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

3rd International Congress on Deuterium Depletion
7-8 May 2015, Budapest, Hungary

UNIVERSITÉ DE STRASBOURG
Inserm U1119

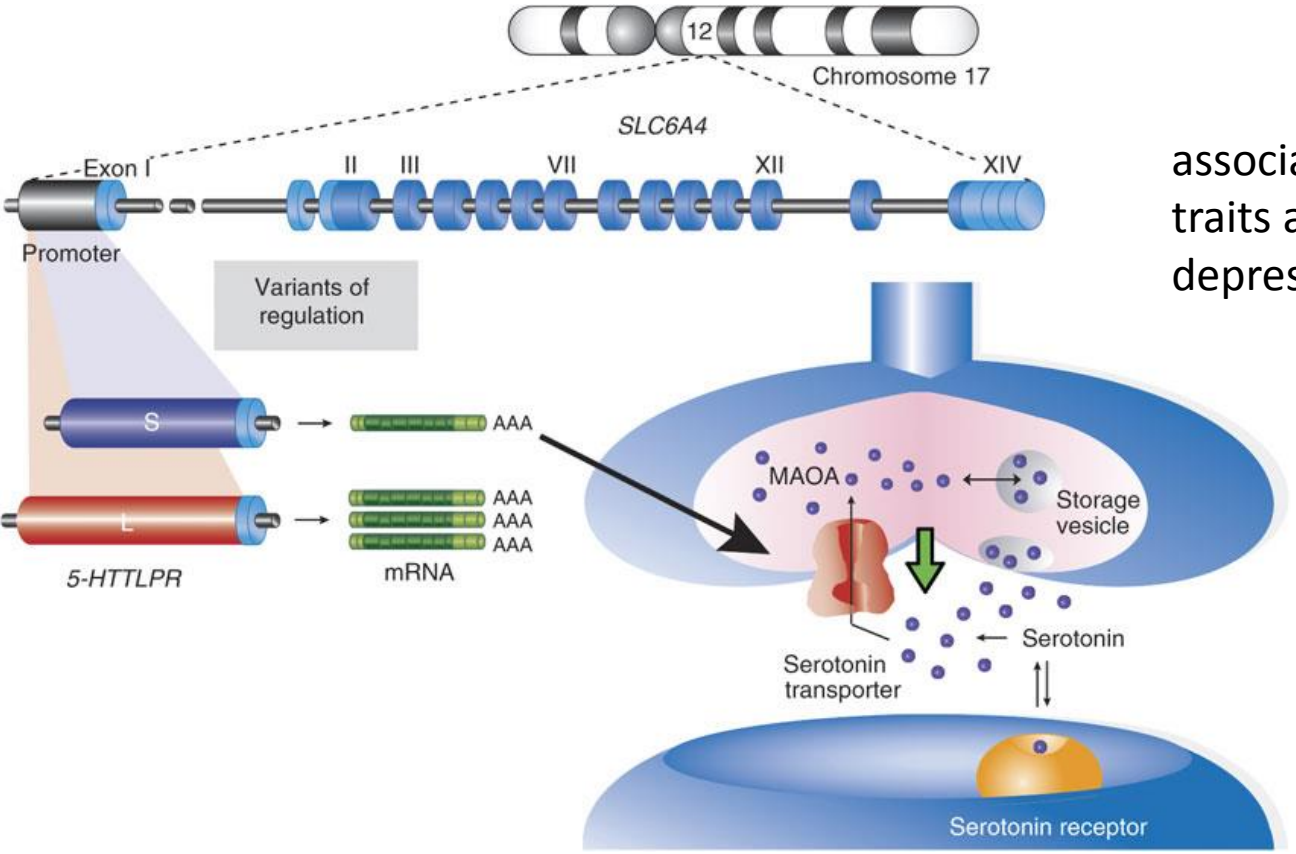
Serotonin and Mood Disorders

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

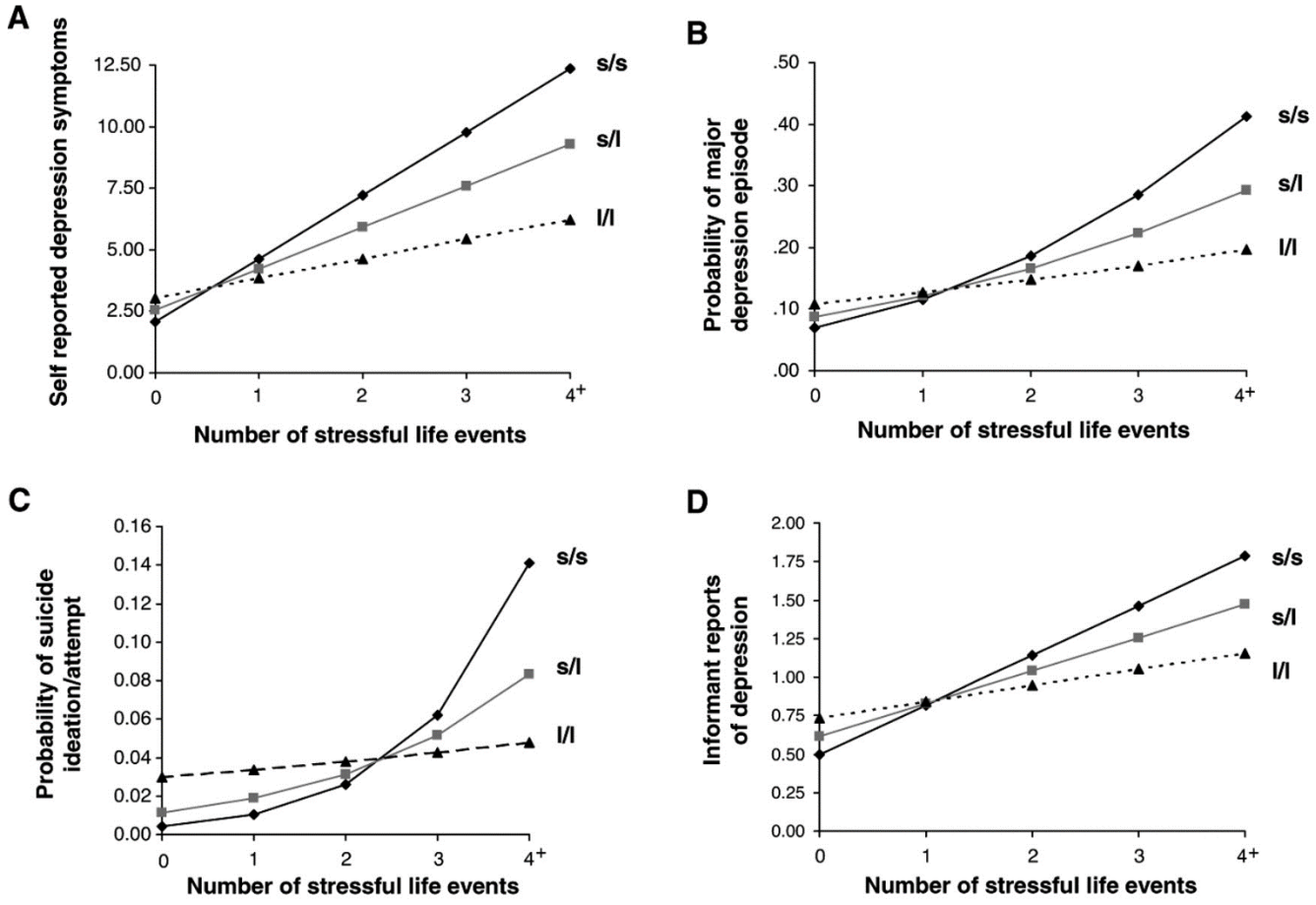
S allele



associated with anxiety-related traits and susceptibility for depression

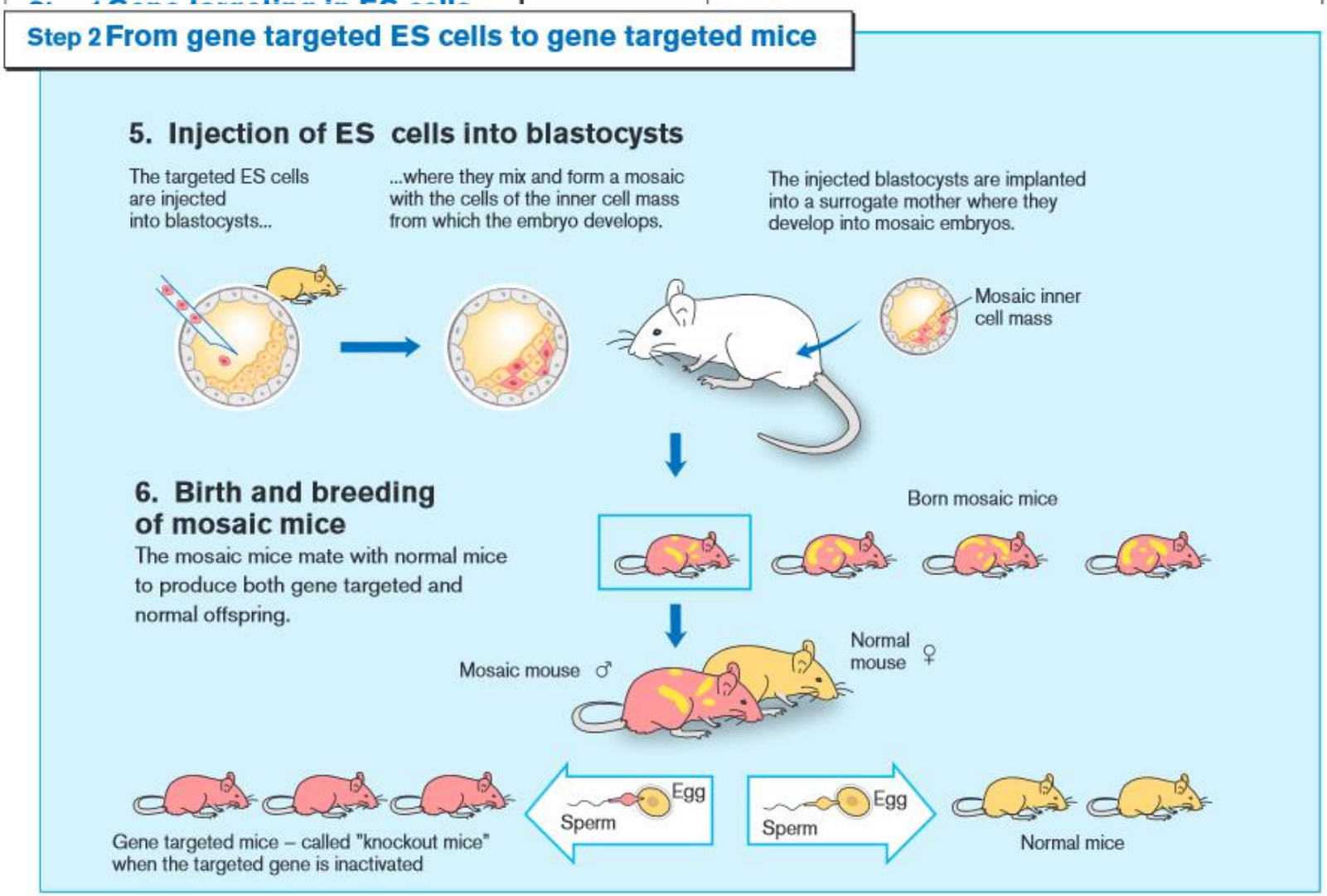
Canli et al Nature Neuroscience 10, 1103 - 1109 (2007)

5HTT S allele and depression

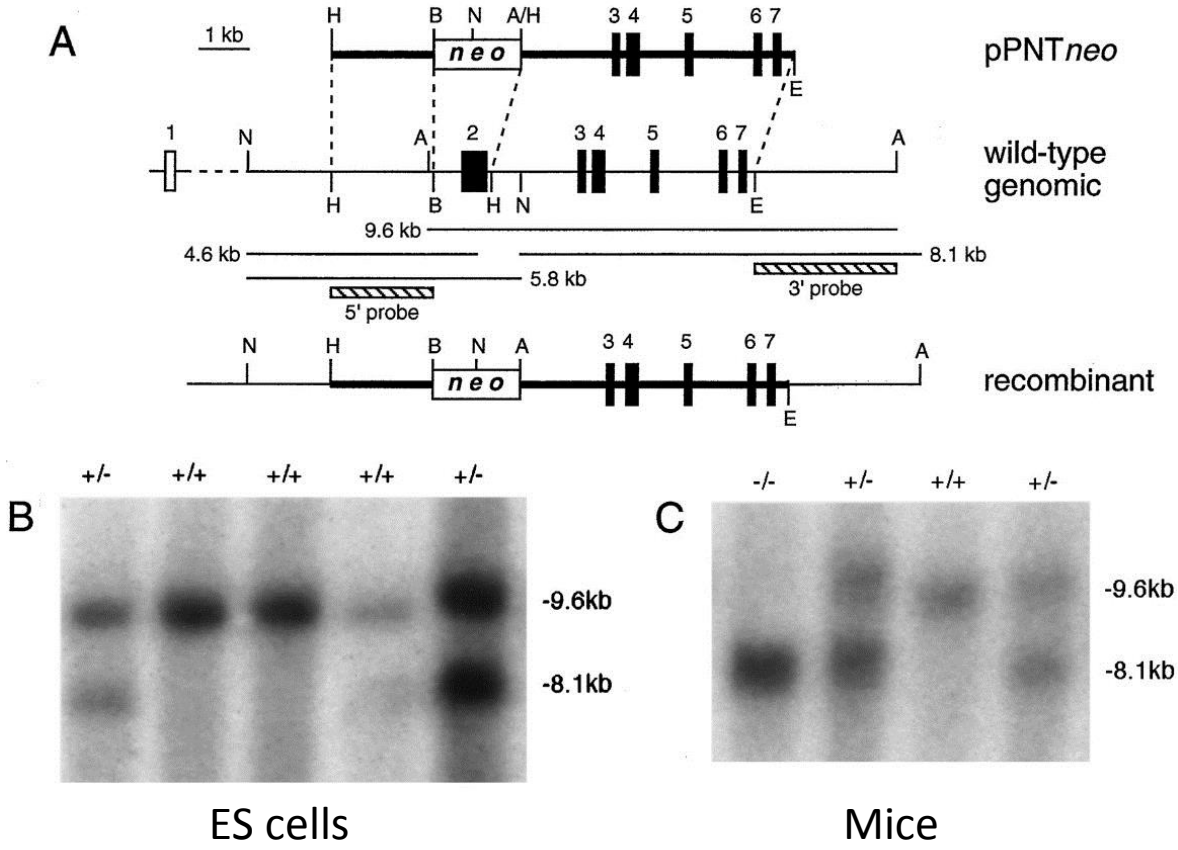


Caspi et al Science 301 (5631): 386-389 (2003)

Generation of a model animal



The SERT mouse (5HTT, Slc6a4)



Bengel et al Molecular Pharmacology vol. 53 no. 4 649-655 (1998)

The SERT mouse (5HTT, Slc6a4)

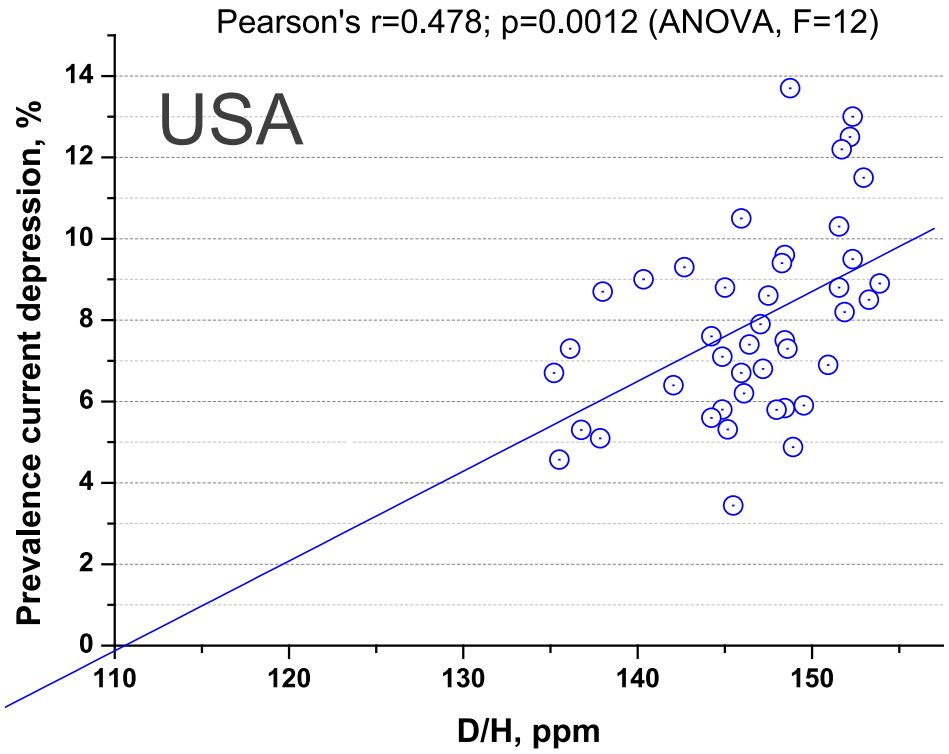
Behavioural features	*Slc6a4*$^{-/-}$	*Slc6a4*$^{+/-}$
Anxiety	↑	↑
Learned fear	↑	NS
Learned helplessness (forced-swim and tail-suspension tests)	↑	NS
Aggression	↓	↓
Acoustic startle response	↑	↑
Exploratory activity	↓	NS
Rotorod agility	↓	NS
Wire hang	↓	↓

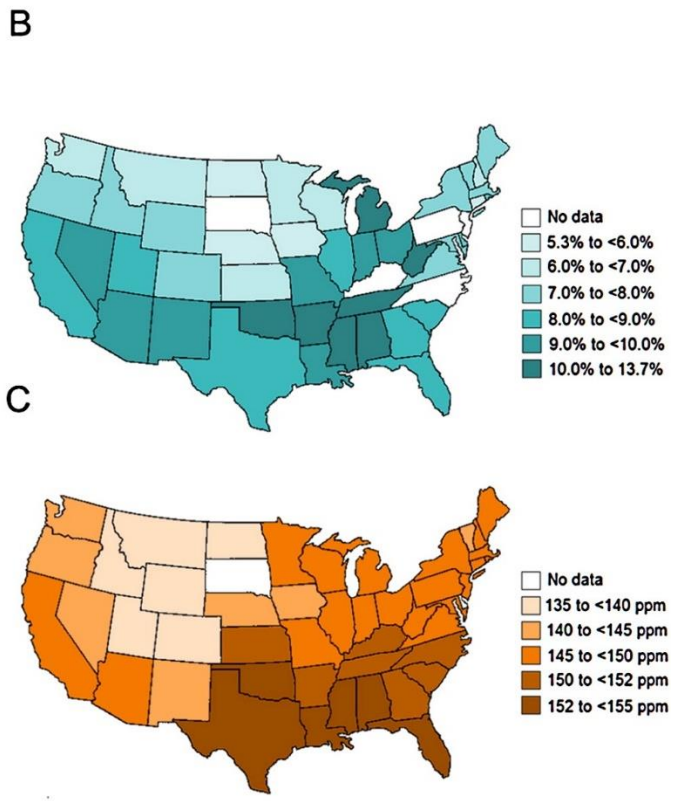
Physiological features	*Slc6a4*$^{-/-}$	*Slc6a4*$^{+/-}$
Glucose	↑	NS
Leptin	↑	NT
Cholesterol	↑	NT
Triglycerides	↑	NT

Physiological features	*Slc6a4*$^{-/-}$	*Slc6a4*$^{+/-}$
Stress responses (ACTH, corticosterone, epinephrine, temperature and motor responses)	↑	↑
Gut motility (diarrhoea, constipation)	↑	NT
Body weight	↑	NS
Glucose tolerance	↓	NT
Insulin sensitivity	↓	NT
Brain glucose utilization	↓	NT
Bone mass and strength	↓	NT
Nociception (nerve injury and thermal)	↓	NT
Bladder function	↓	NS
Hypoxia-induced pulmonary hypertension	↓	NT
Raphe serotonin neuron firing rate	↓	↓
REM sleep	↑	↑
EEG power spectra, 'bursting'	Δ	NS

Murphy et al Nature Reviews Neuroscience 9, 85-96 (2008)

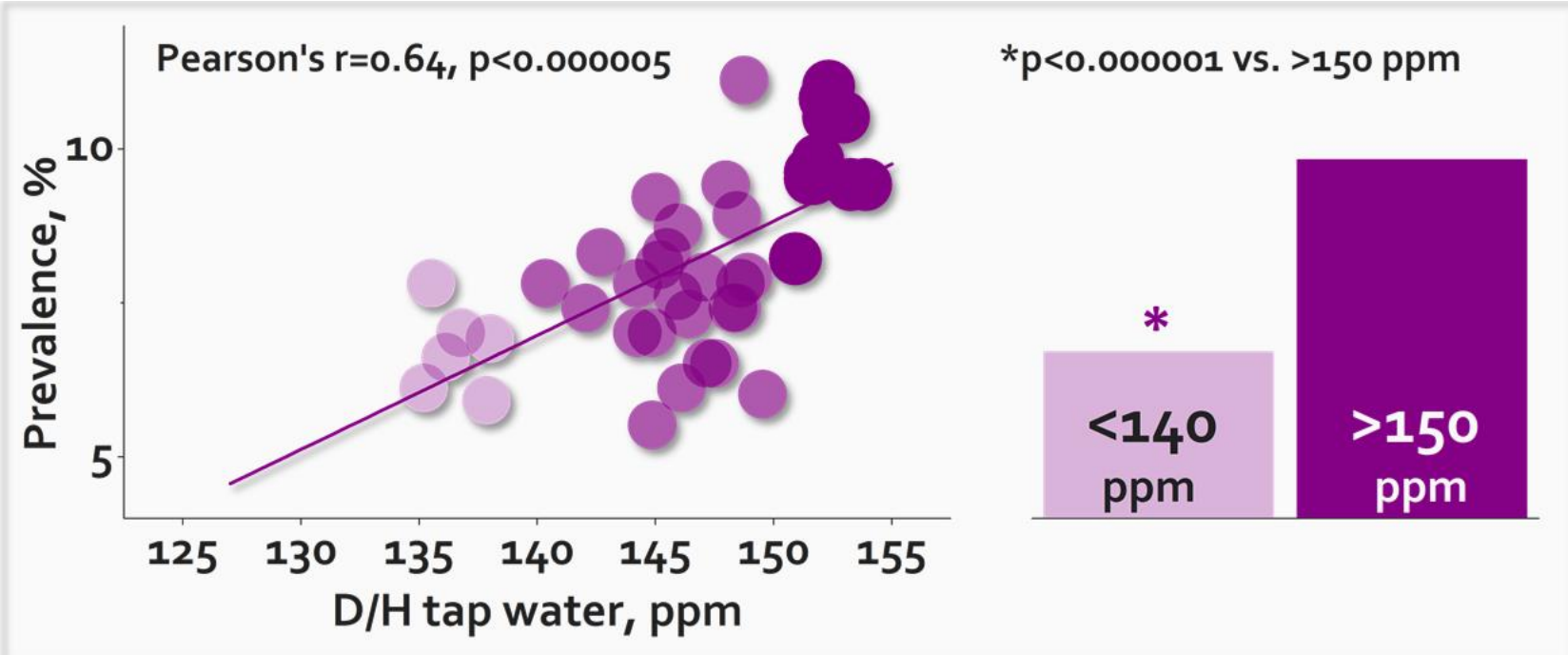
Depression rates and deuterium content of tap water





Upddated from Strekalova et al Behavioural Brain Research, 277: 237 – 244 (2015)

Diabetes prevalence and deuterium content of tap water



Modified from Strekalova et al Behavioural Brain Research, 277: 237 – 244 (2015) with CDC's Division of Diabetes Translation, National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

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)

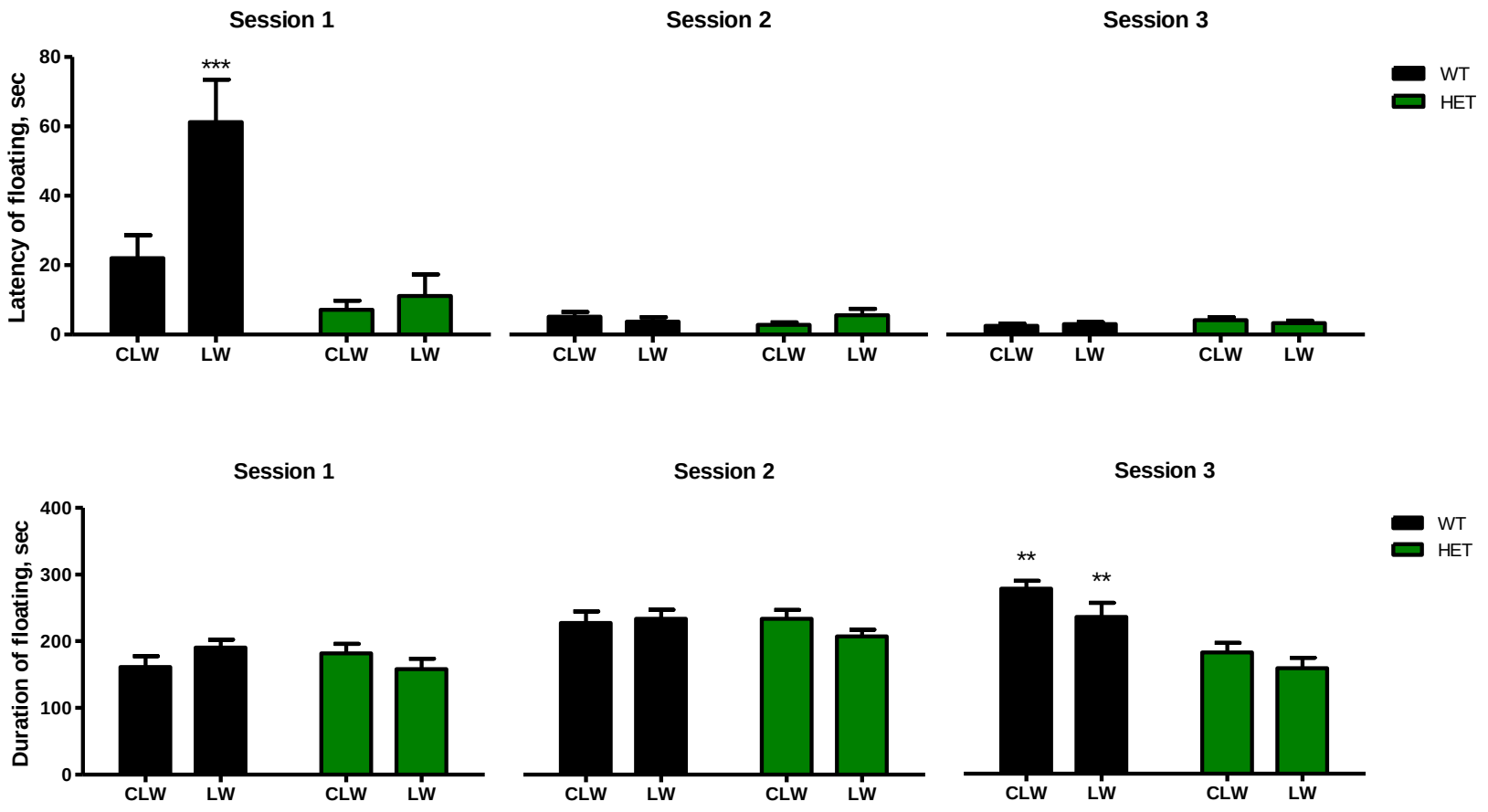
Modified Porsolt forced swim test

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

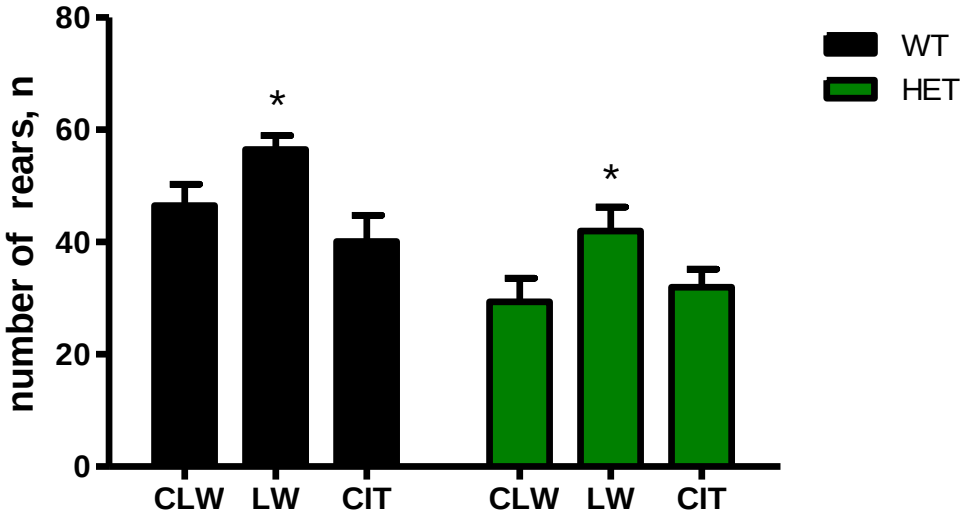
Two 6 min sessions during 2 consecutive days

Third 6 min session 120 hours after the 2nd

Modified Porsolt forced swim test

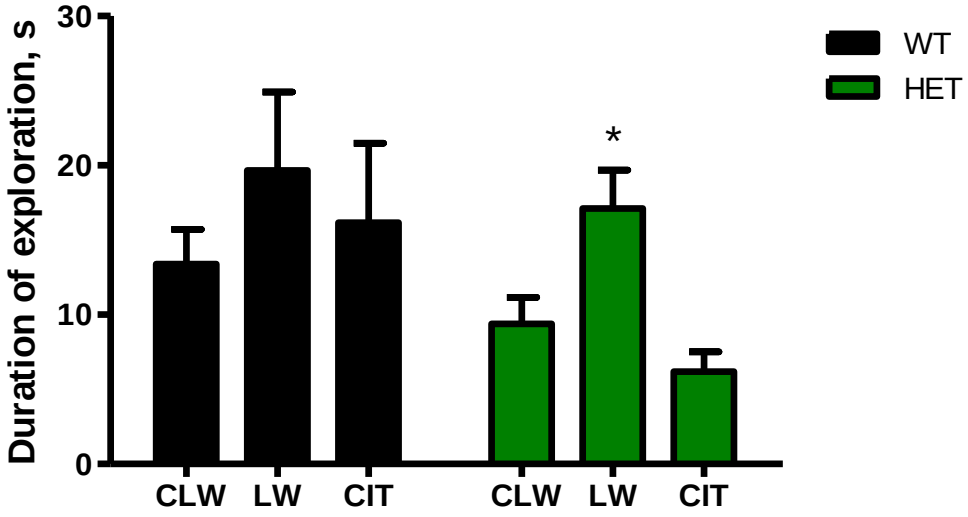


Effect of CLW, LW and Cit on rearing



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

Novel object exploration



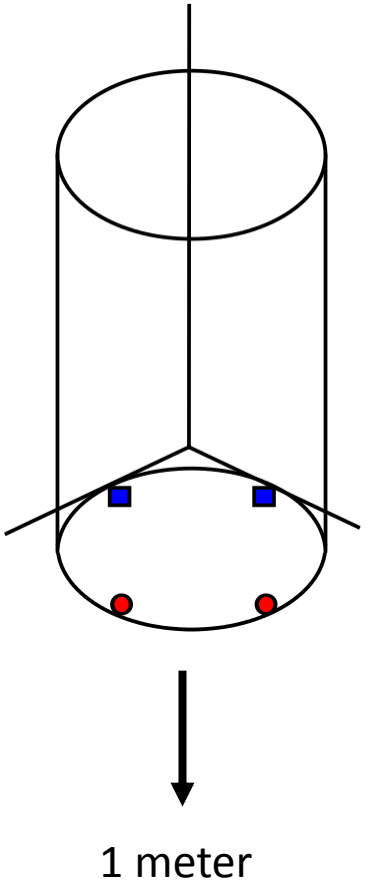
15 min session under 5 lux

Novel object recognition

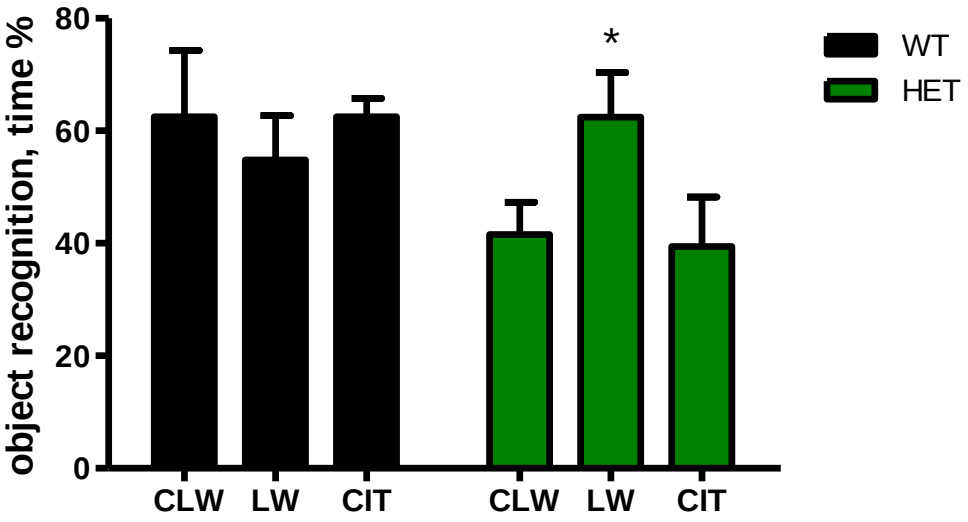
1st day animals allowed to explore 2 objects for 15 min

2nd day new object is placed at the edge

Latency to discover new object and preference is measured



Novel object recognition



Dark/Light Box

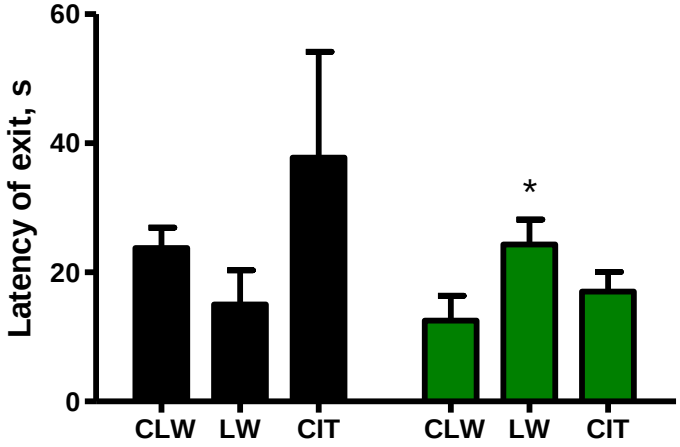
Test for anxiety related behavior

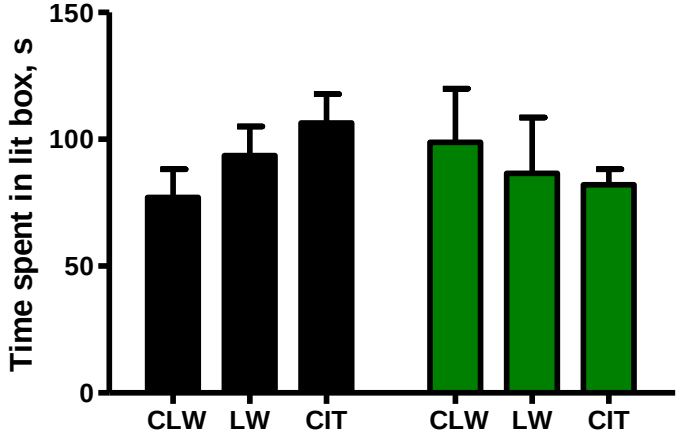
Screens anxiolytic compounds

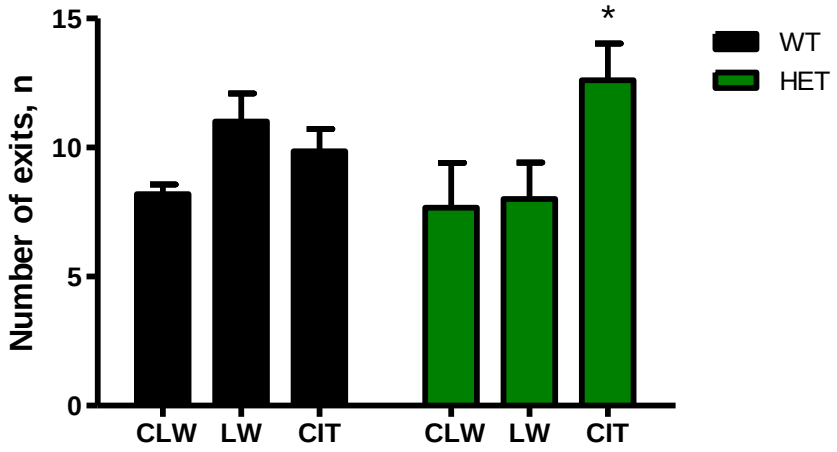
5 min session

Lit compartment intensity at 25 lux

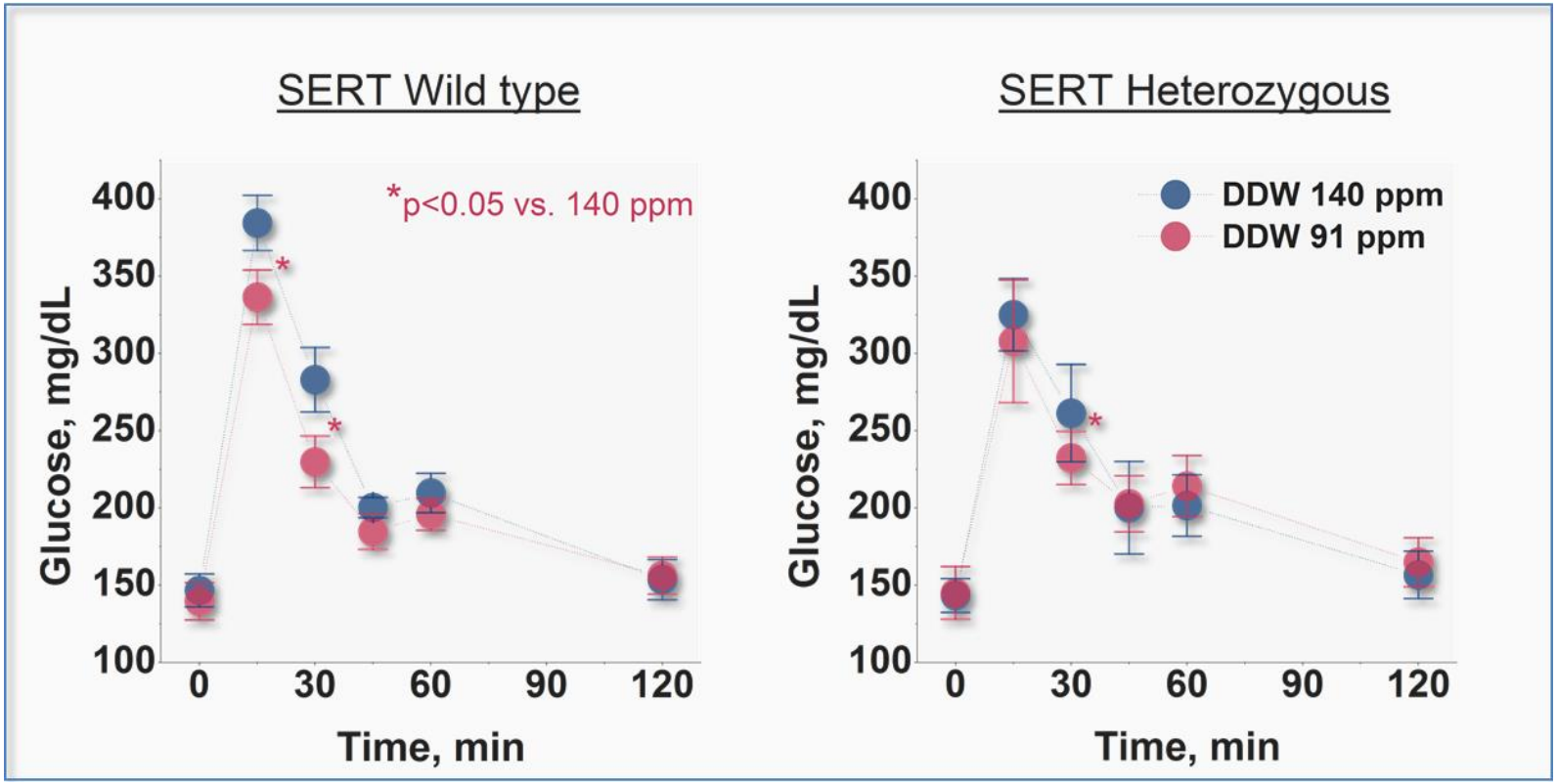
Dark/Light Box







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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