

Deuterium content of water and glucose tolerance: potential role for the prevalence of affective disturbances



3rd International Congress  
on Deuterium Depletion  
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UNIVERSITÉ DE STRASBOURG



Inserm  
U1119

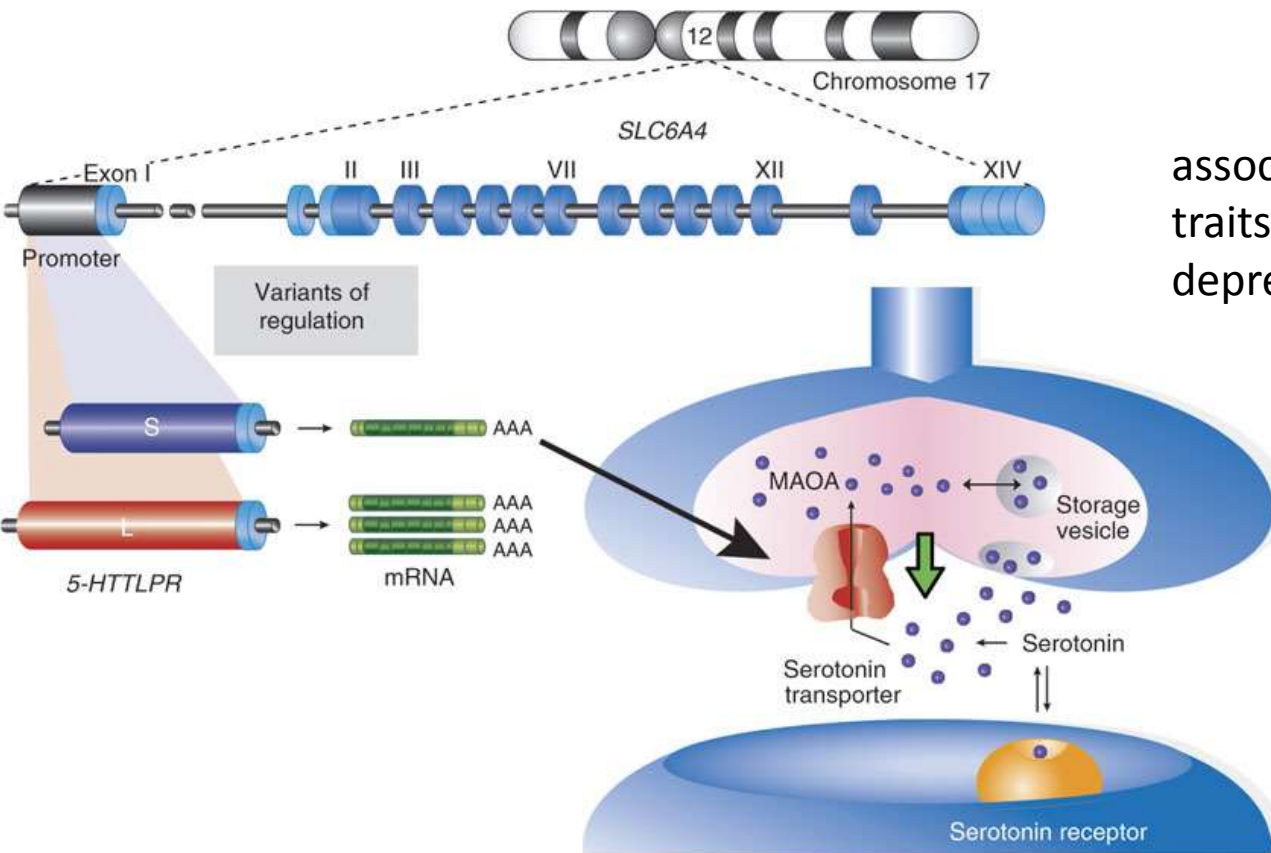
# Serotonin and Mood Disorders

The serotonin transporter (5HTT) is implicated in mood disorders and depression

5HTT contains a gene-linked polymorphic region giving rise to a short and long allele

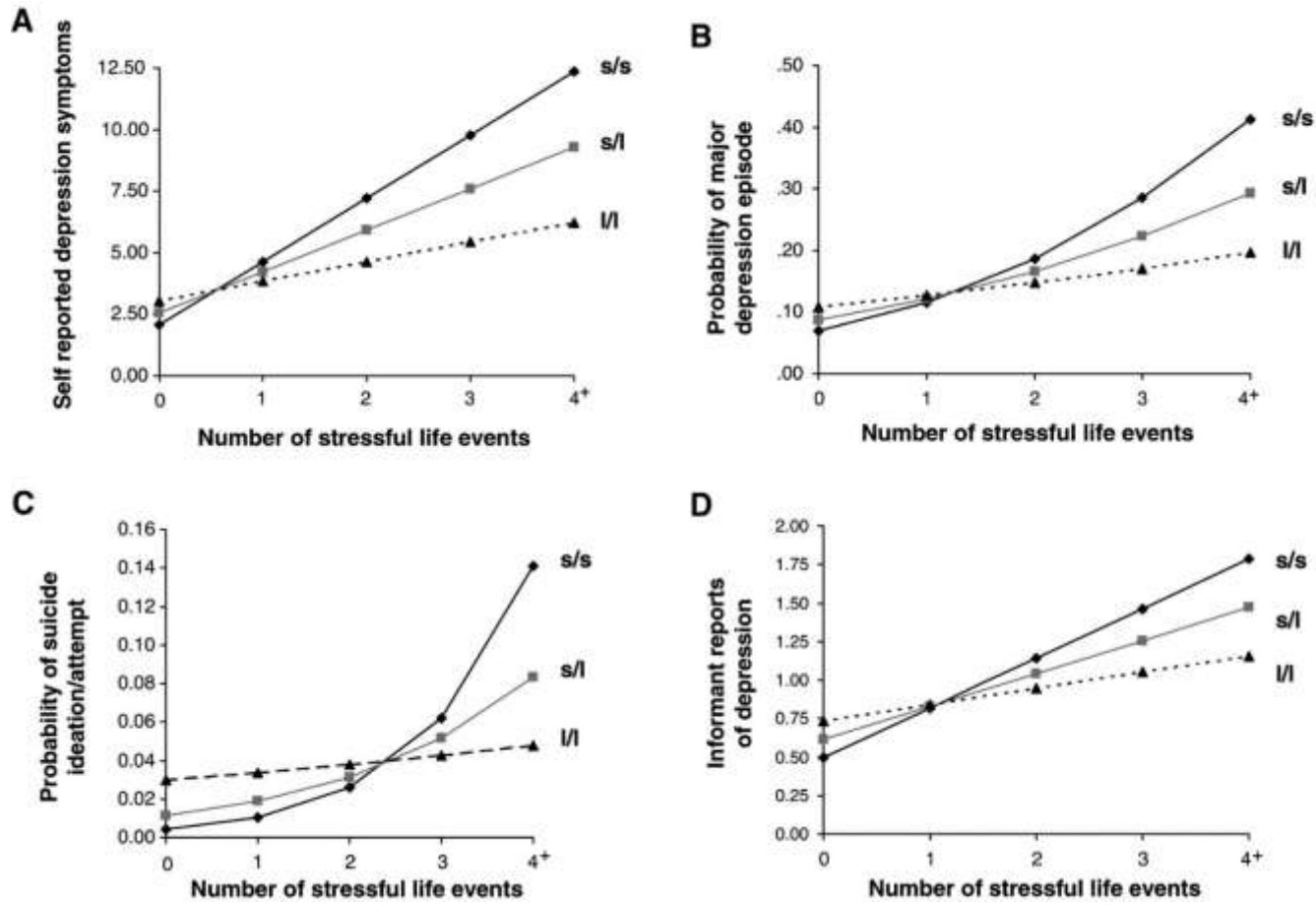
The short allele results in lower transcriptional efficiency of the promoter

# S allele



associated with anxiety-related traits and susceptibility for depression

# 5HTT S allele and depression





# Generation of a model animal

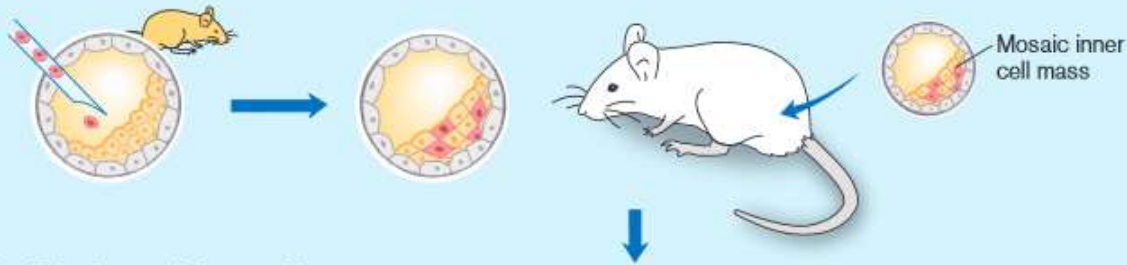
## Step 2 From gene targeted ES cells to gene targeted mice

### 5. Injection of ES cells into blastocysts

The targeted ES cells are injected into blastocysts...

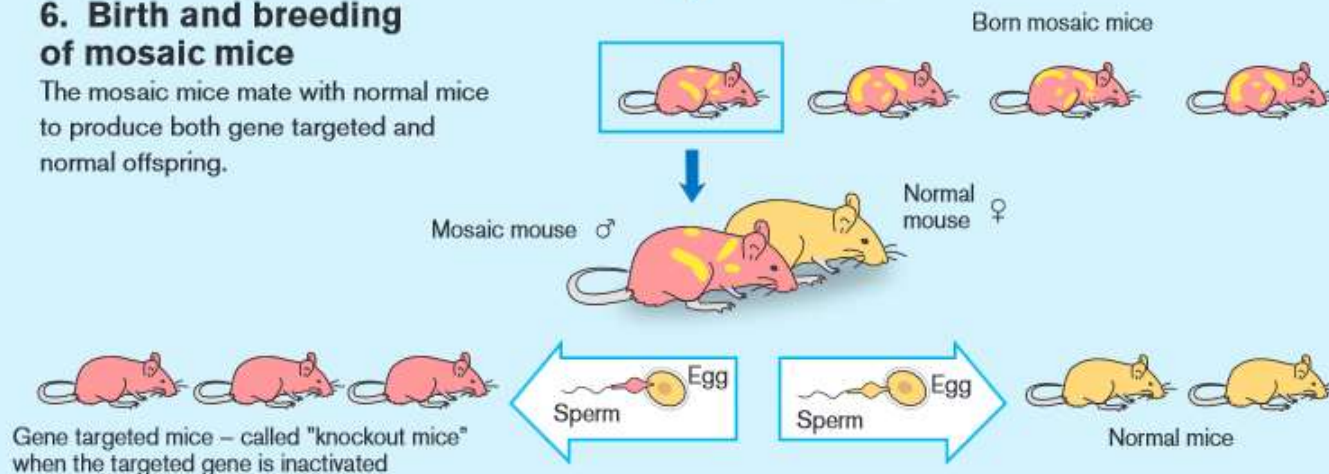
...where they mix and form a mosaic with the cells of the inner cell mass from which the embryo develops.

The injected blastocysts are implanted into a surrogate mother where they develop into mosaic embryos.

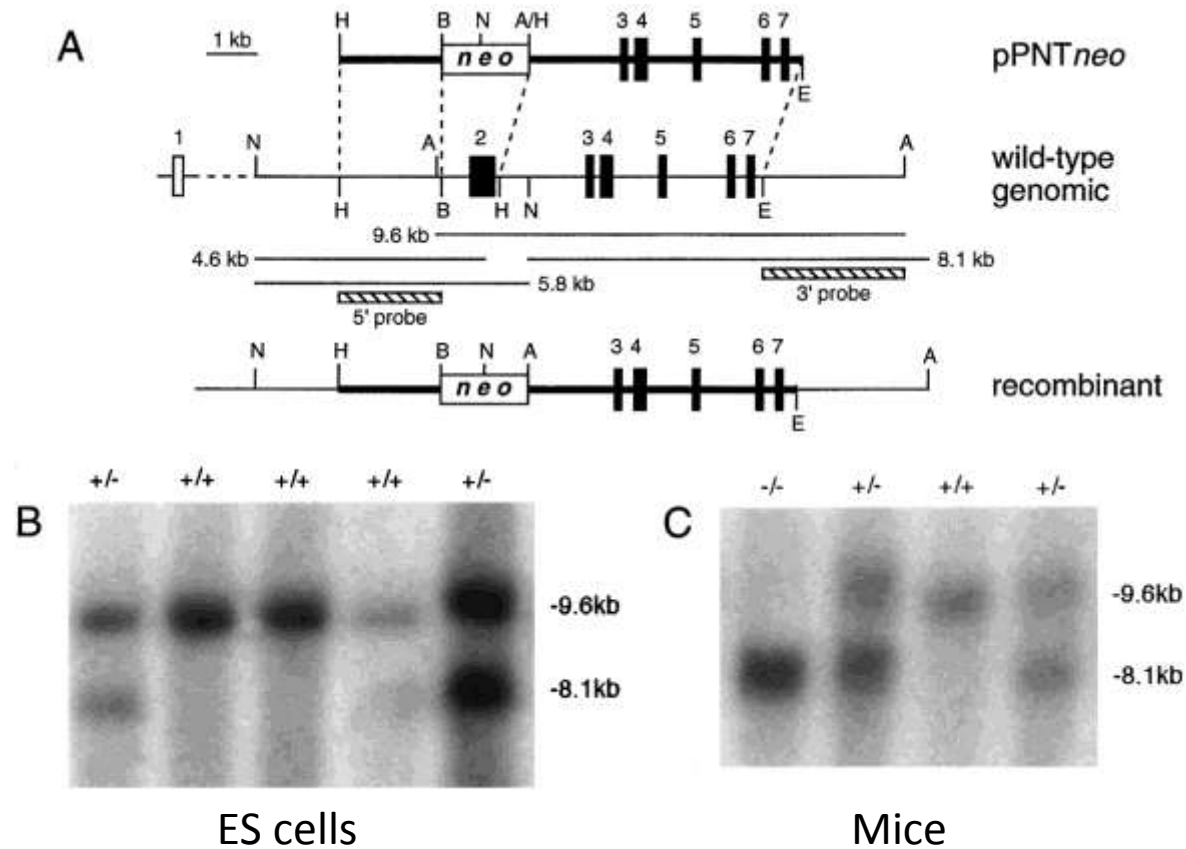


### 6. Birth and breeding of mosaic mice

The mosaic mice mate with normal mice to produce both gene targeted and normal offspring.



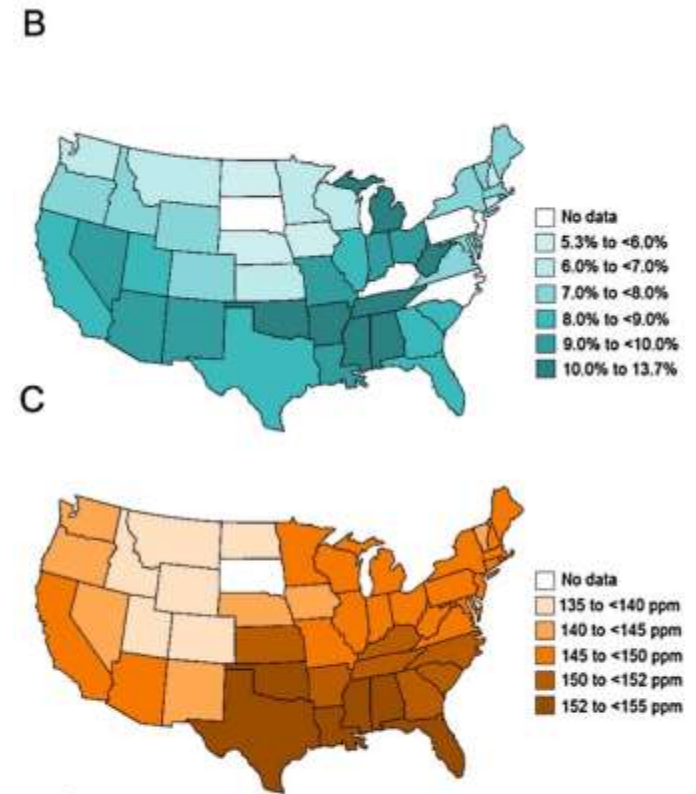
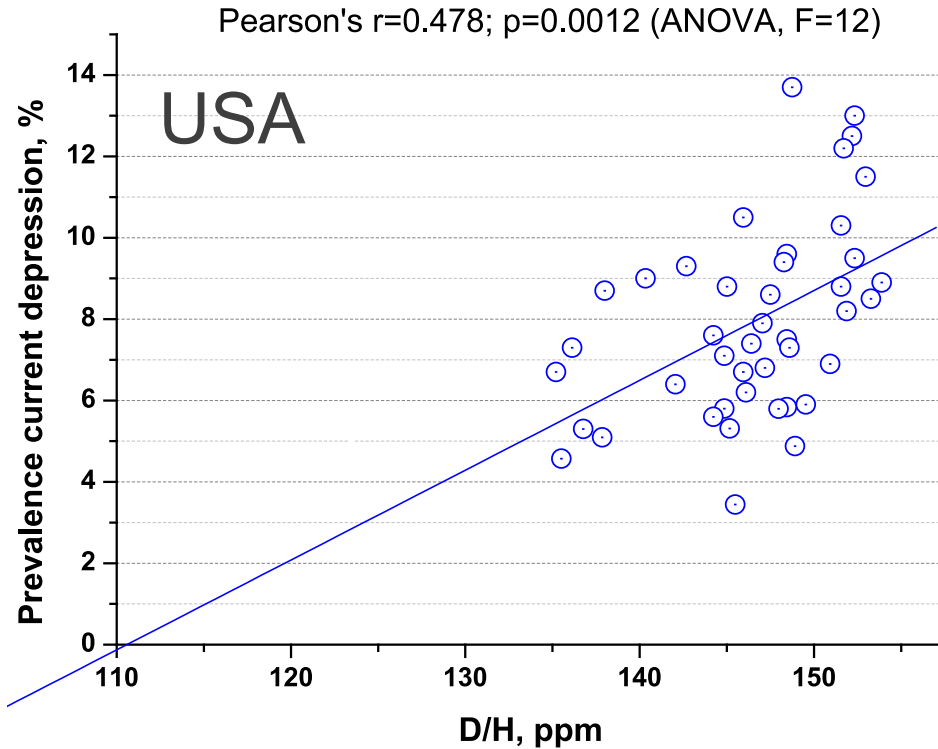
# The SERT mouse (5HTT, Slc6a4)



# The SERT mouse (5HTT, Slc6a4)

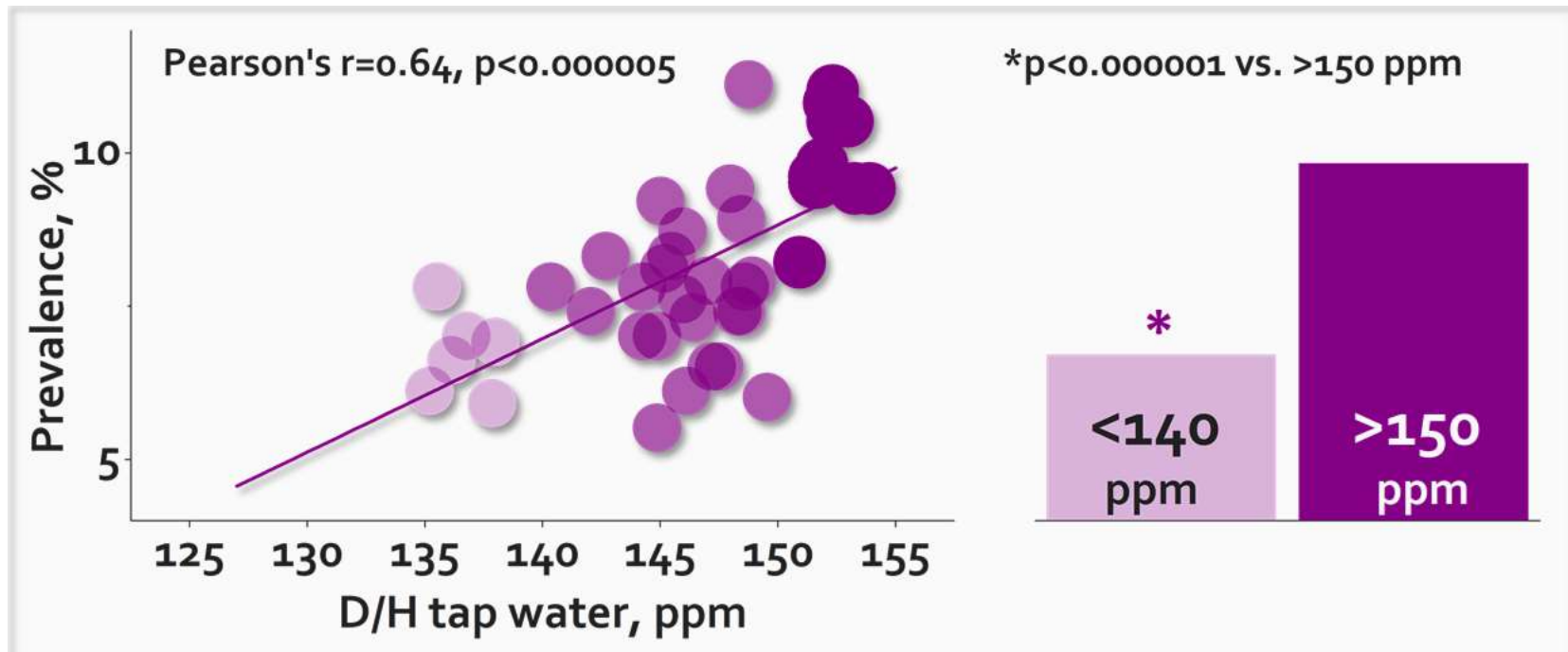
	<i>Slc6a4</i> <sup>-/-</sup>	<i>Slc6a4</i> <sup>+/-</sup>		<i>Slc6a4</i> <sup>-/-</sup>	<i>Slc6a4</i> <sup>+/-</sup>
<b>Behavioural features</b>			<b>Physiological features</b>		
Anxiety	↑	↑	Stress responses (ACTH, corticosterone, epinephrine, temperature and motor responses)	↑	↑
Learned fear	↑	NS	Gut motility (diarrhoea, constipation)	↑	NT
Learned helplessness (forced-swim and tail-suspension tests)	↑	NS	Body weight	↑	NS
Aggression	↓	↓	Glucose tolerance	↓	NT
Acoustic startle response	↑	↑	Insulin sensitivity	↓	NT
Exploratory activity	↓	NS	Brain glucose utilization	↓	NT
Rotorod agility	↓	NS	Bone mass and strength	↓	NT
Wire hang	↓	↓	Nociception (nerve injury and thermal)	↓	NT
			Bladder function	↓	NS
<b>Physiological features</b>	<i>Slc6a4</i> <sup>-/-</sup>	<i>Slc6a4</i> <sup>+/-</sup>	Hypoxia-induced pulmonary hypertension	↓	NT
Glucose	↑	NS	Raphe serotonin neuron firing rate	↓	↓
Leptin	↑	NT	REM sleep	↑	↑
Cholesterol	↑	NT	EEG power spectra, 'bursting'	Δ	NS
Triglycerides	↑	NT			

# Depression rates and deuterium content of tap water





# Diabetes prevalence and deuterium content of tap water



# Study Design

3.5 week old 5HTT+/- mice

14 days of drug treatment

*control light water (CLW) deuterium content of  
155 ppm*

*light water (LW) 91 ppm deuterium*

*Citalopram (Cit) positive control (15mg/Kg/day, via  
water)*

Behavioral tests

GTT (ip 1.5 mg/g)

# Modified Porsolt forced swim test

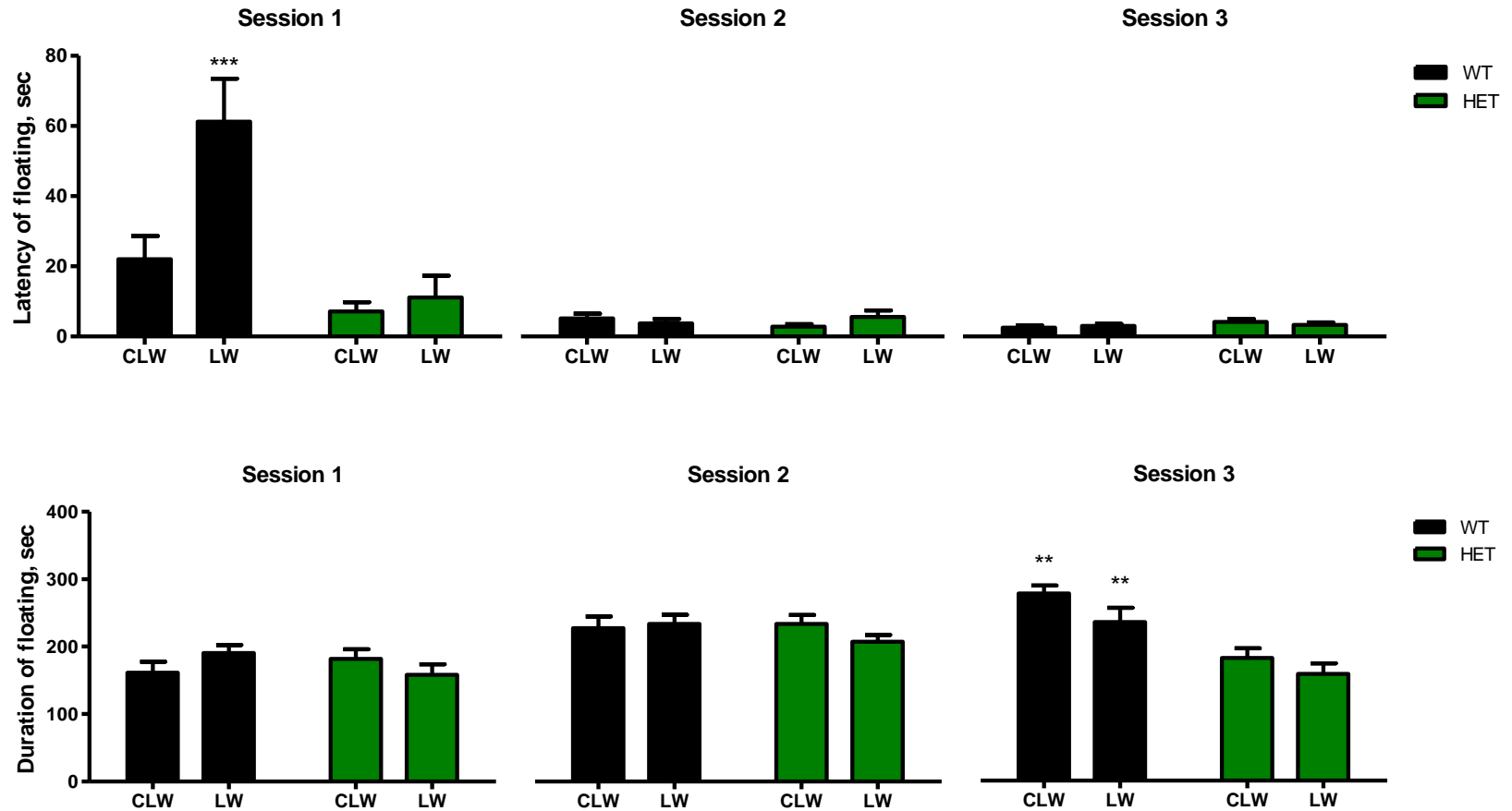
Modified to test for learned helplessness and for brain plasticity triggered by stress

Two 6 min sessions during 2 consecutive days

Third 6 min session 120 hours after the 2<sup>nd</sup>

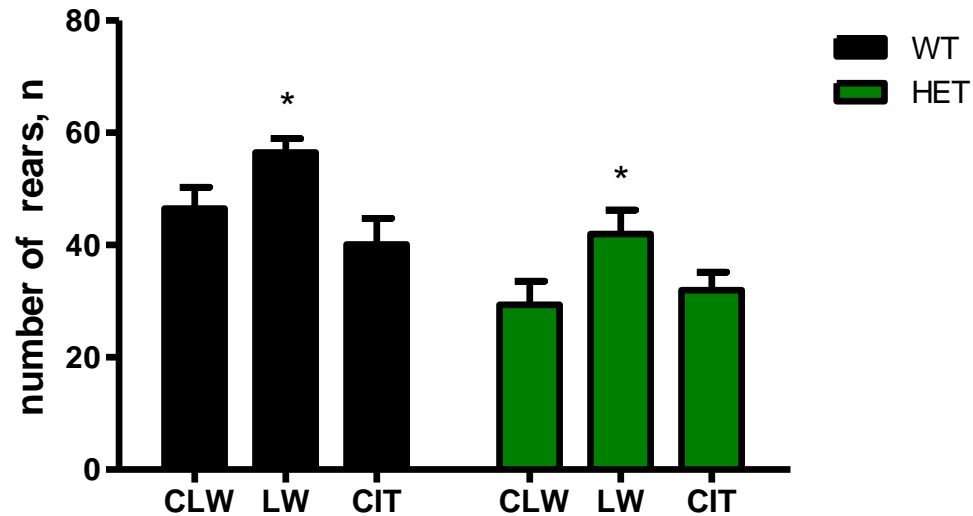


# Modified Porsolt forced swim test



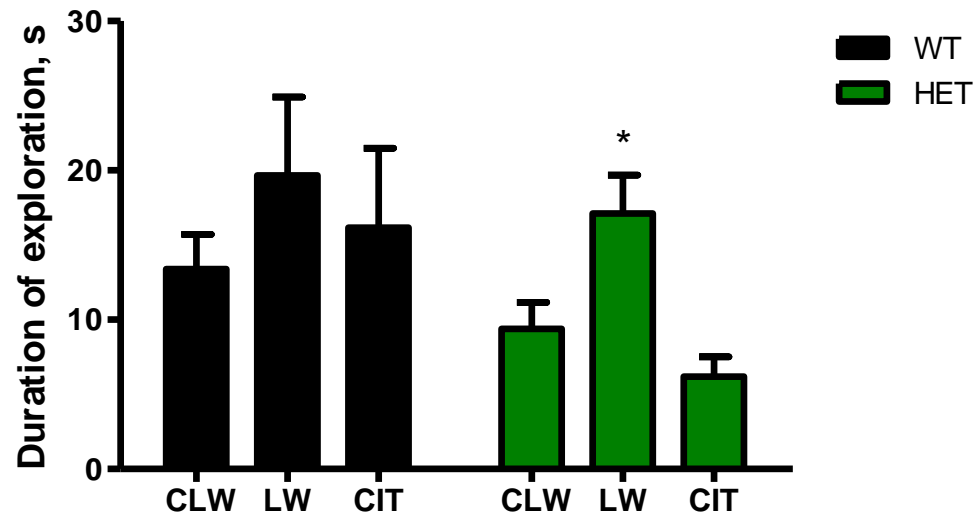


# Effect of CLW, LW and Cit on rearing



5 min session in novel cage with fresh bedding and red lighting

# Novel object exploration



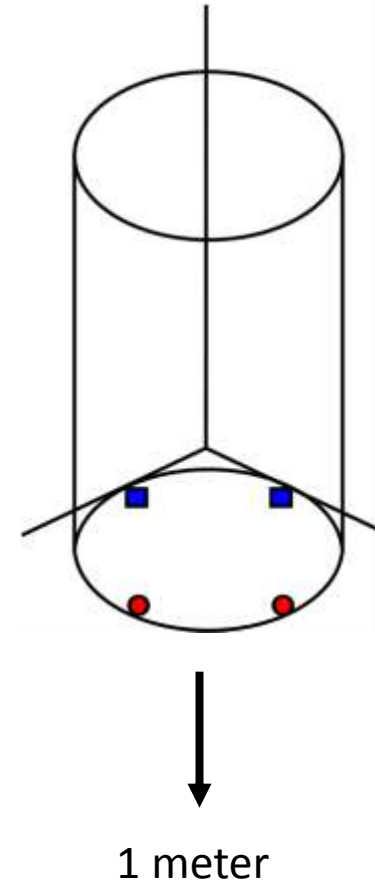
15 min session under 5 lux

# Novel object recognition

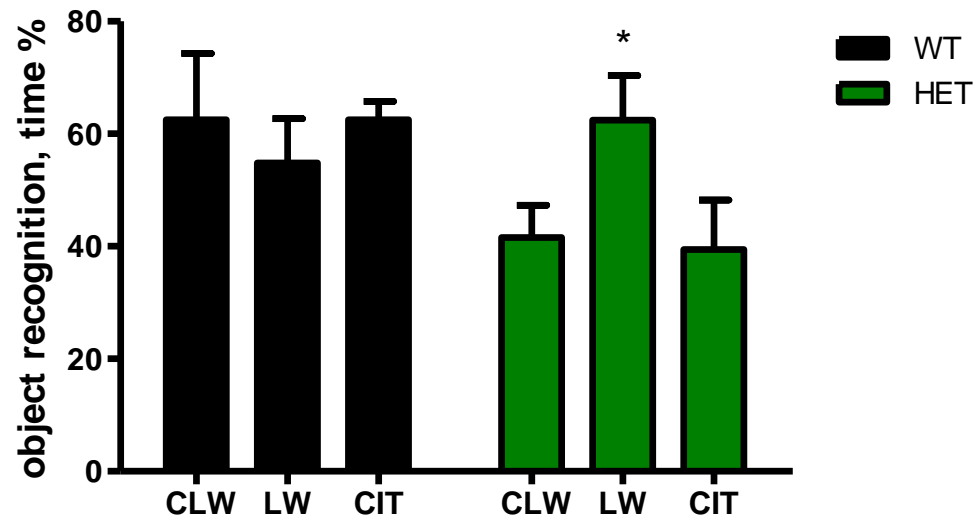
1<sup>st</sup> day animals allowed to explore 2 objects for 15 min

2<sup>nd</sup> day new object is placed at the edge

Latency to discover new object and preference is measured



# Novel object recognition



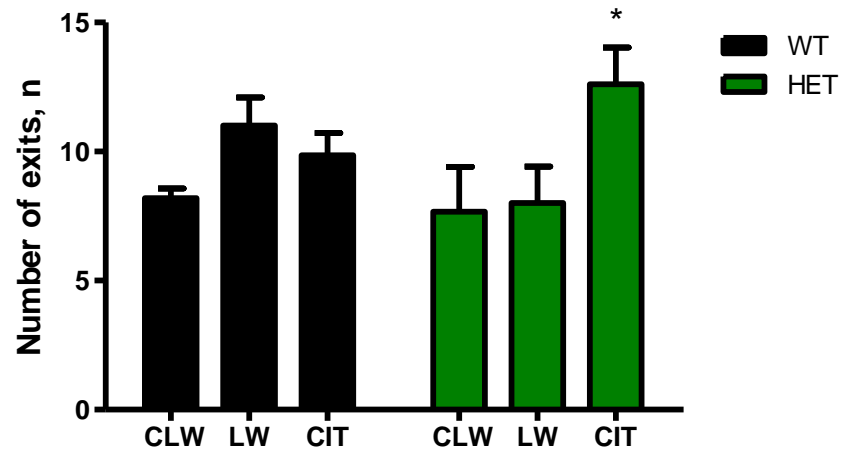
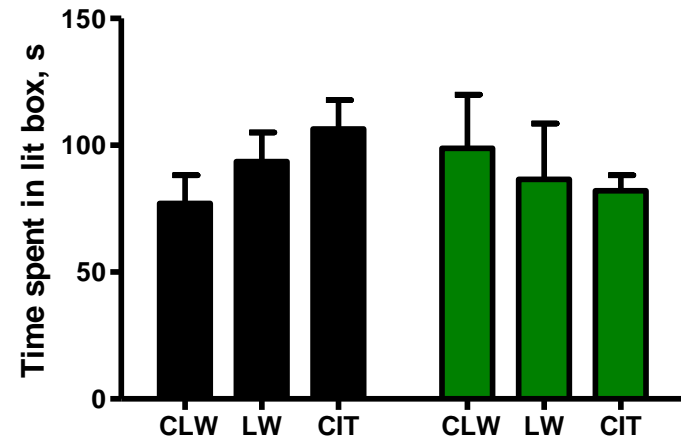
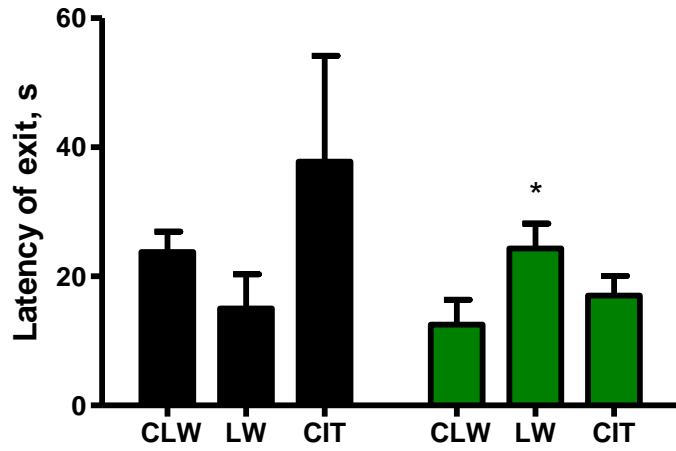


# Dark/Light Box

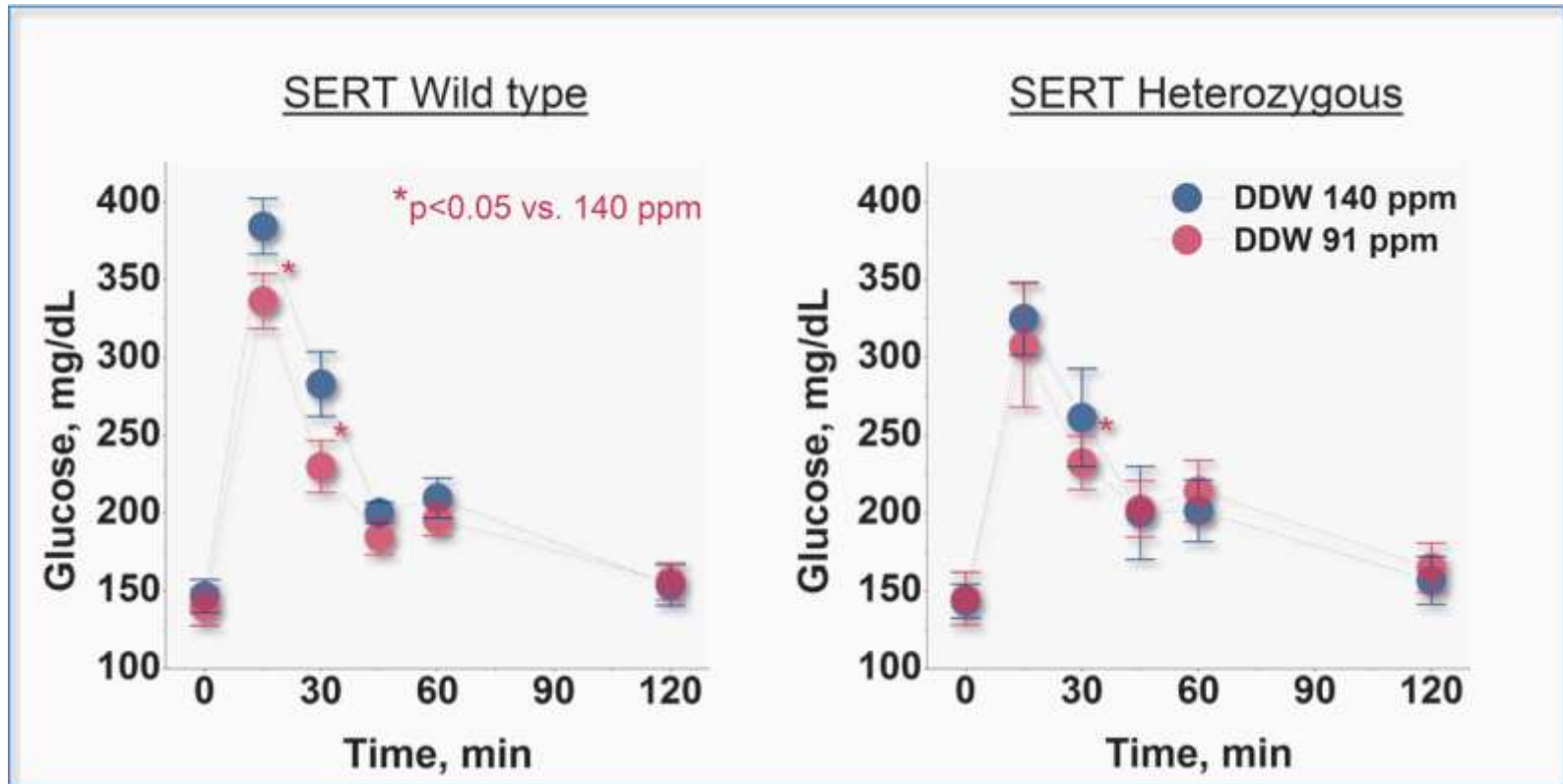
Test for anxiety related behavior  
Screens anxiolytic compounds  
5 min session  
Lit compartment intensity at 25 lux



# Dark/Light Box



# Glucose tolerance



Fasted 18 hours, 1.5 mg/g ip glucose

# Summary

5 HTT +/- aged females show lower cognitive performance and increased symptoms of anxiety

LW was more effective in WT SERT animals but had efficacy in both groups for anxiety

LW shows promise for improved glucose utilization



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