Translating animal models into human psychiatric (brain) disorders

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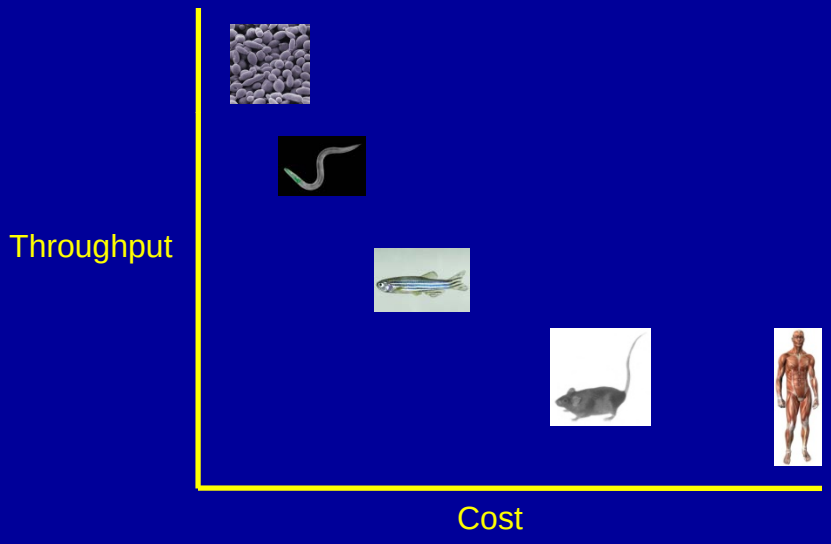
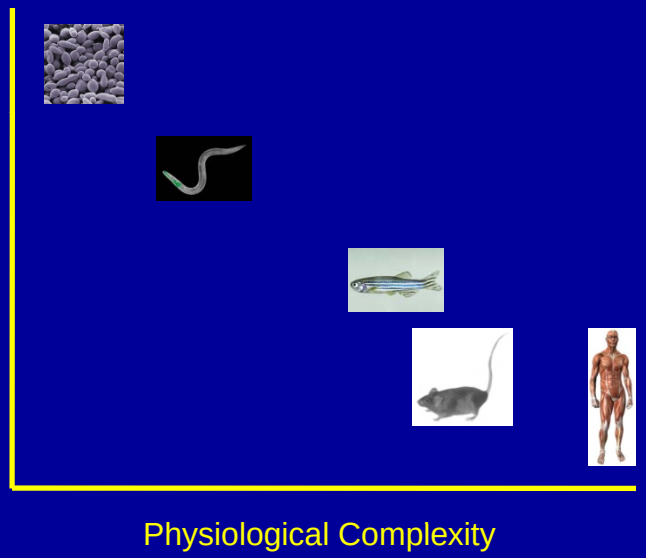
TU, January 28, 2009

Animal models are used to study:

- Effects of environment (e.g., stressors) on brain and behavior
- Adverse effects of genetic mutations
- Gene x Environment interactions
- Drug effects, side effects of drugs
- Drug interactions

Why use animal models?



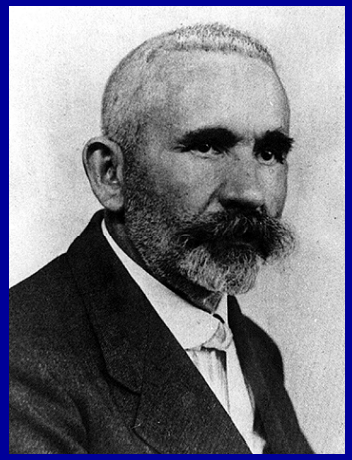


Kokel and Peterson, 2008

Overview

- Mice
- Zebrafish

Are mice a valid approximation/model of human brain disorders?



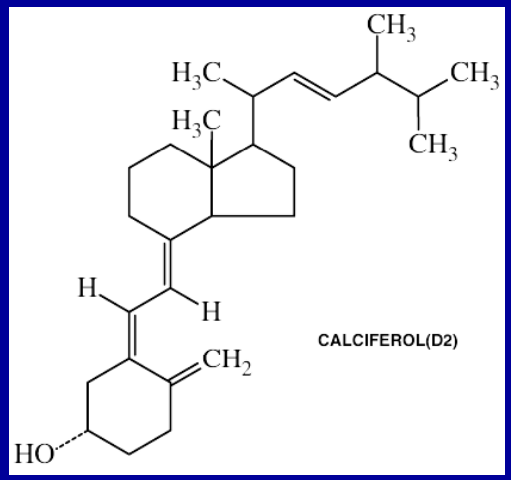
Personal experience of working with two interesting genetic mouse models

Vitamin D receptor (VDR) knockout mice

Serotonin transporter (SERT) knockout mice

Domains: anxiety, serotonin toxicity, drug abuse, obesity, social deficits

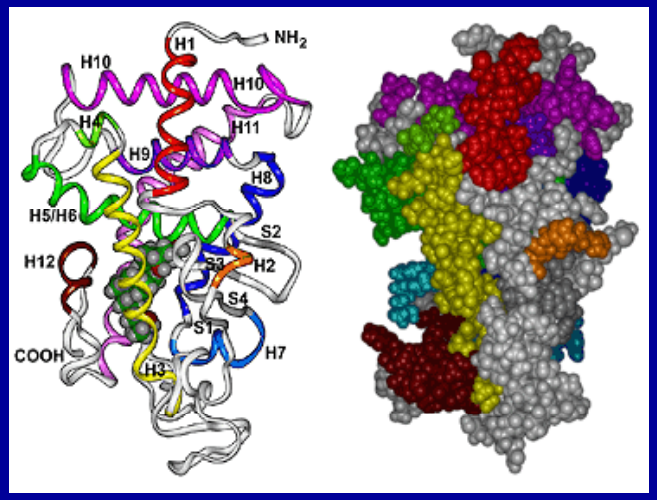
Steroid hormone Vitamin D



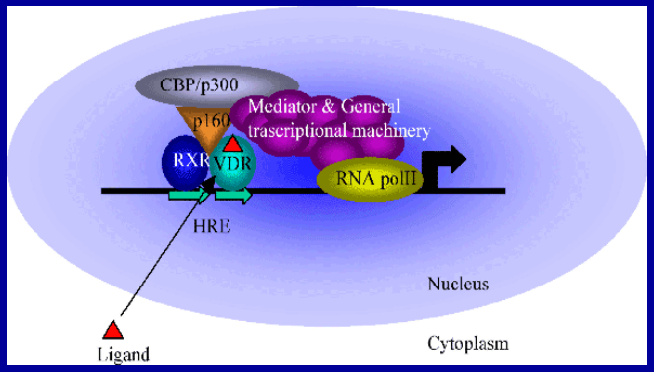
Biology of Vitamin D:

Vitamin D is a seco-steroid hormon regulating Ca++ metabolism, cell growh and differentiation

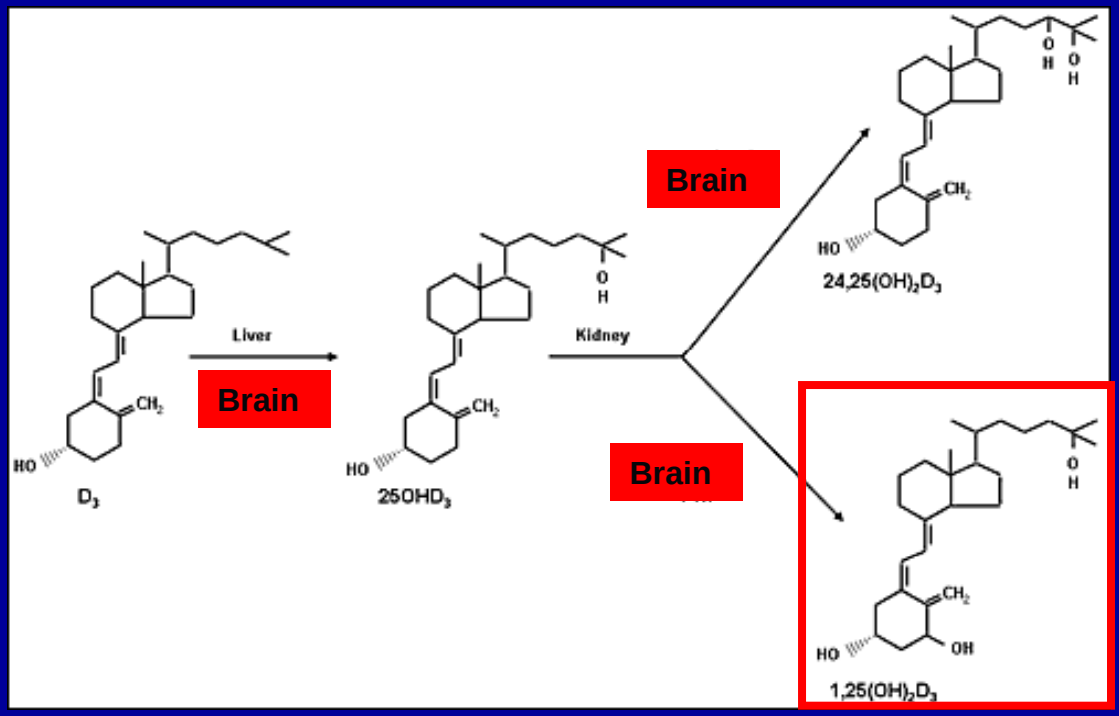
Vitamin D acts through the nuclear receptor (VDR), a member of steroid receptors superfamily



VDR – ligand-activated transcription factors



Brain and VDR



Vitamin D is a novel neuro-active steroid hormone or a neurosteroid

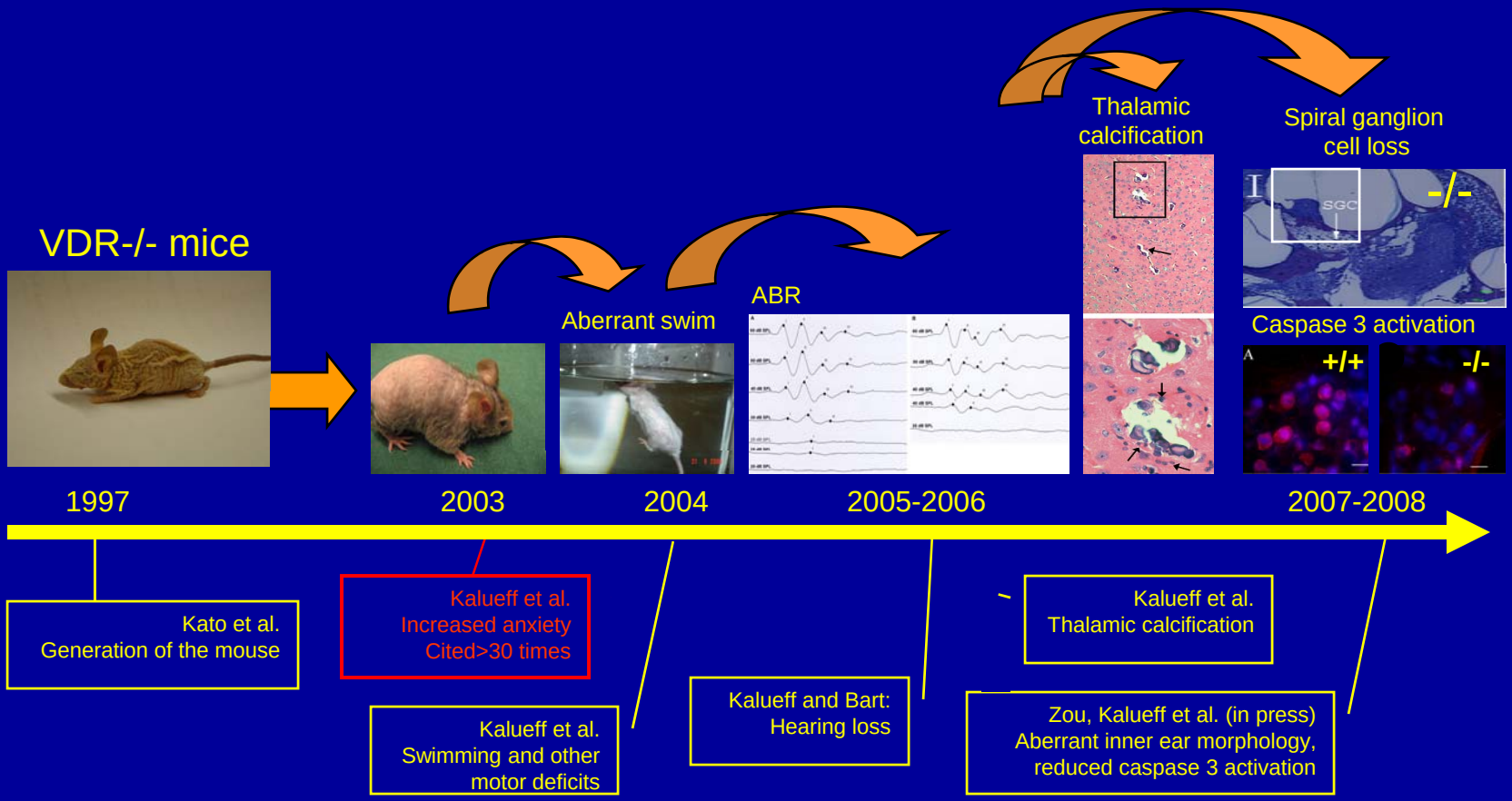
1,25(OH)2-D

Brain produces and inactivates Vitamin D hormone

CNS is rich in functional VDR

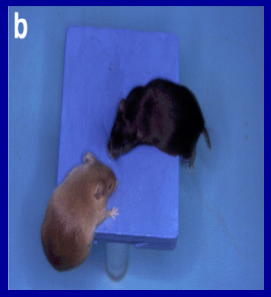
Brain represents a target tissue for the Vitamin D action via VDR (including the induction of brain genes and modulation of key neuromediators)

Vitamin D receptor knockout mouse model



VDR-/- mice

Aberrant grooming



1997 2004 2005 2006-2008

Kalueff et al.
Increased grooming phenotype

Kalueff et al.:Impaired sequencing of grooming

Kalueff et al.
Increased seizure sensitivity

Kalueff et al. Minasyan et al.
Keisala et al.
Social deficits
Aberrant nest building
Maternal deficits
Prolactin dysregulations
Scecific cognitive abnormalities

Neophobic responses

VDR-/- mice represent a genetic model of affective and neurological disorders associated with Vitamin D deficit and VDR genetic variations

Vitamin D and the brain

Over 900 different genes are now known to be able to bind the vitamin D receptor, through which vitamin D mediates its effects

Major depression is associated with low vitamin D levels (Stumpf, 1972)

Several studies have reported mood-elevating effects of vitamin D therapy

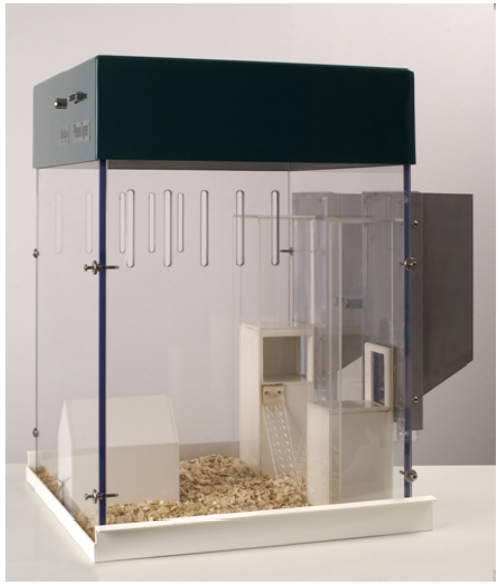
VDR genetic deficits are associated with depression, schizophrenia and suicidality (Ozer et al., 2005)

Vitamin D supplementation is crucial for groups whose vitamin D status is exceptionally low: infants, the elderly, and African Americans

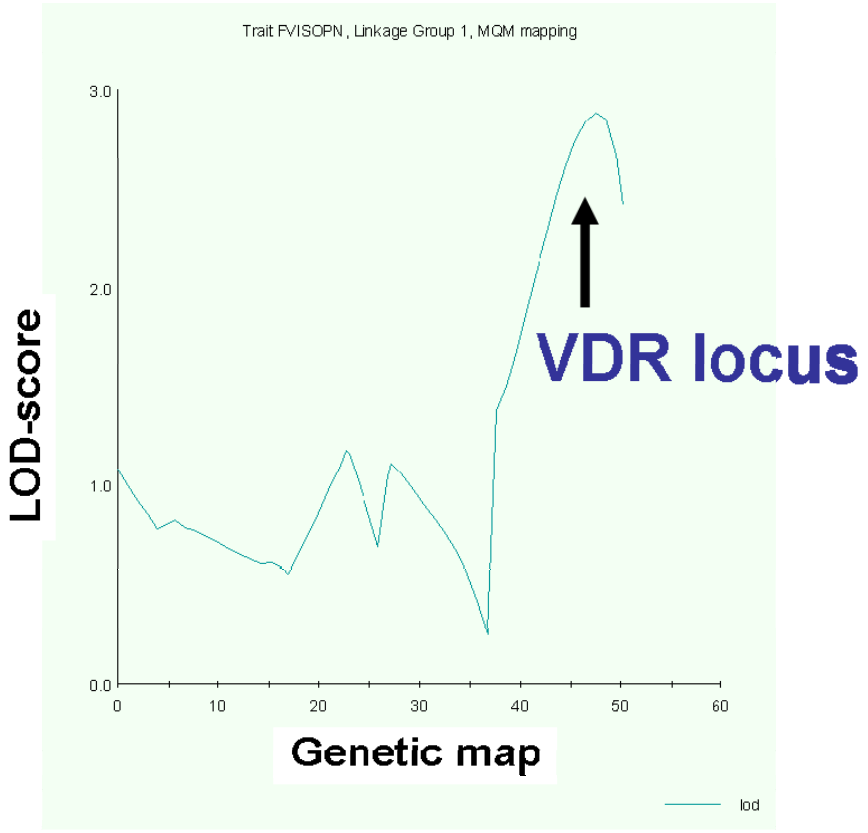
VDR knockout mouse data strongly support the role of vitamin D dysfunctions in stress-related brain disorders

VDR – a neophobic gene?

Automated home cage environment

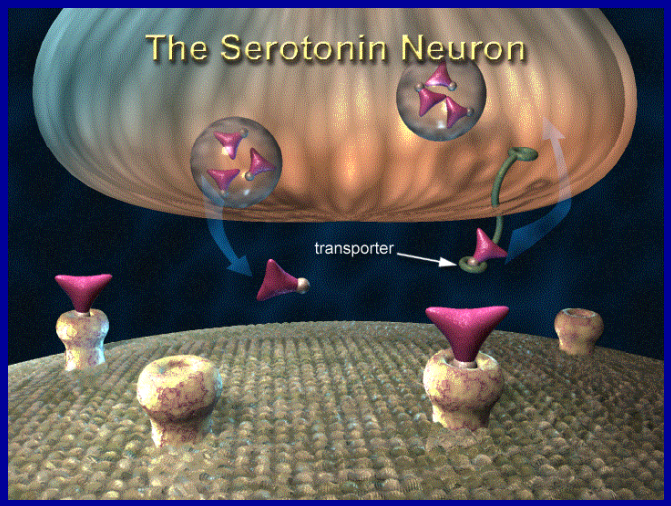


 # Visits on the exposed feeding platform during first HOUR



Kas et al., Behavioral Neuroscience 2008
Kas et al., Genes, Brain and Behaviour, in press
de Mooij-van Malsen et al, in preparation

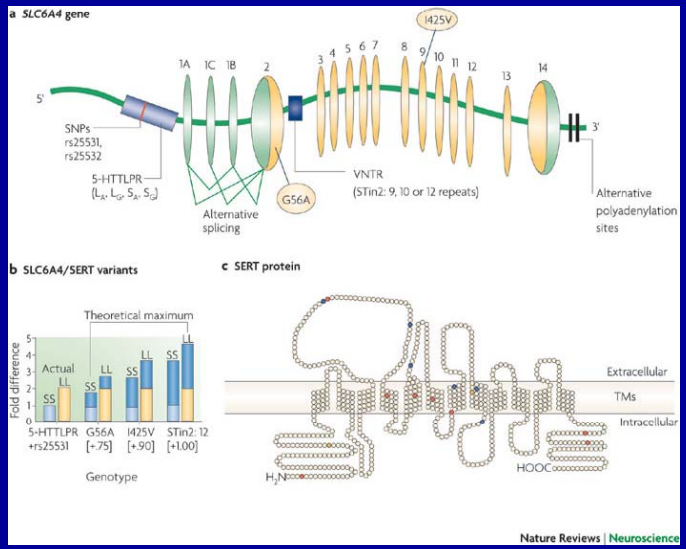
Serotonin transporter (SERT)

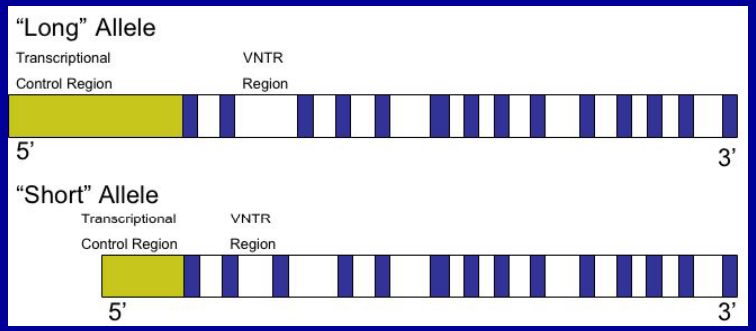


Serotonin transporter (SERT) is the key regulator of serotonergic neurotransmission

SERT is a target of many psychotropic drugs [SSRIs]

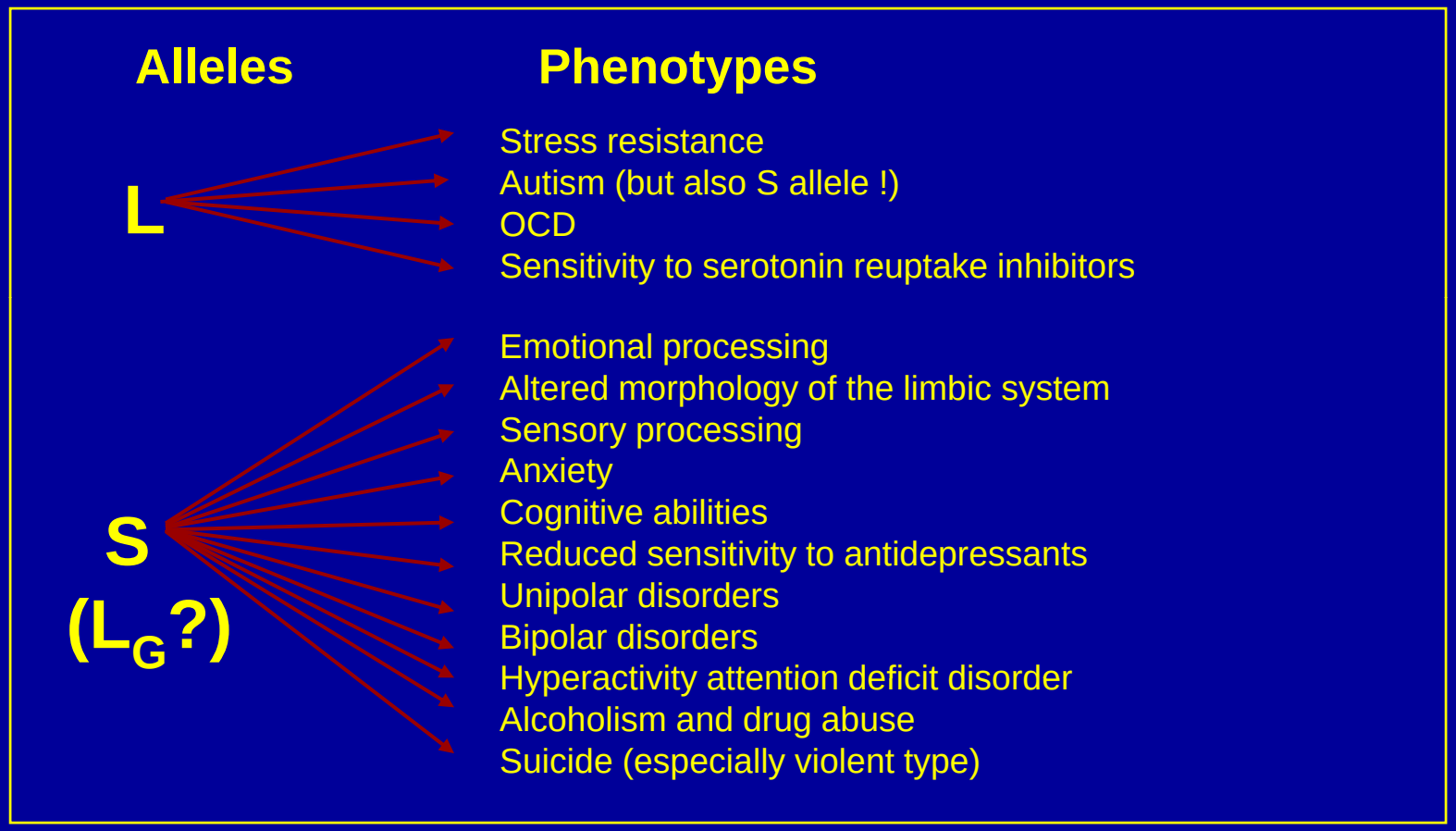
Mice with reduced SERT function may be an interesting model of brain disorders





Murphy and Lesch, 2008

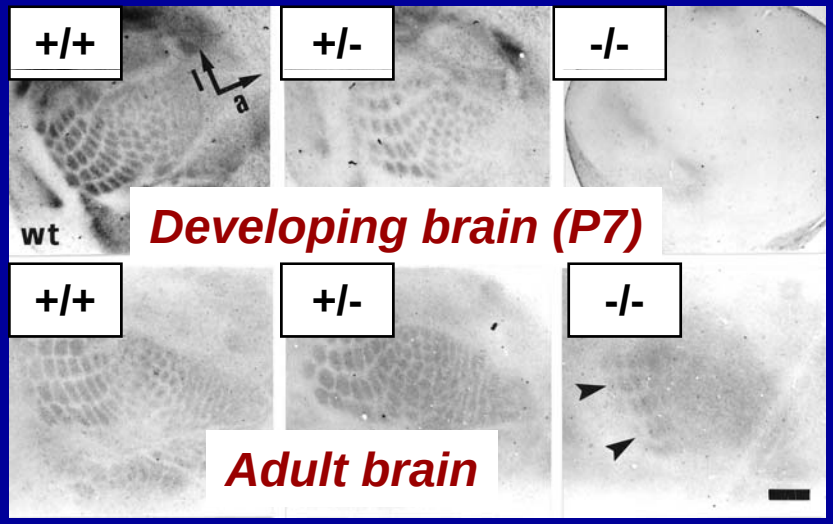
SERT alleles and psychiatric disorders



Kalueff et al., Trends Pharm Sci, 2007

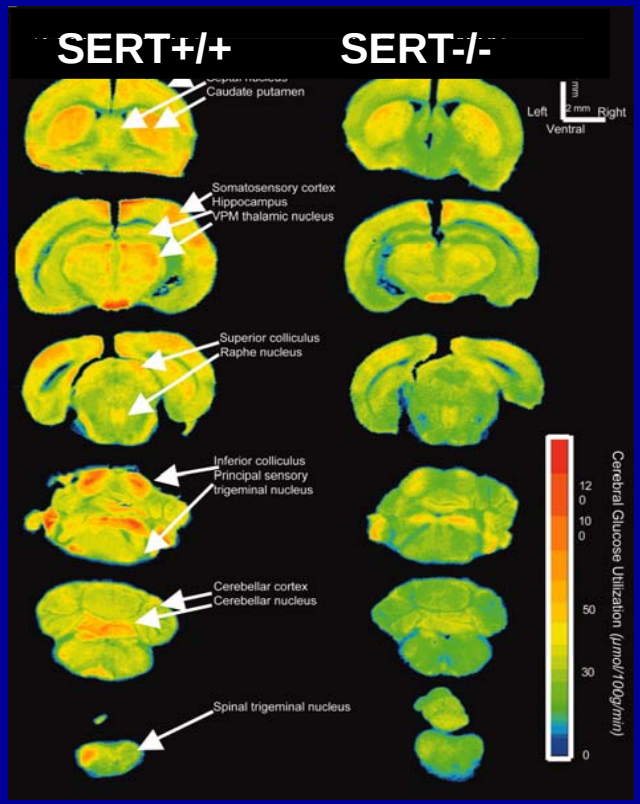
SERT-/- mice: developmental brain anomalies

Barrel pattern in the primary somatosensory cortex of SERT mice



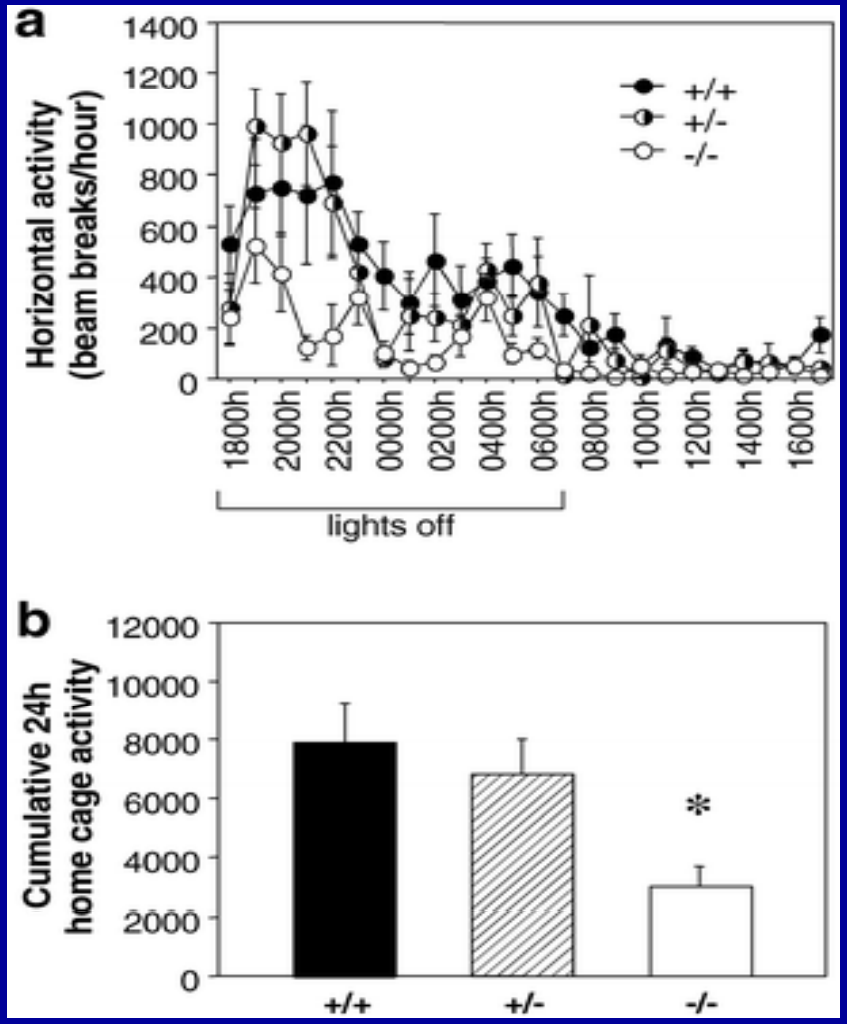
Persico et al., 2001, J. Neurosci.

Metabolic activation (glucose utilization) of whisker-to-somatosensory cortex pathway by whisker stimulation



Esaki et al., 2005, PNAS

General hypoactivity

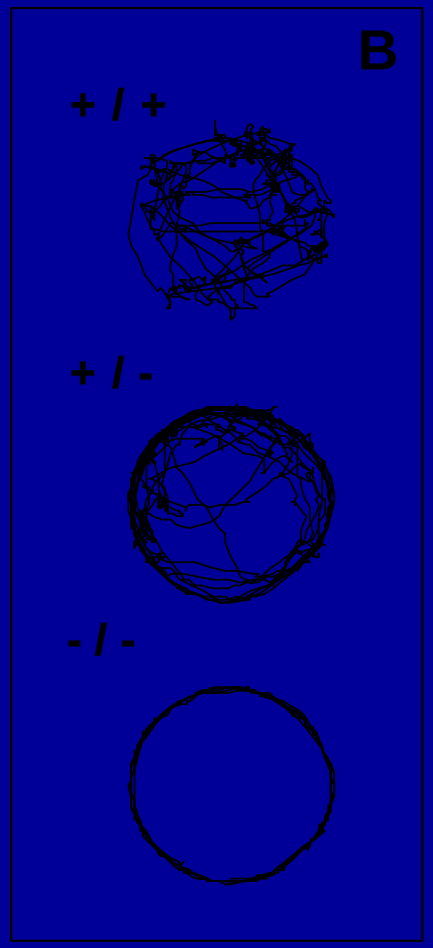


Dramatic reduction of 24-h motor activity in SERT-/- mice

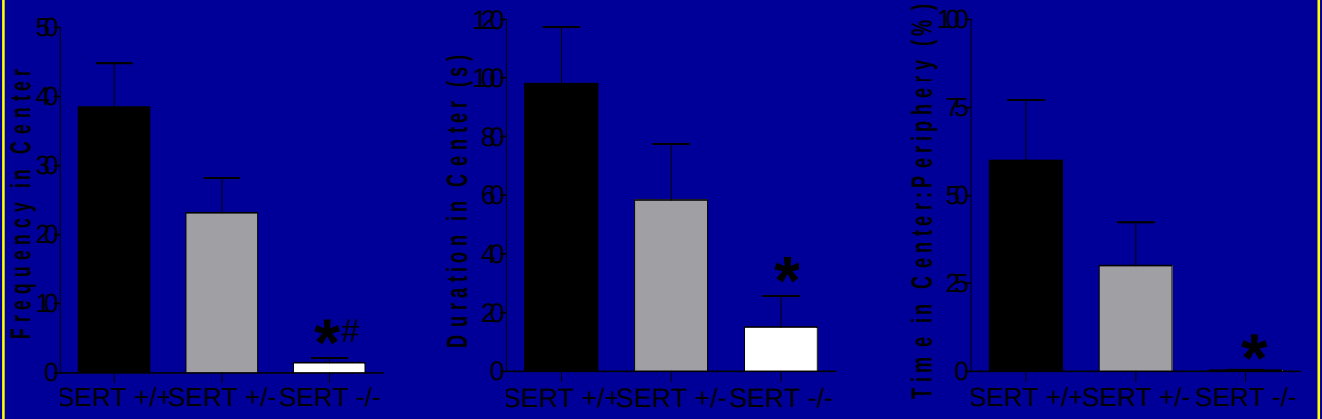
Holmes et al., 2002, Psychopharmacology

Anxiety

Increased thigmotaxis (peripheral vs. central activity) in SERT-/- mice



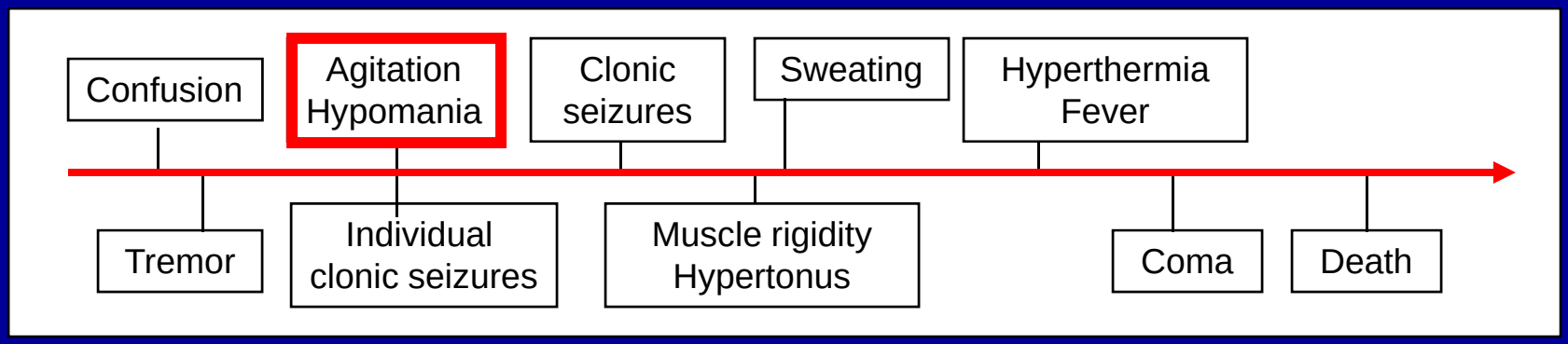
Reduced exploration activity in SERT-/- mice



Kalueff et al., Genes Brain Behav, 2007

Phenotyping serotonin syndrome (SS)

A serious disorder associated with increased serotonergic tone
On the rise globally, due to the growing intake of serotonergic drugs

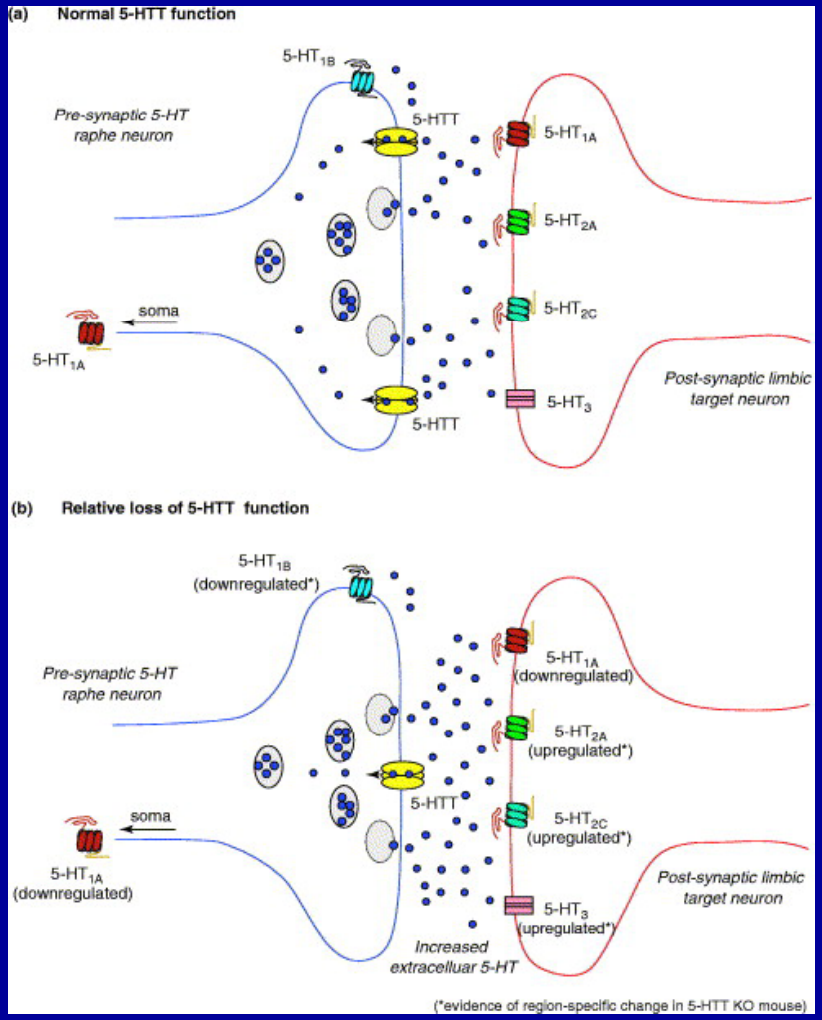


Animal SS-like behavior can be induced by various serotonergic drugs

Symptoms: Tremor, hind leg abduction, low/flat body position, Straub tail, head weaving, head twitches, hyperthermia, backward gait

The growing number of mutant or transgenic animals display various serotonergic abnormalities

The importance of modeling SS-related phenotypes in animals



SERT and SS ?

Normal brain serotonin
in SERT+/+ mice

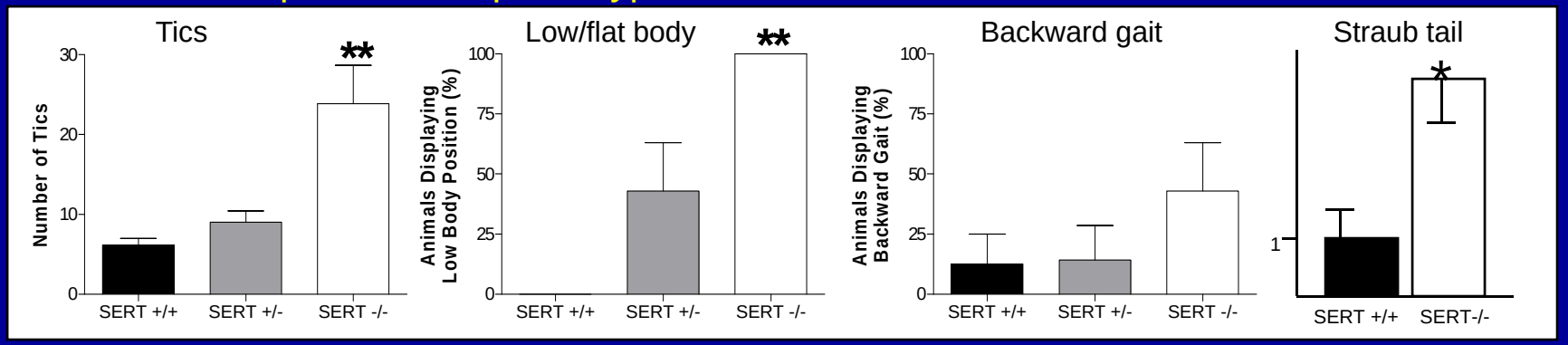
Excess of brain serotonin
in SERT-/- and SERT+/- mice

HYPOTHESIS: Mice with reduced SERT expression and function may be relevant to SS

Pro: 10-fold elevation of brain serotonin in SERT-/- mice (Li et al., 2003)

Genetic model of SS ?

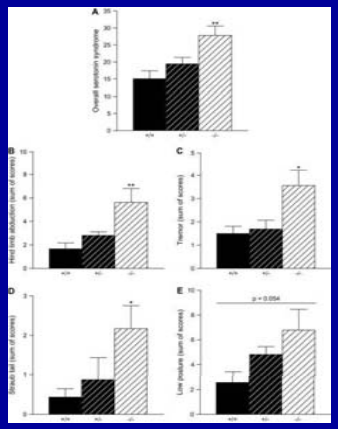
SERT-/- mice: spontaneous phenotype



Kalueff et al., 2007

Further pharmacological validation

MAO Inhibitor tranyl-cypromine



Fox et al., 2007, Neuropharmacology

SS-like behaviors	Spontaneous SERT-/-	Drug-evoked SERT-/-
• Muscle rigidity	+	+
• Tremor	+	+
• Forepaw treading		+
• Head weaving		+
• Myoclonus (seizures)		
• Ticing, back muscle contraction	+	+
• Flat/low body posture	+	+
• Incoordination	+	+
• Hind limb abduction	+	+
• Backward gait		+
• Hyperthermia	+	+
• Straub tail	+	+

Neurophenotype → Hypothesis → Model

SERT-/- mice: the first genetic animal model of SS

Kalueff et al., 2007

Aberrant social behaviors

Common symptom of many neuropsychiatric disorders:

- Anxiety, social anxiety
- Autism
- Williams syndrome
- Schizophrenia

Socio-cognitive dysfunctions:

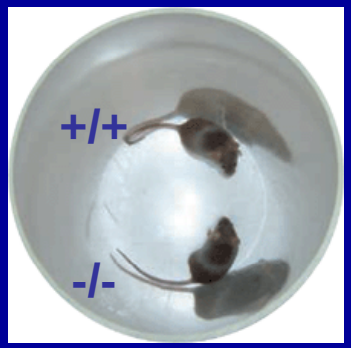
- Alzheimer's
- Parkinson's
- Stroke

The growing number of mutant or transgenic animals with abnormal social behaviors:

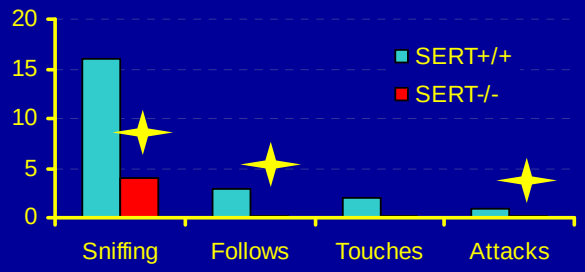
- >230 genotypes in the Mouse Genome Informatics database (Nov 2007)

The importance of examining social deficits in animal models of various brain disorders

Social confrontation test

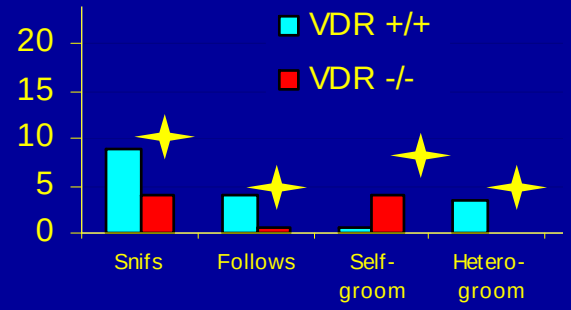


Social deficits in SERT-/- mice



Kalueff et al., Genes Brain Behav., 2007

Social deficits in VDR-/- mice



Kalueff et al., J. Neurosci. Res., 2006

Why Zebrafish?

- Experimental Accessibility
- Genetic Availability
- Optical Transparency
- Less Sentient
- Robustness of phenotype

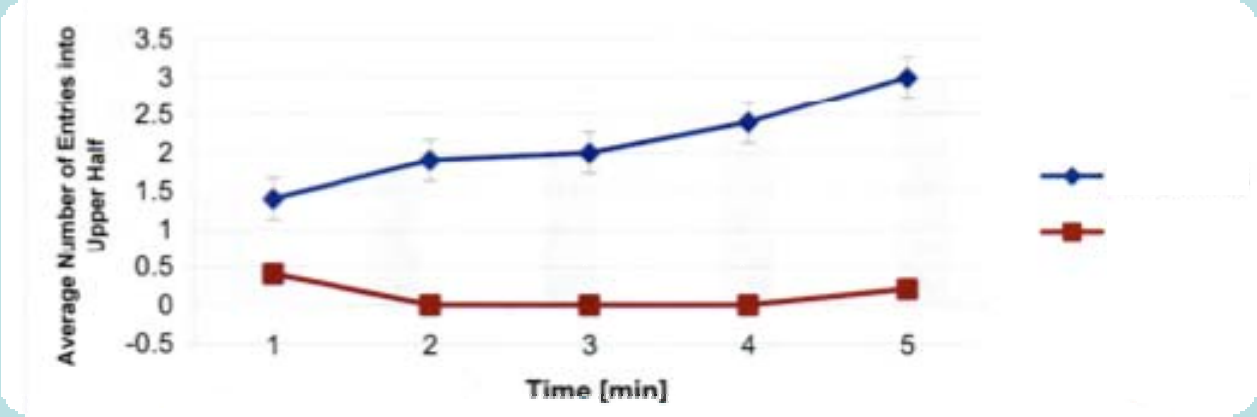
Paradigms and endpoints

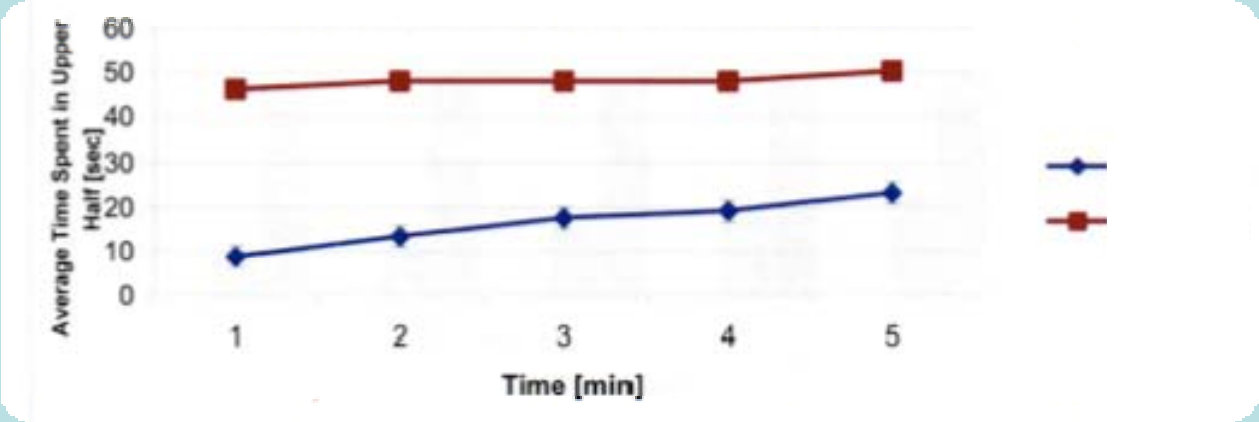
- Novel Tank test
  - Latency to upper half
  - Transitions to upper half
  - Duration in upper half
  - Erratic movements
  - Freezing bouts
  - Duration frozen

6 min observation, per minute distribution recorded

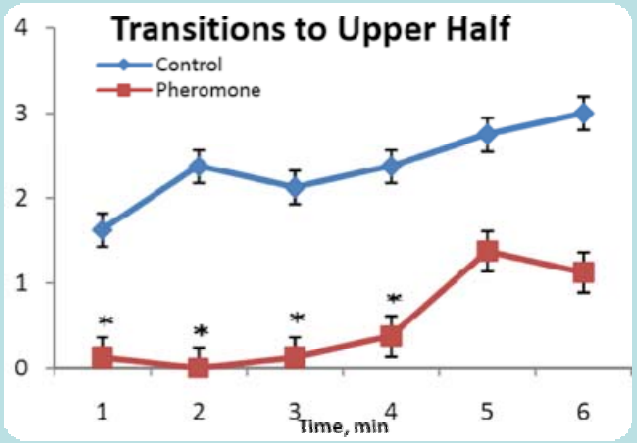
Acute Leaf Fish Exposure

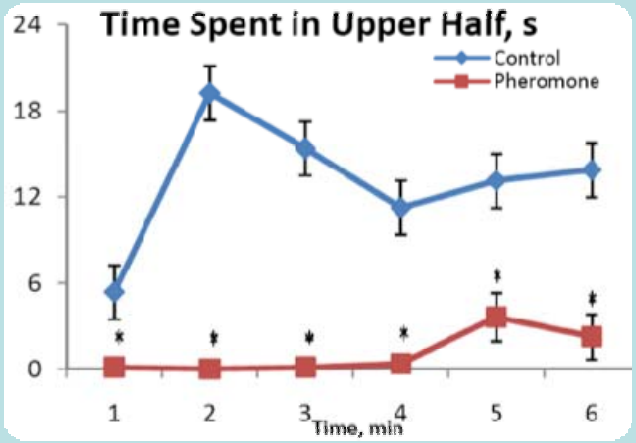
Acute Leaf Fish Exposure

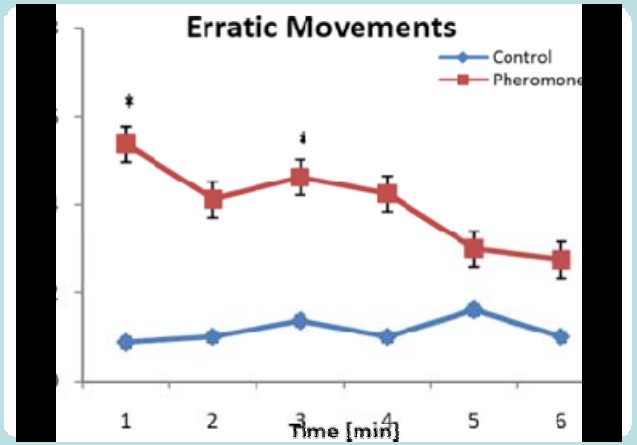


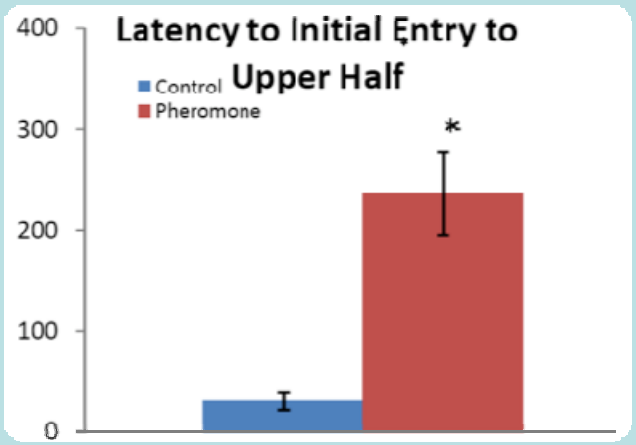


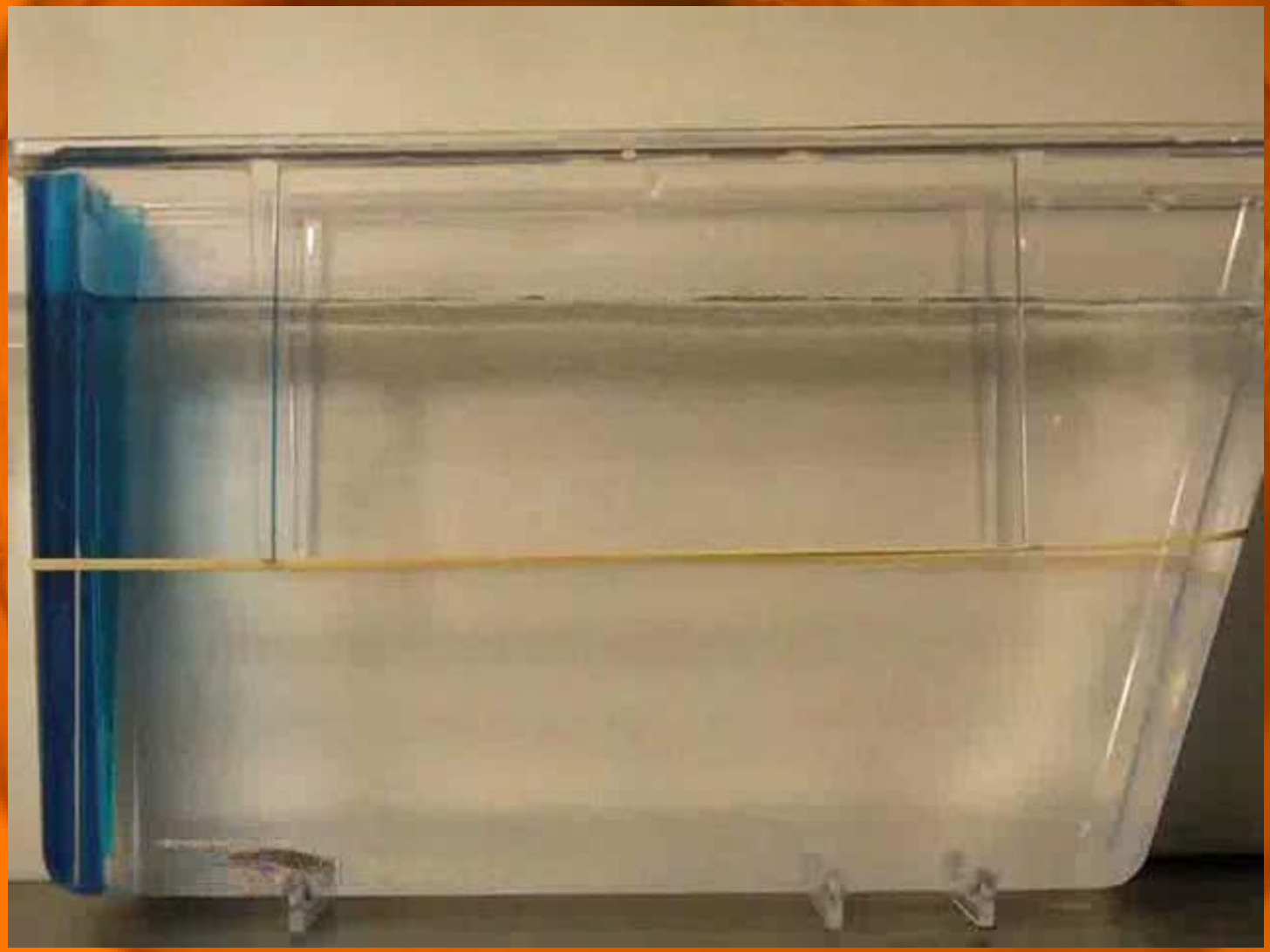
Alarm Pheromone Exposure



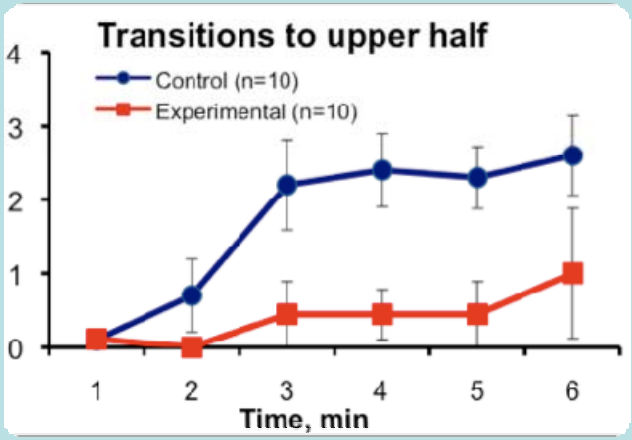


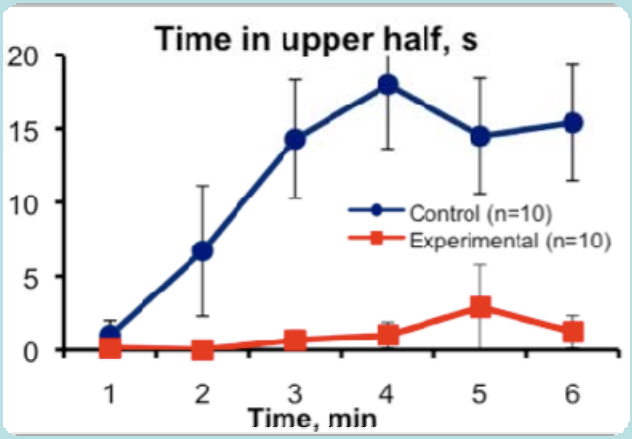


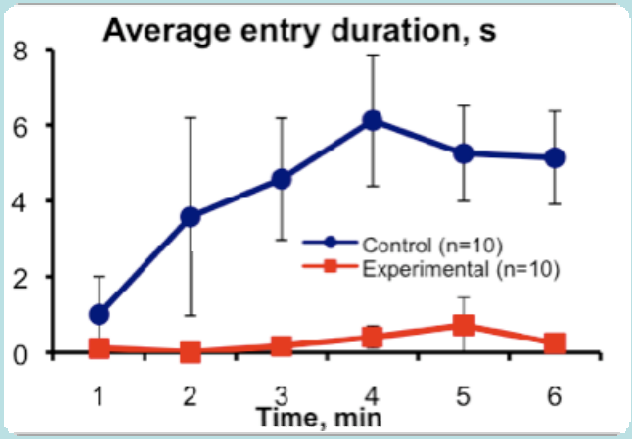


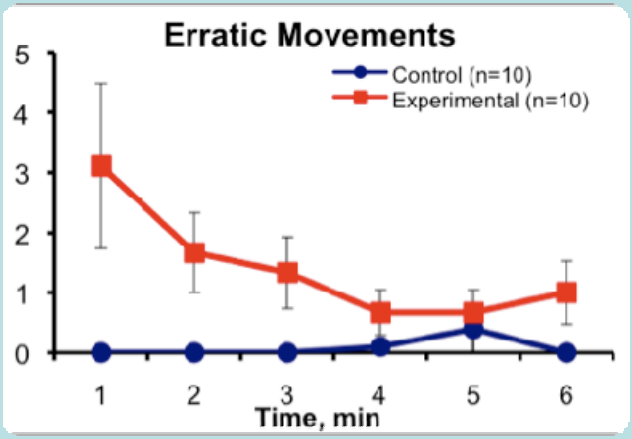


Diazepam Withdrawal

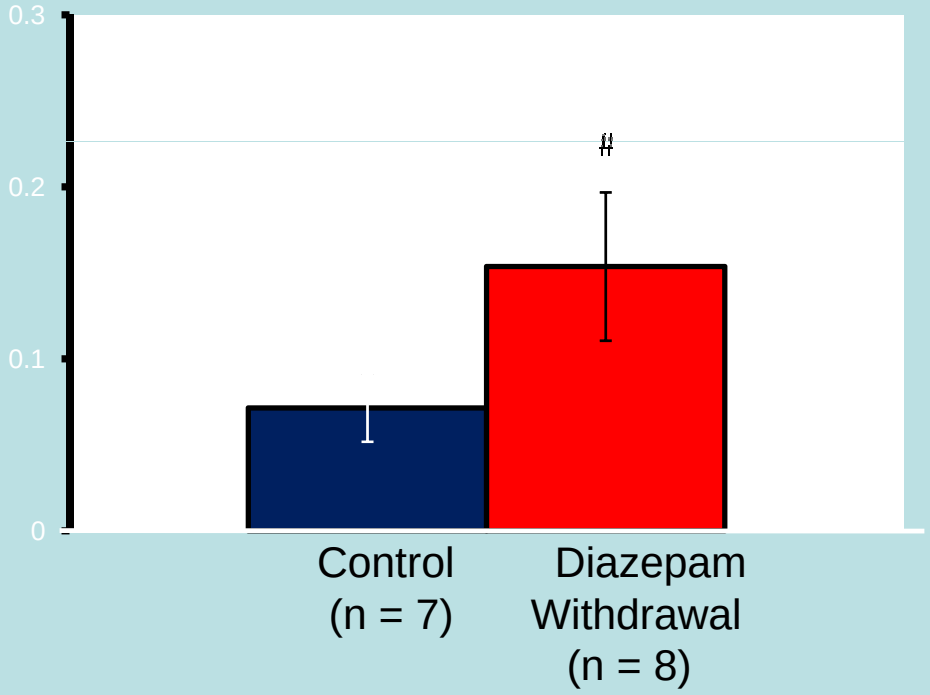




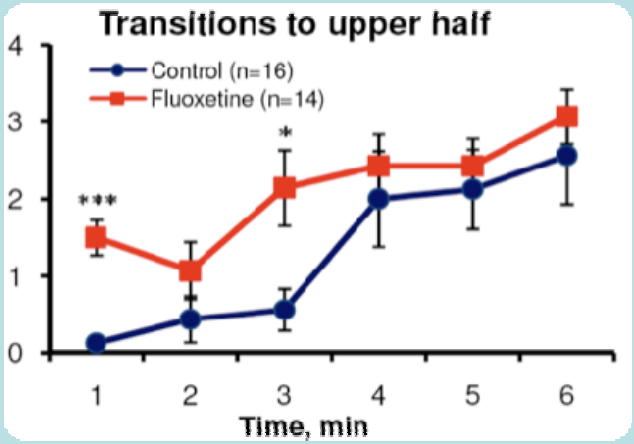


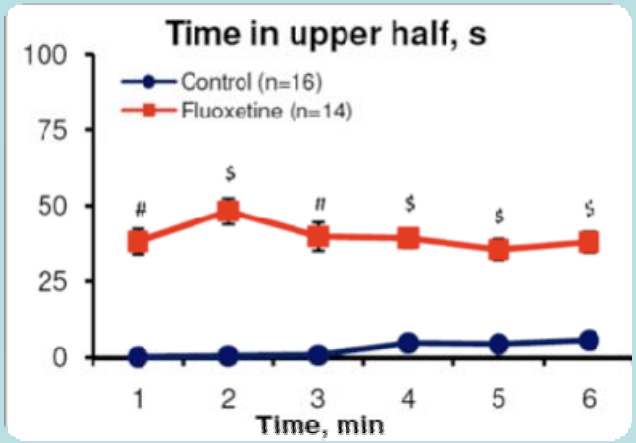


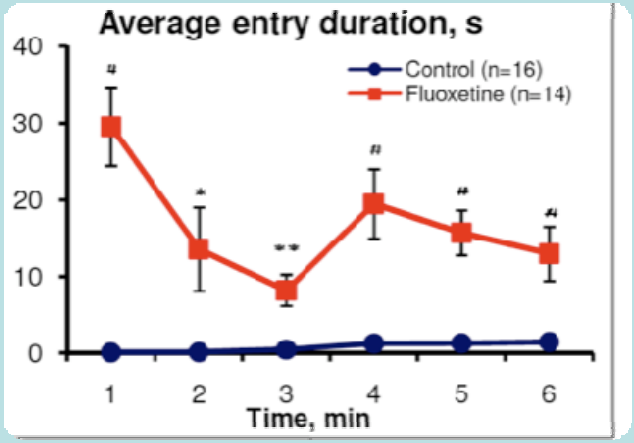
Total Cortisol

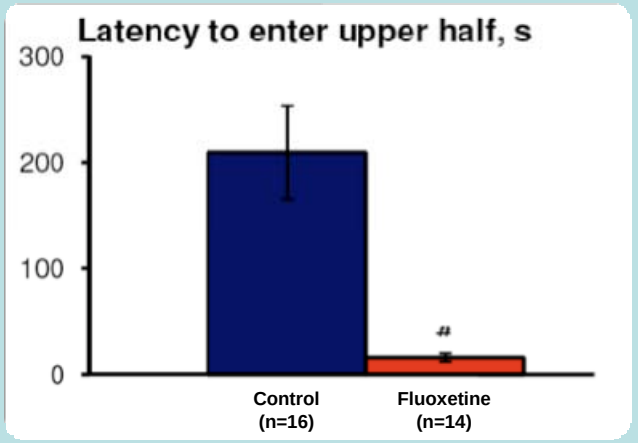


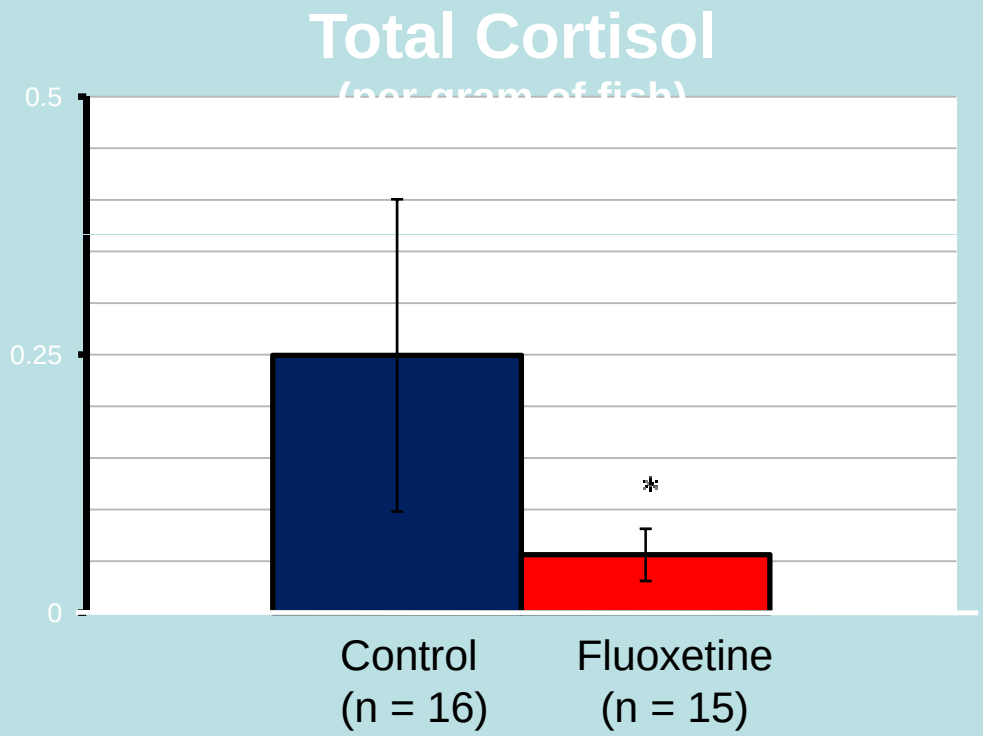
Chronic Fluoxetine Exposure










Total Cortisol
0.5
0.25
0
*
Control
(n = 16)
Fluoxetine
(n = 15)

Conclusions

- Object of stress research
- Correlation of behavioral and physiological responses
- Sensitive to pharmacological and stress manipulations
- Very robust, clear-cut phenotype

Conclusions

- Yes, we can!..

… use animals to model human brain disorders,

… even those traditionally considered to be very complex or too “human” (e.g., autism)

… behind every phenotype is a gene, or molecule, or group of genes and molecules

Thanks to:

UTA
- Dr Anna Minasyan, PhD
- Tiina Keisala, MS

GU
- Carisa Bergner
- Ruper Egan

TU
- Peter Hart
- Jonathan Cachat
- Peter Canavello

Qs:
www.kaluefflab.com