision making in WT mice.
- Differential effects of TAAR1 activation on risky decision making across genotypes may reflect differences in baseline dopamine tone.
- There may exist an inverted U-shaped relationship between dopamine tone and risk-based decision making (as observed with attention and working memory)¹⁵.
- Reducing presynaptic dopamine release via TAAR1 activation may have shifted the hyperdopaminergic DAT KD mice into an optimal range of this putative dopamine-decision making curve, while shifting WT mice outside of this range.



Roberts et al., 2021, Cogn Affect Behav Neurosci.



REFERENCES

1) Adida et al., 2016, *Biol Psychiatry*; 2) Richard-Devantoy et al., 2016, *J Affect Disord*; 3) Nejtek et al., 2013, *Psychiatry Res*; 4) Young et al., 2011, *J Psychopharmacol*; 5) van Erkuhuizen et al., 2014, *Psychopharmacology (Berl)*; 6) Milavne-Petiot et al., 2017, *Psychopharmacology (Berl)*; 7) Anand et al., 2011, *Bipolar Disord*; 8) Yatham et al., 2022, *JAMA Psychiatry*; 9) Young et al., 2007, *Neurosci Biobehav Rev*; 10) van Erkuhuizen et al., 2017, *J Neuropsychopharmacol*; 11) Leo et al., 2014, *Neuropharmacology*; 12) Revel et al., 2013, *Mol Psychiatry*; 13) Revel et al., 2011, *Proc Natl Acad Sci USA*; 14) Nowakowski et al., 2016, *Pharmacol Biochem Behav*; 15) Zeeb et al., 2009, *Neuropsychopharmacology*.

FUNDING: R01 DA051295