

Chronic corticosterone impairs effortful motivation and risky decision-making in mice



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Major depressive disorder (MDD)

- MDD is the second-most common psychiatric diagnosis in the United States¹
- MDD is significantly disabling resulting in high cost of care²
- Despite well-established behavioral deficits in people with MDD, individual heterogeneity and unclear pathology have hindered development of targeted treatments
- SSRIs, despite being front line treatments, show low efficacy for treating amotivated states and have undesirable side effects^{3,4,5}
- However, few alternatives exist in treating MDD

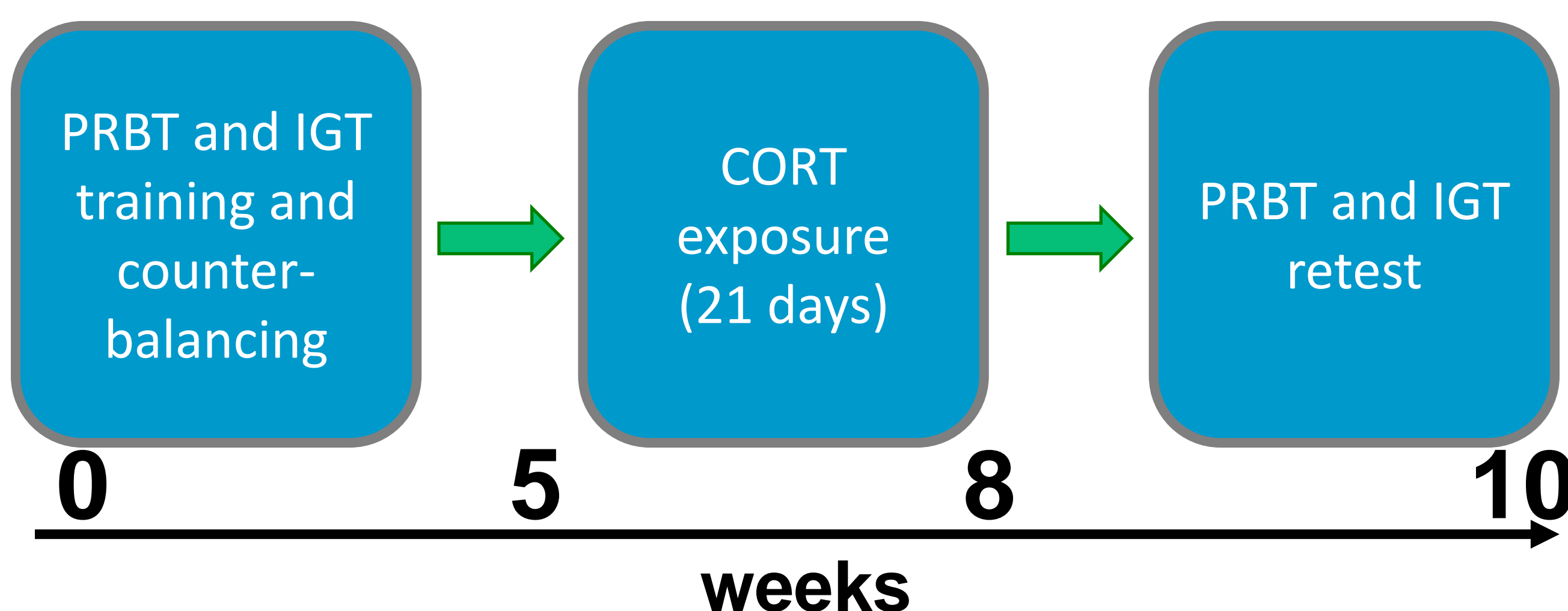
Modeling MDD

- Traditional models and tests in preclinical studies of MDD have issues of validity⁶
- Environmental stress manipulations evoke strong effects, but inconsistency in implementation can produce reliability issues
- Translation of preclinical results is hindered by lack of cross-species assessments:
 - The progressive ratio breakpoint task (PRBT) and Iowa gambling task (IGT) assess motivation and risk-taking respectively and are testable in humans and animals
- Models built around depression-relevant manipulations with cross-species translational behaviors in mind have a higher chance of successful validation and thus treatment development

Corticosterone and MDD

- Corticosterone (CORT) is a stress hormone elevated in MDD⁷
- Chronic stress increases CORT in mice and can evoke depression-like behavior⁸
- Chronic administration of CORT can recreate MDD-like behaviors
- CORT in drinking water decreased operant responding for food and increased immobility in tail suspension⁹
- CORT in drinking water also decreased breakpoint and impaired reversal learning, associated with impaired reward processing¹⁰

Experimental timeline



- C57BL/6J mice (n = 30, 50% female) were trained to stability in PRBT and IGT and counterbalanced to CORT treatment or regular drinking water based on performance
- Half were given CORT (35 ug/mL) in drinking water for 21 days
- Mice were then re-tested in PRBT and IGT
- Mice were assessed for motor behavior changes in behavioral pattern monitor (BPM; not shown)

Figure 1: Progressive ratio breakpoint task (PRBT)

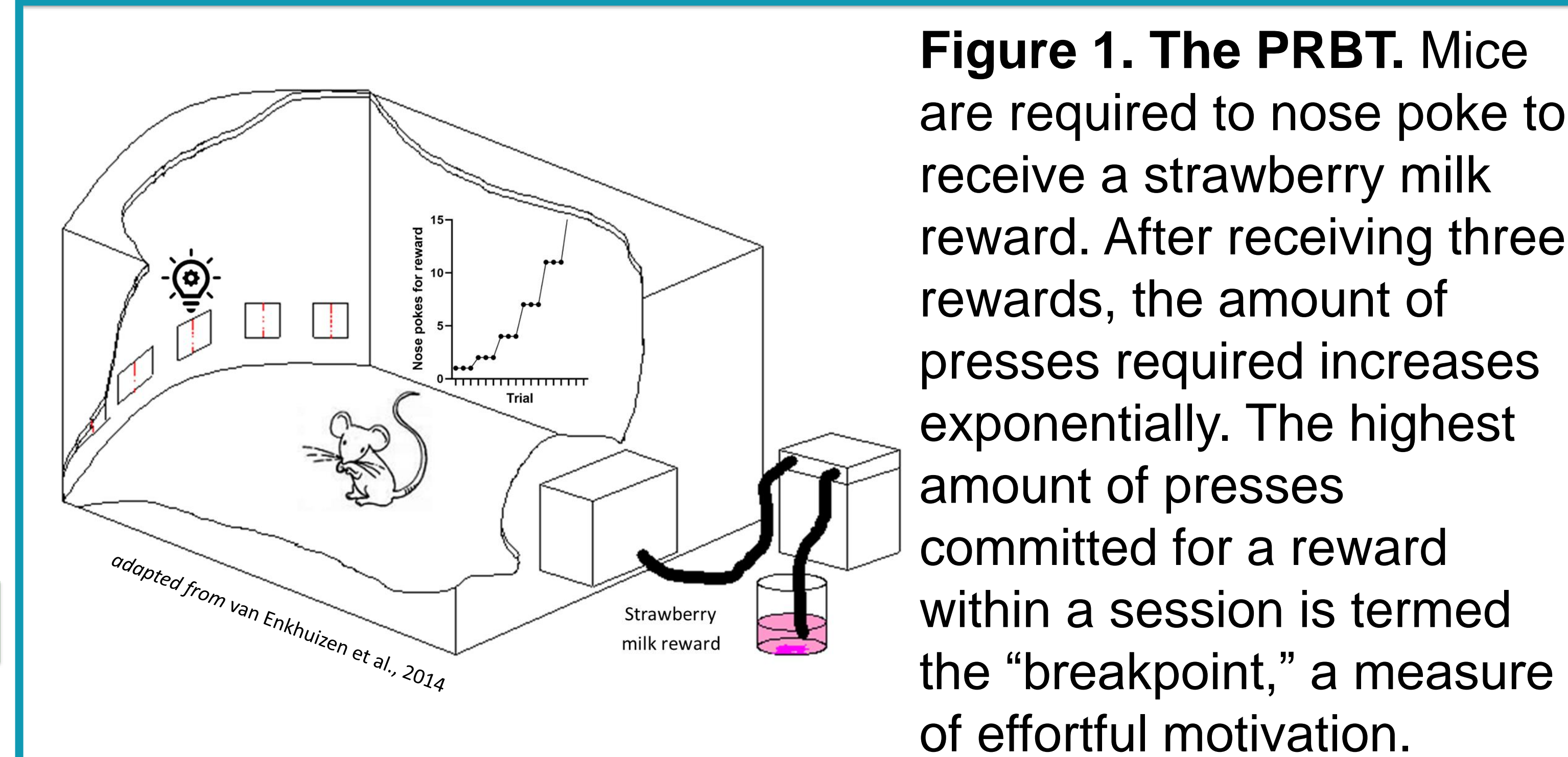


Figure 2: Chronic CORT decreased effortful motivation

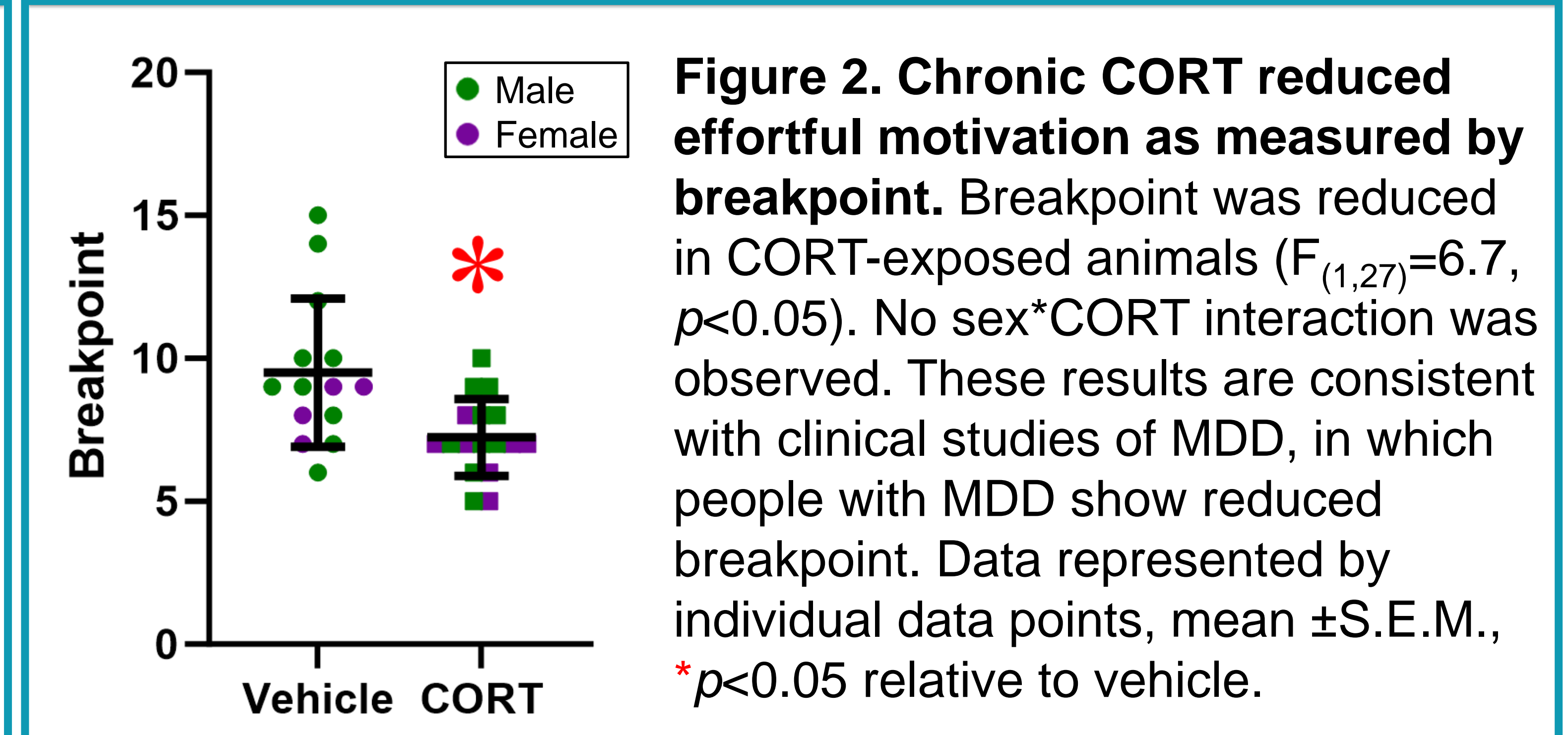


Figure 3: Iowa gambling task (IGT) testing in mice

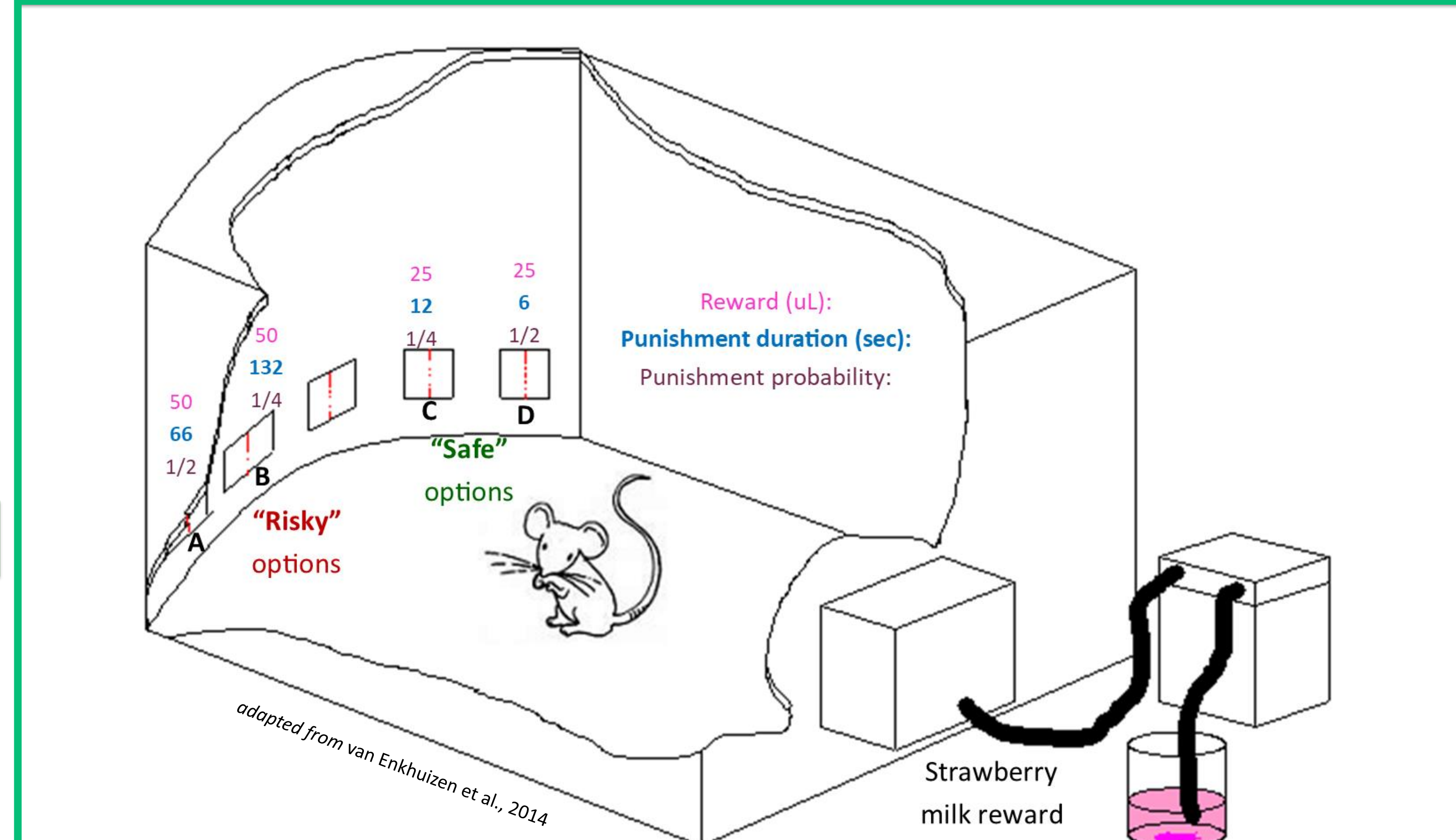
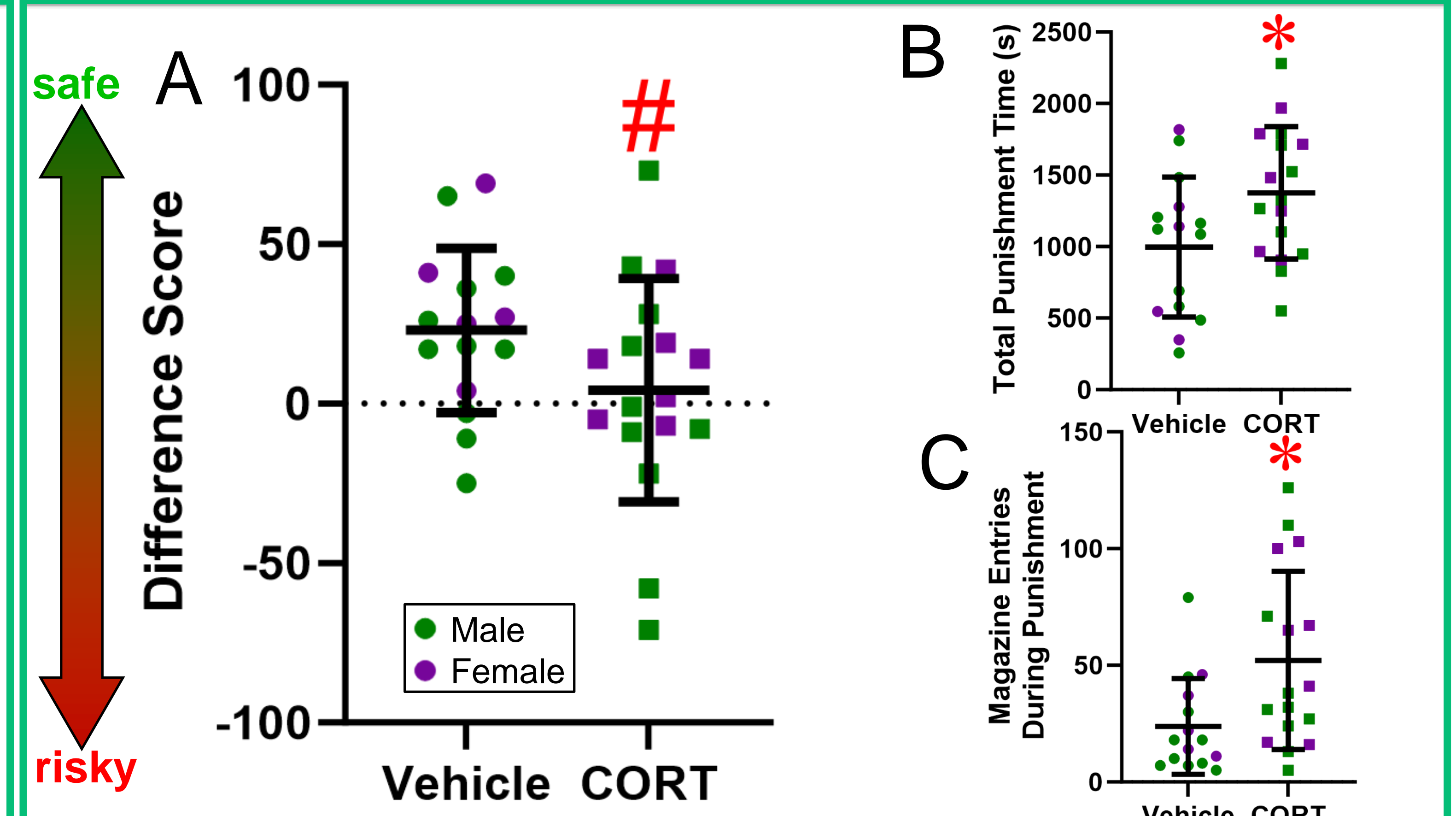


Figure 4: Chronic CORT increased risk-taking in the IGT



Conclusions

- Chronic CORT resulted in a depression-like behavioral profile in mice similar to what is observed both clinically and in other validated preclinical models of MDD
- CORT decreased effortful motivation as measured by PRBT (Fig. 2A) and impaired risky decision-making as measured by IGT (Fig. 4A)
- Overall motor activity was not affected by CORT (data not shown), indicating a lack of sedative or other effects of CORT

References

1. Karrouri et al., 2021. 2. Kessler et al., 2005. 3. McLauchlan et al., 2022. 4. Padala et al., 2020. 5. Santarsieri et al., 2015. 6. Commons et al., 2017. 7. Zobel et al., 2001. 8. Iniguez et al., 2014. 9. Gourley et al., 2008. 10. Dieterich et al., 2019. 11. van Enkhuizen et al., 2014

Future directions

- This model can be used to assess efficacy of drugs with potential antidepressant effects
- The connection between elevated CORT and deficits in effortful motivation and risky decision-making can be leveraged to study diseases other than MDD characterized by these features
- This work represents a step towards closing the translational gap between preclinical models of psychiatric disorders and clinical applications

Acknowledgments

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- We declare no conflicts of interest