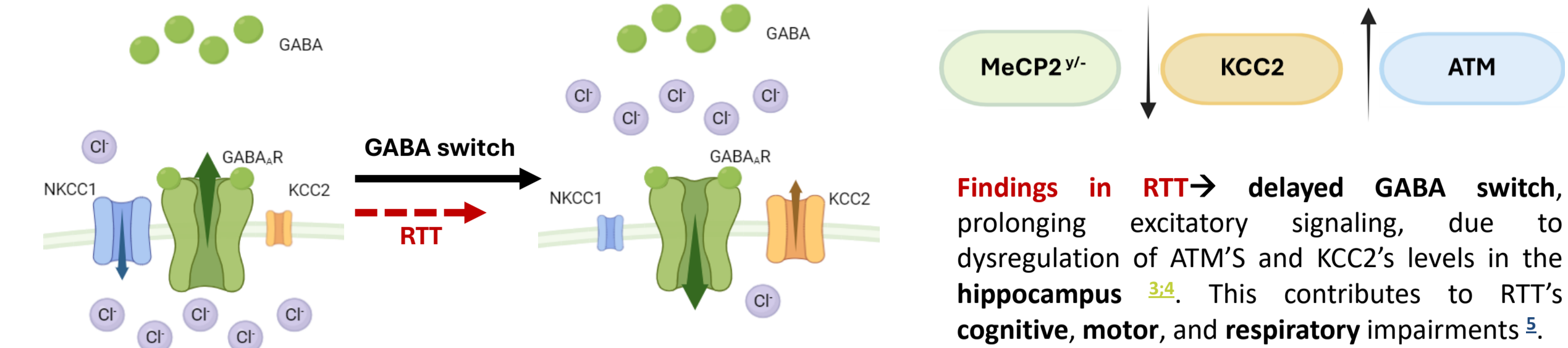


# THE THERAPEUTIC POTENTIAL OF ATM INHIBITION IN RETT SYNDROME: INSIGHTS FROM BEHAVIORAL AND MOLECULAR STUDIES

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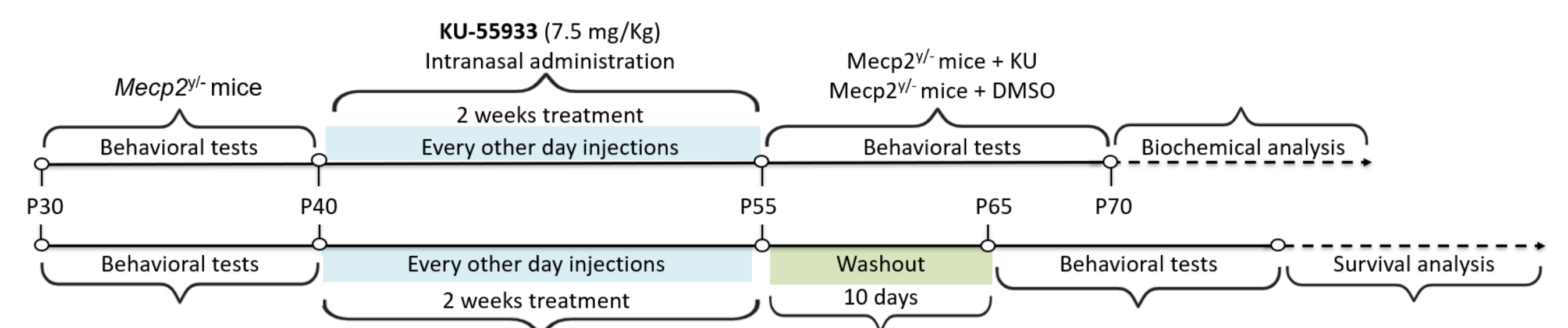
## Background

**What is ATM?** → Ataxia Telangiectasia Mutated is involved in the DNA damage response. However, it also regulates KCC2 expression<sup>1,2</sup>, controlling the excitatory and inhibitory (E/I) balance.  
**What is KCC2?** → a potassium chloride co-transporter, main determinant of the "excitatory-to-inhibitory GABA switch".  
**What is the "GABA Switch"?** → process by which GABA shifts from being an excitatory to an inhibitory neurotransmitter, fundamental step allowing GABA's trophic role throughout brain development.



## Objective and Experimental strategy

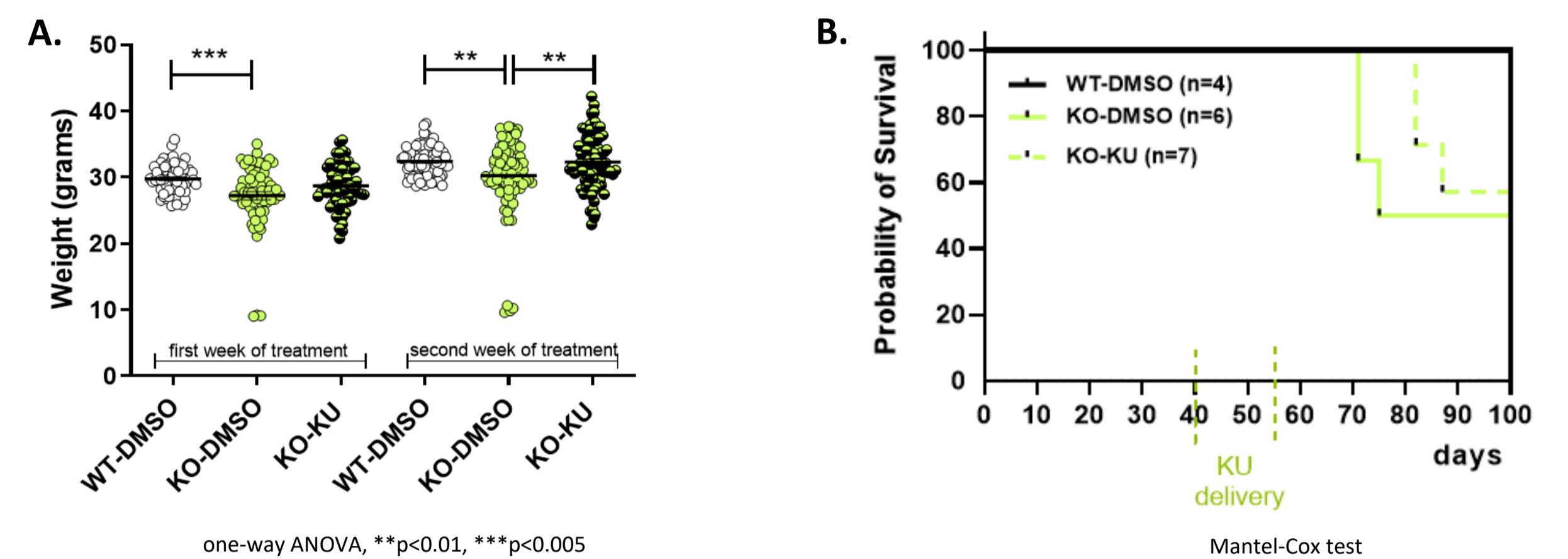
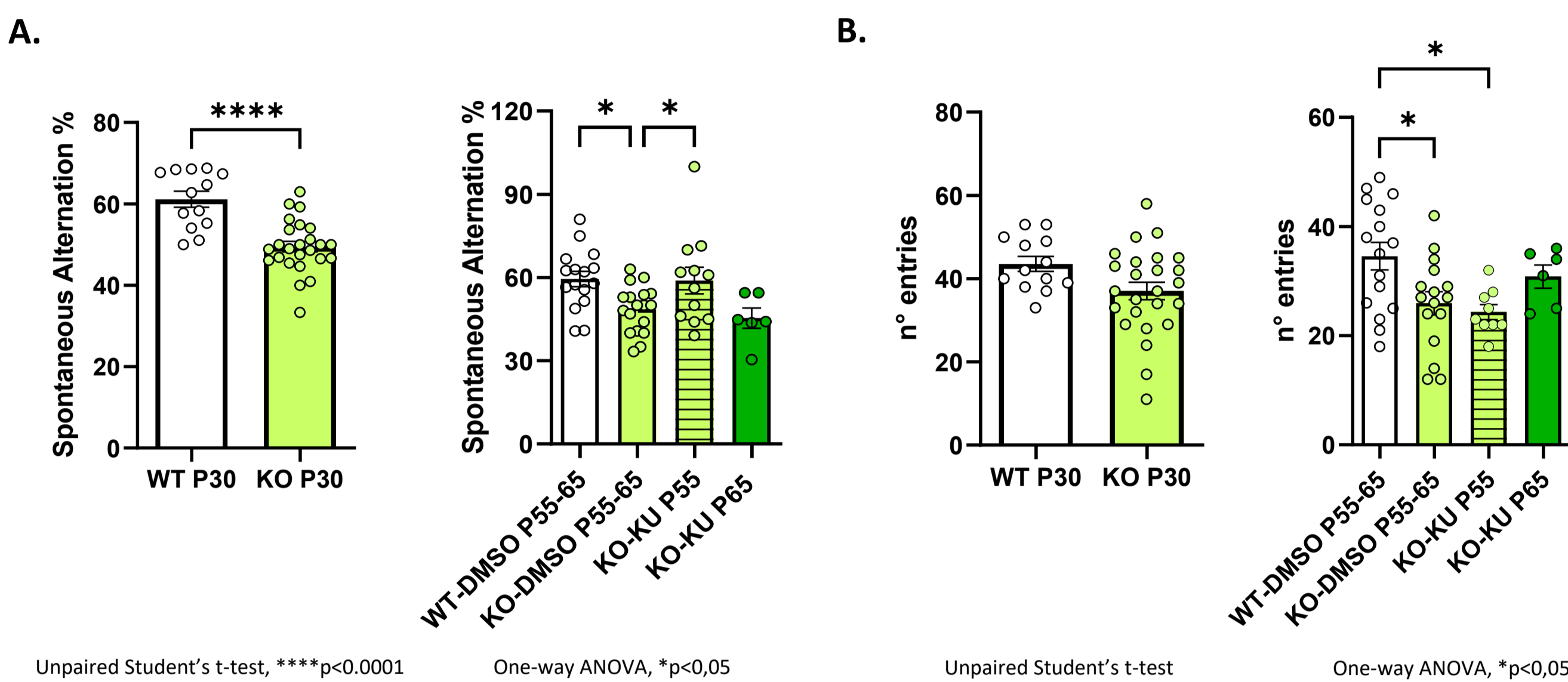
**Hypothesis** → ATM inhibition through KU-55933 as novel therapeutic approach, correcting GABAergic dysfunction, thereby improving the clinical phenotype in *Mecp2*<sup>0/0</sup> mouse model of RTT.  
**Preliminary findings** → In vitro experiments have been promising<sup>6</sup>, restoring KCC2 function.



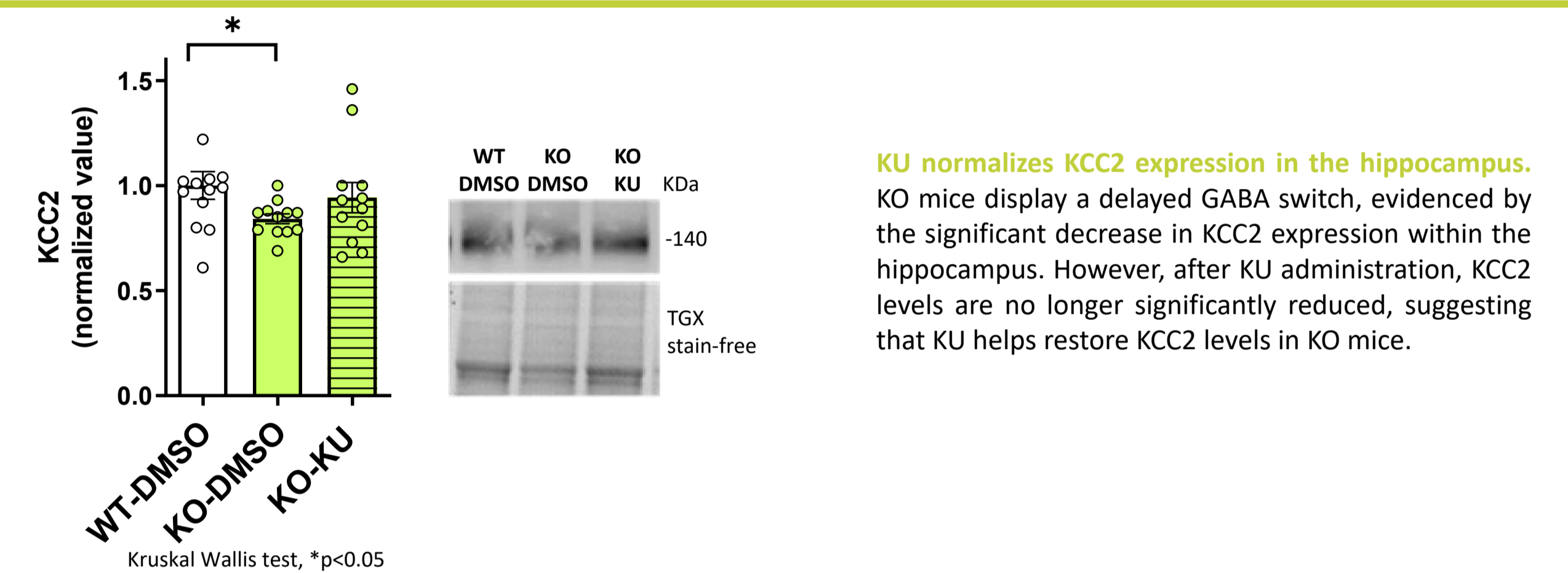
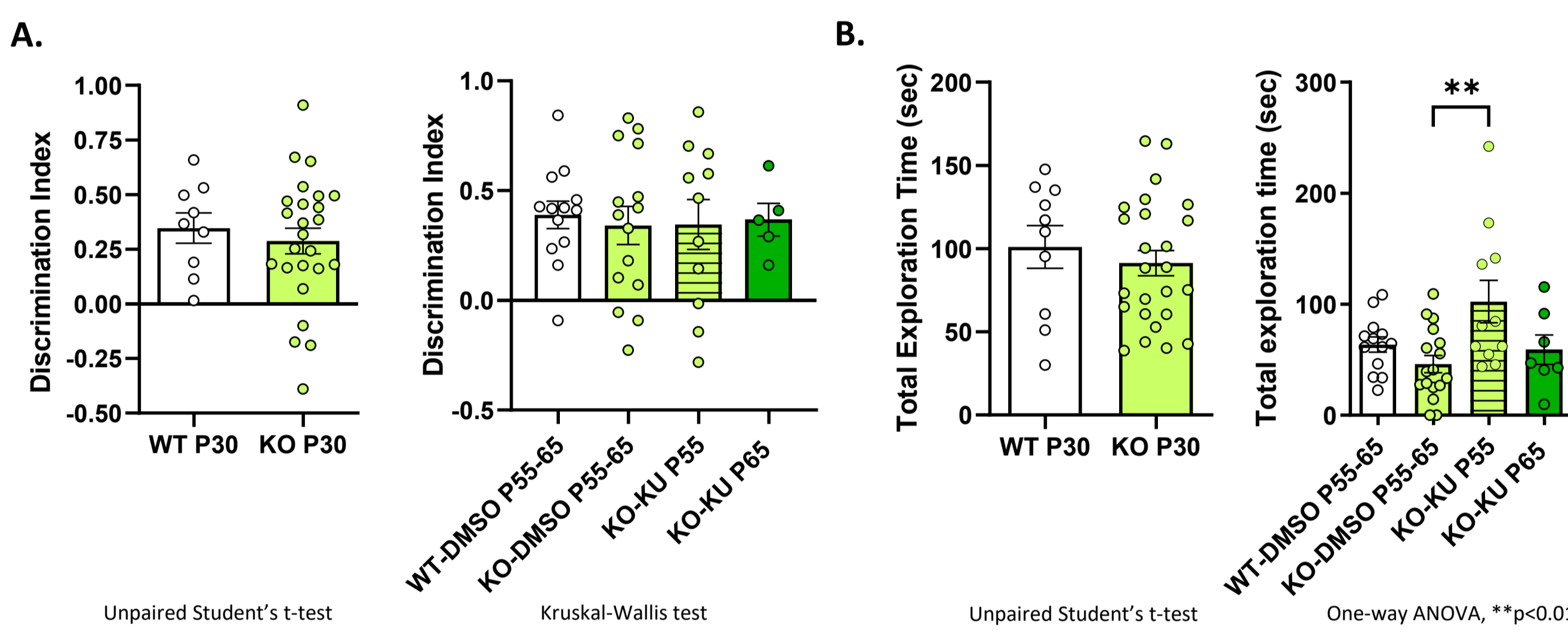
**Aim 1** → effects of KU's intranasal administration on cognitive performance, motor skills, respiratory function.  
**Aim 2** → molecular changes associated, focusing on KCC2 levels and the E/I balance.  
**Aim 3** → long-lasting efficacy of KU and consequences on the general health of the mice.

## Results

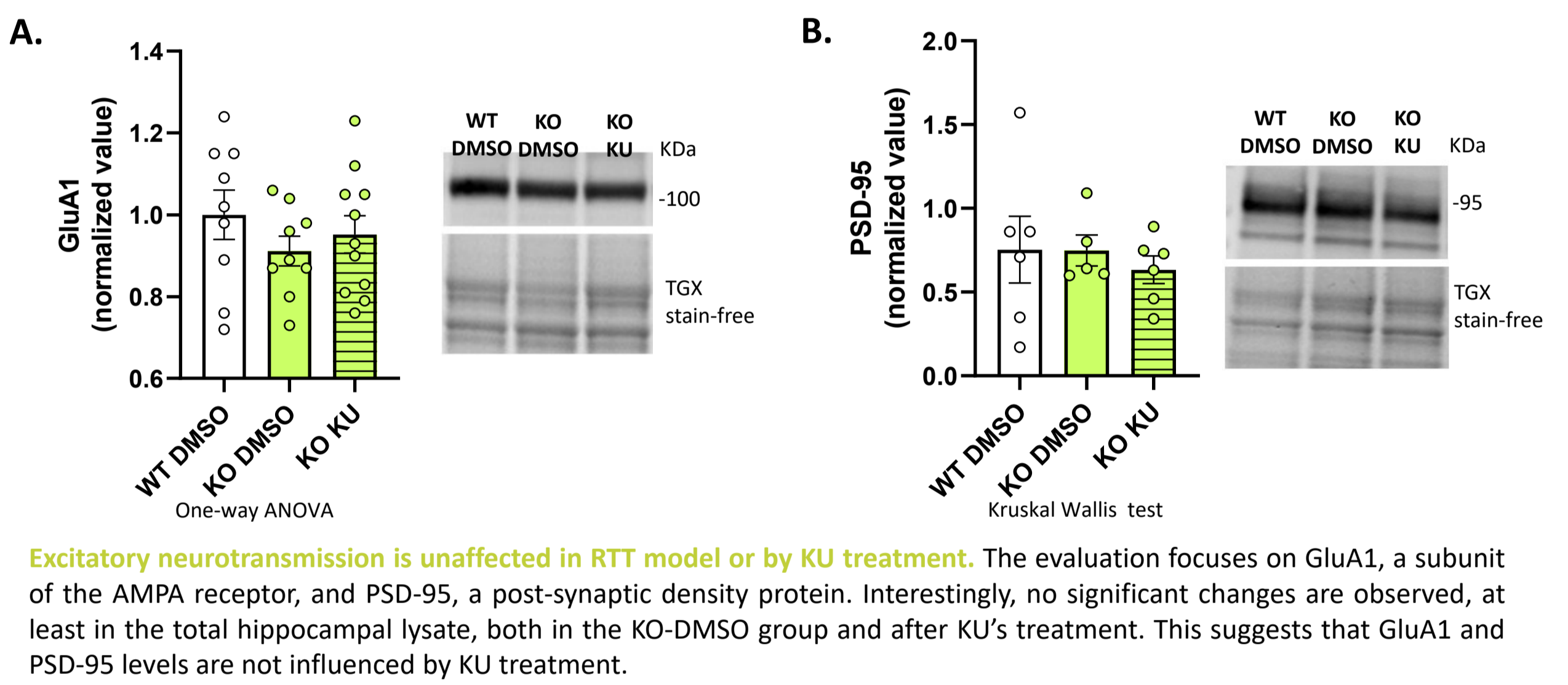
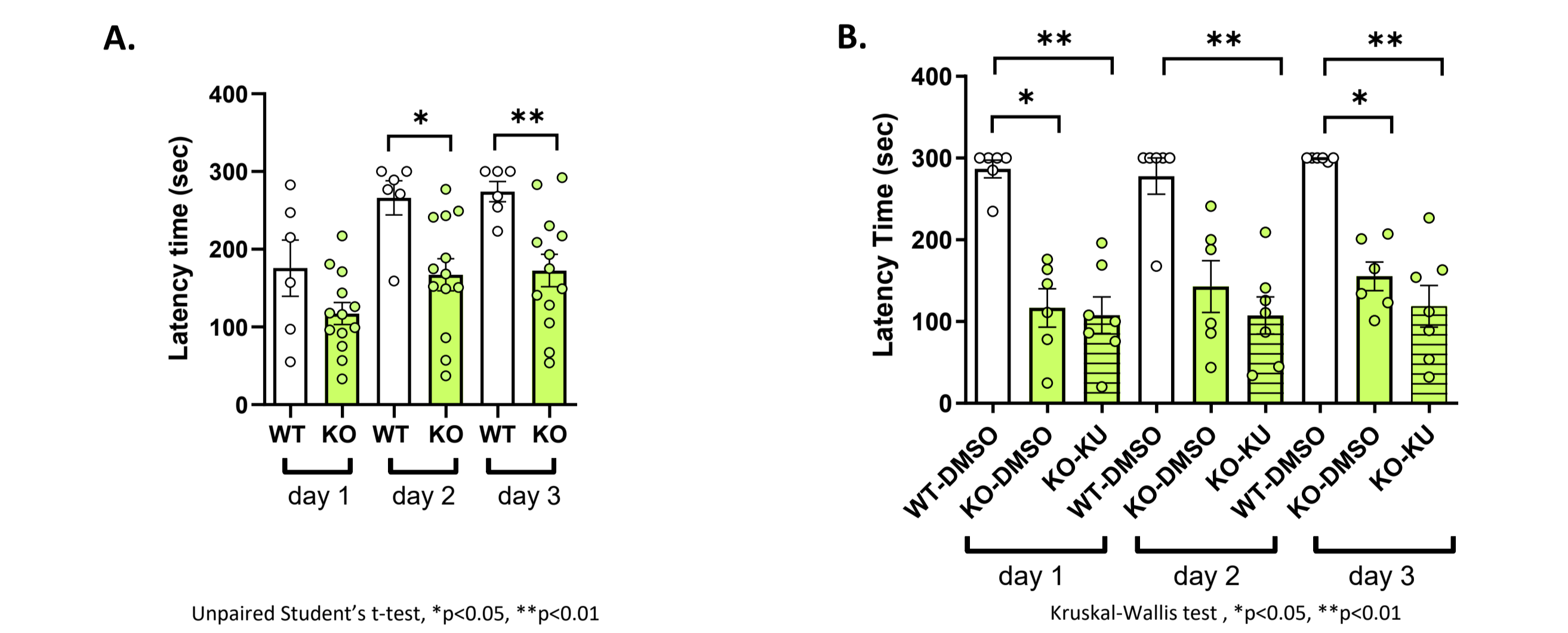
### Y-maze



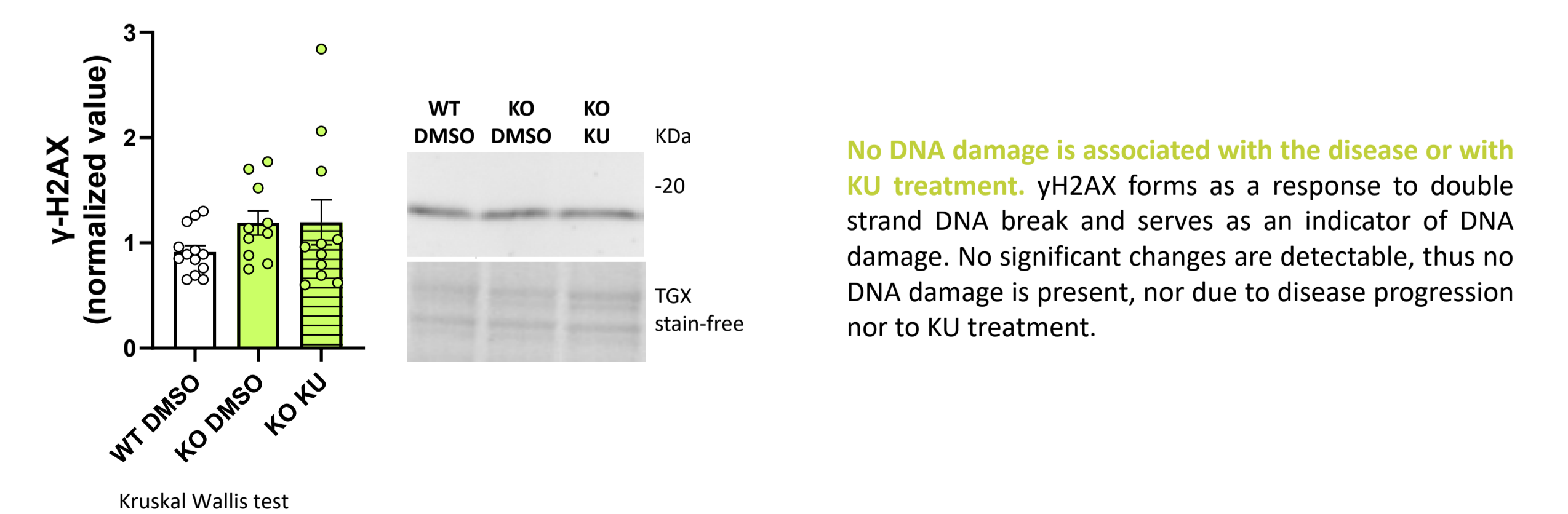
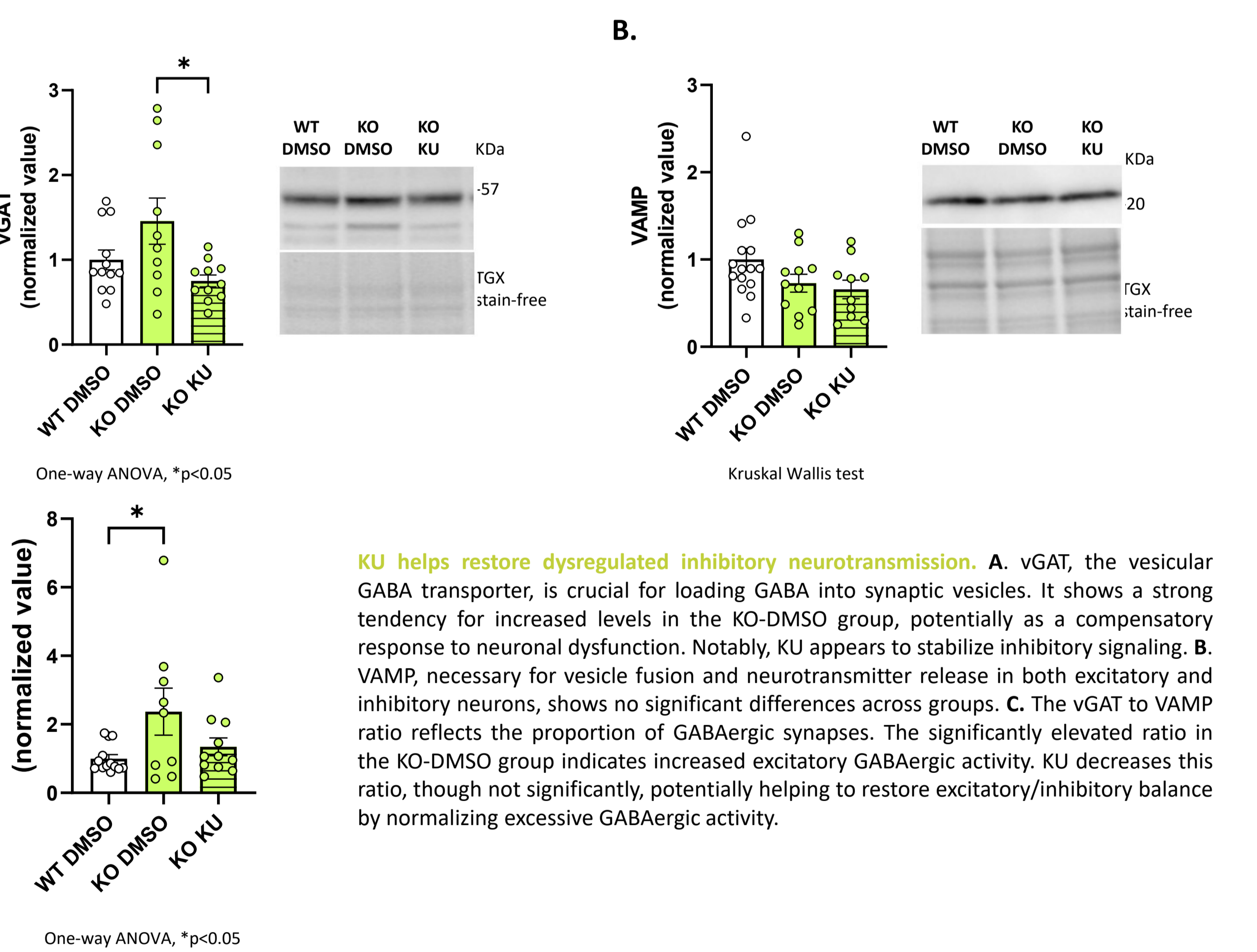
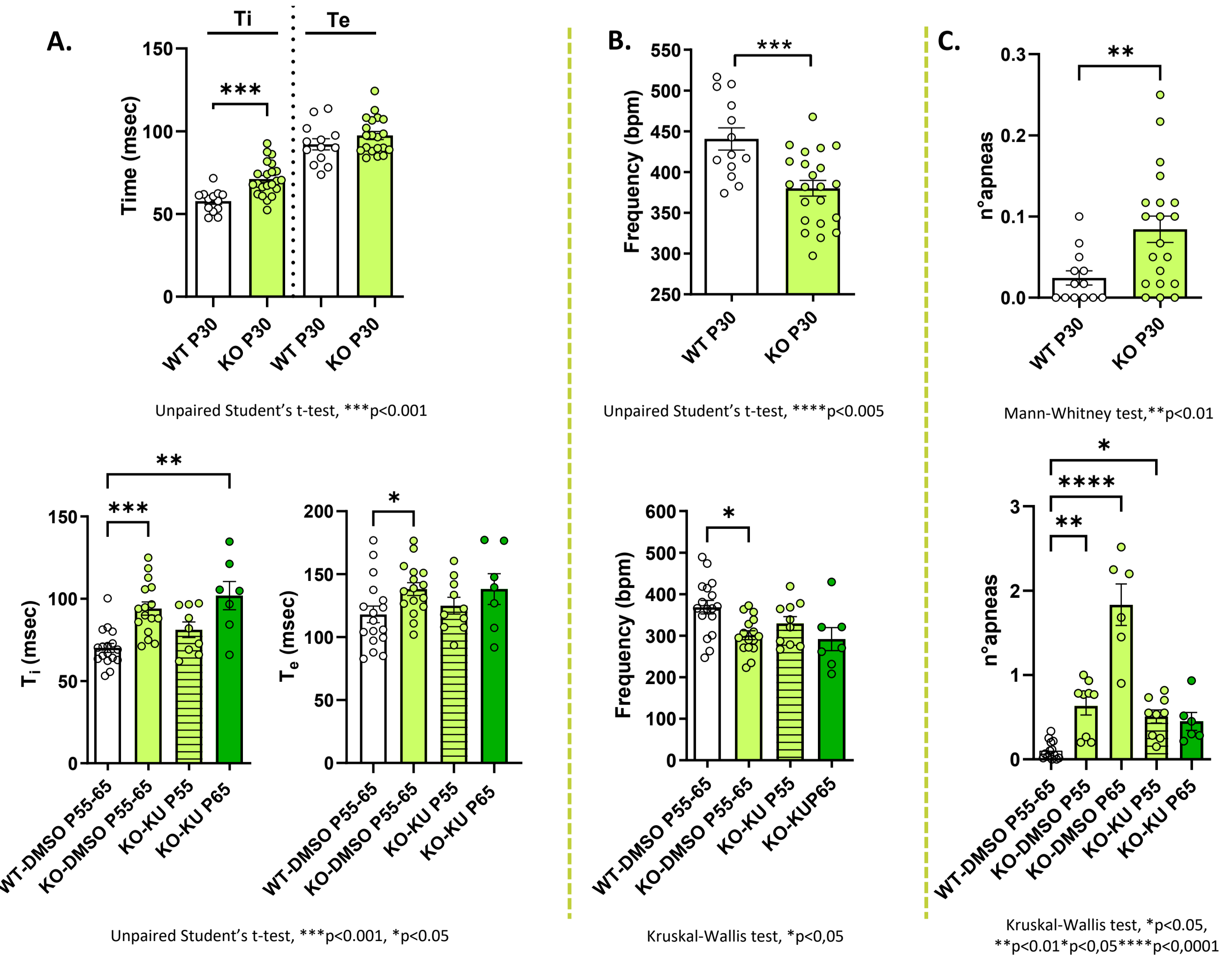
### NOR



### Rotarod



### Plethysmography



## Conclusion and future perspectives

These data show that KU effectively ameliorates some RTT symptoms, particularly the cognitive and respiratory one, addressing both symptomatic aspects and some underlying molecular abnormalities. However, the effects are not long-lasting, requiring administration every other day for a sustained benefits, except for the worsening of the apneas frequency, which is prevented by KU. Further biochemical analysis will investigate KU's effects on various brain regions, including the cortex, cerebellum, and brainstem, crucial for understanding different behavioral phenotypes. Additionally, Triton insoluble fractions (TIF) enriched in post-synaptic proteins will be examined to clarify the role of excitatory neurotransmission in RTT pathology.

## References

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