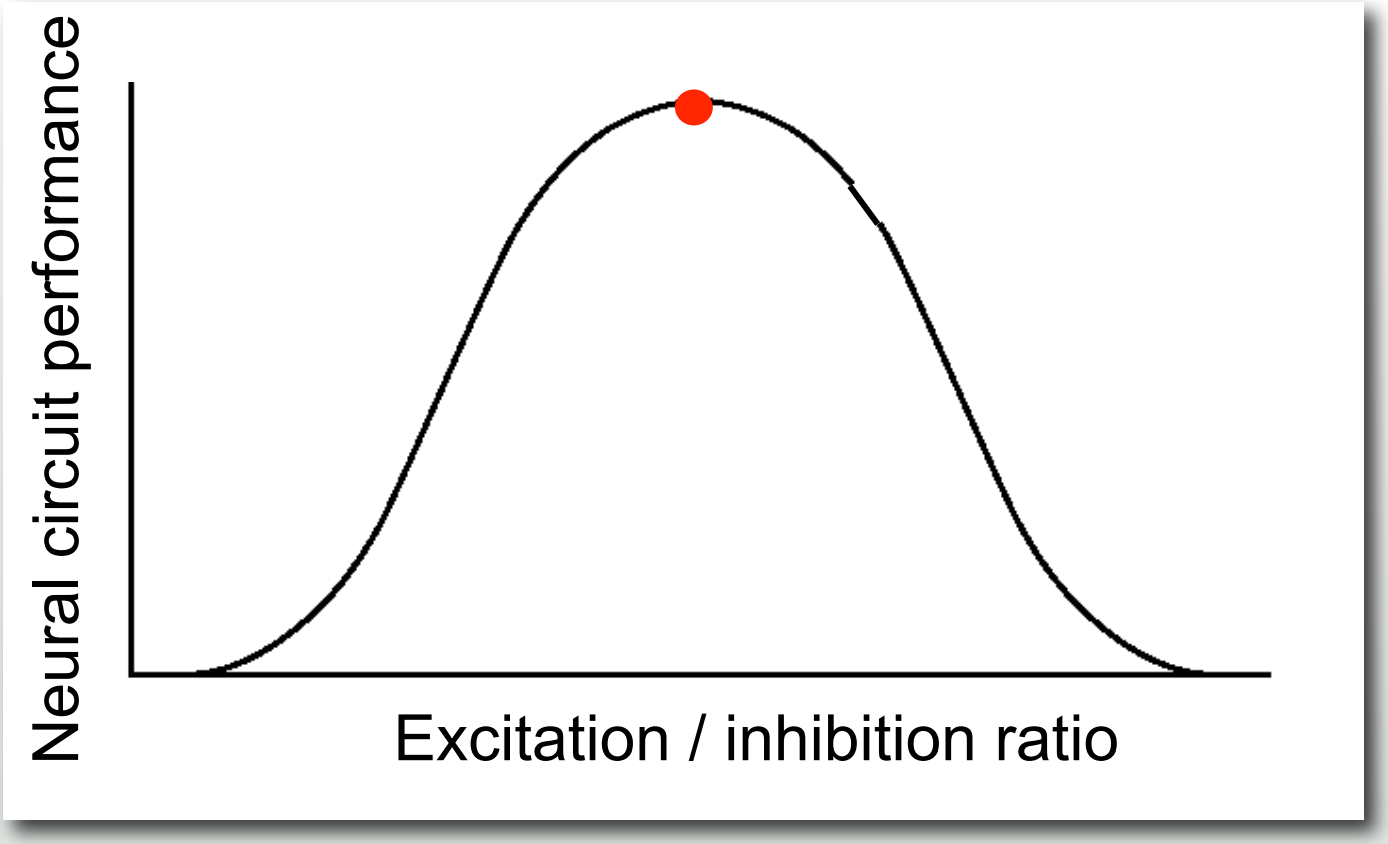
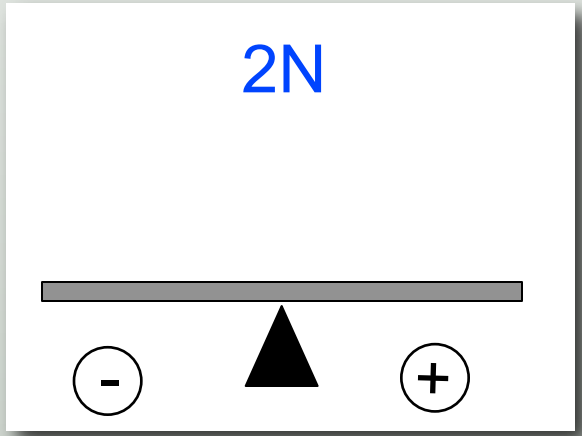
Excessive inhibitory tone also suppresses learning and memory function in Down Syndrome.

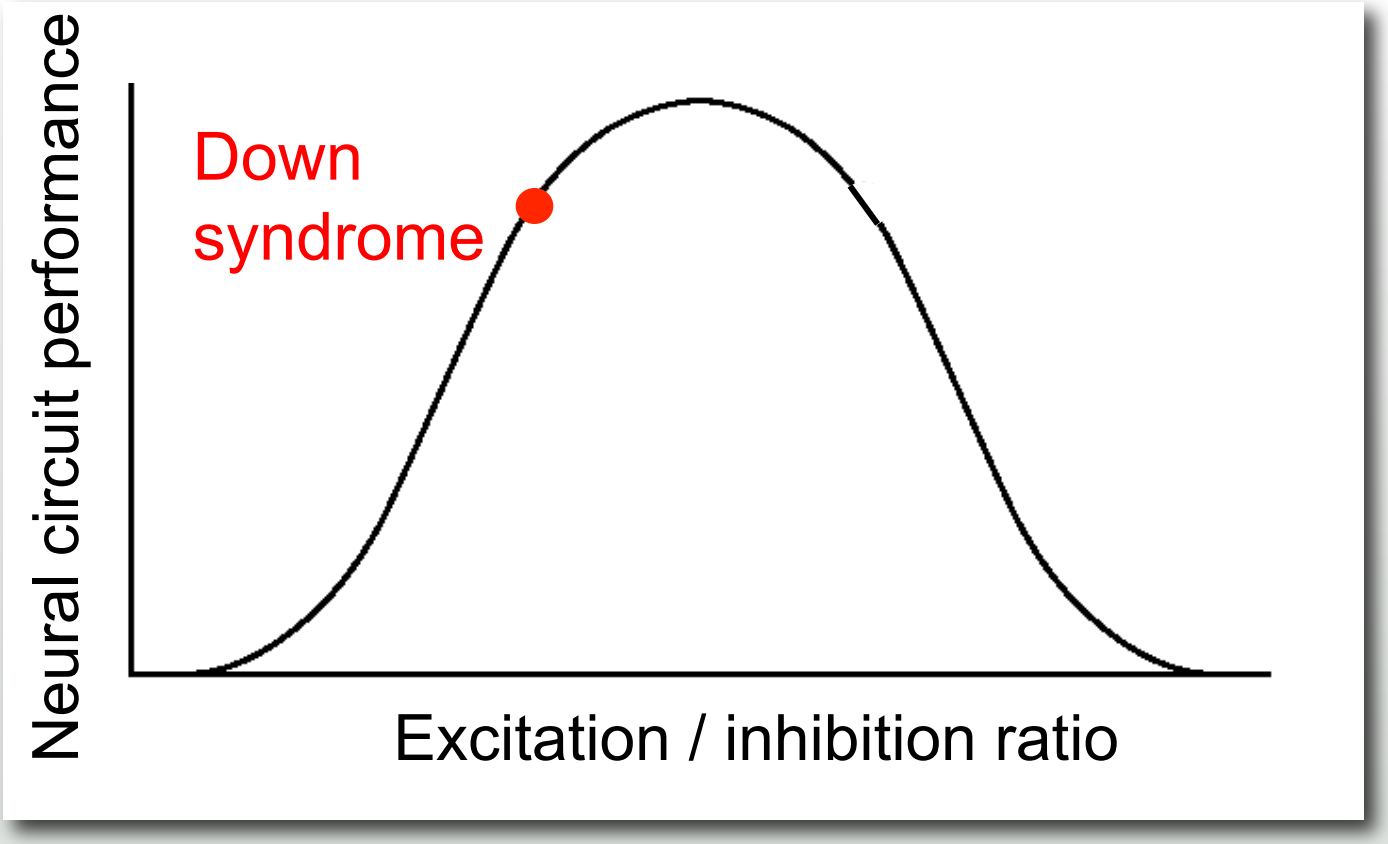
Central hypothesis

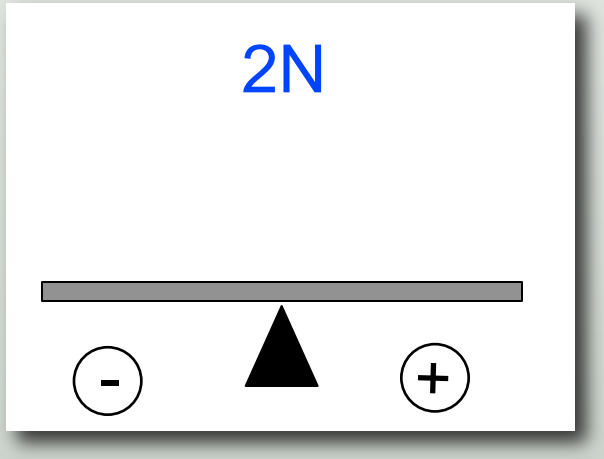
Excessive inhibition of critical circuits contributes to reduced cognitive function in Down syndrome.

This imbalance blocks learning and may be fixed with drugs


Neural circuit performance
Excitation / inhibition ratio


2N
-
+


Down
syndrome
Neural circuit performance
Excitation / inhibition ratio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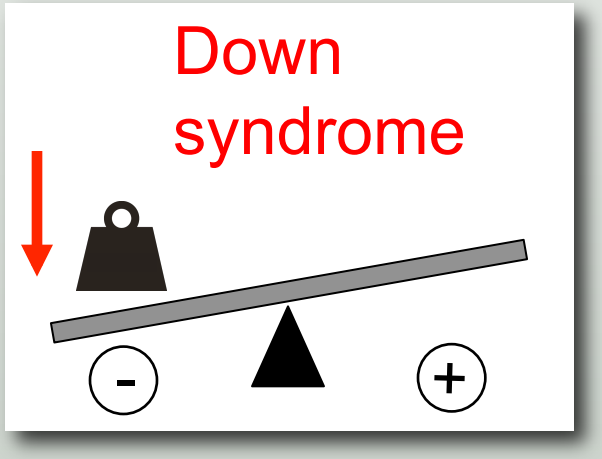
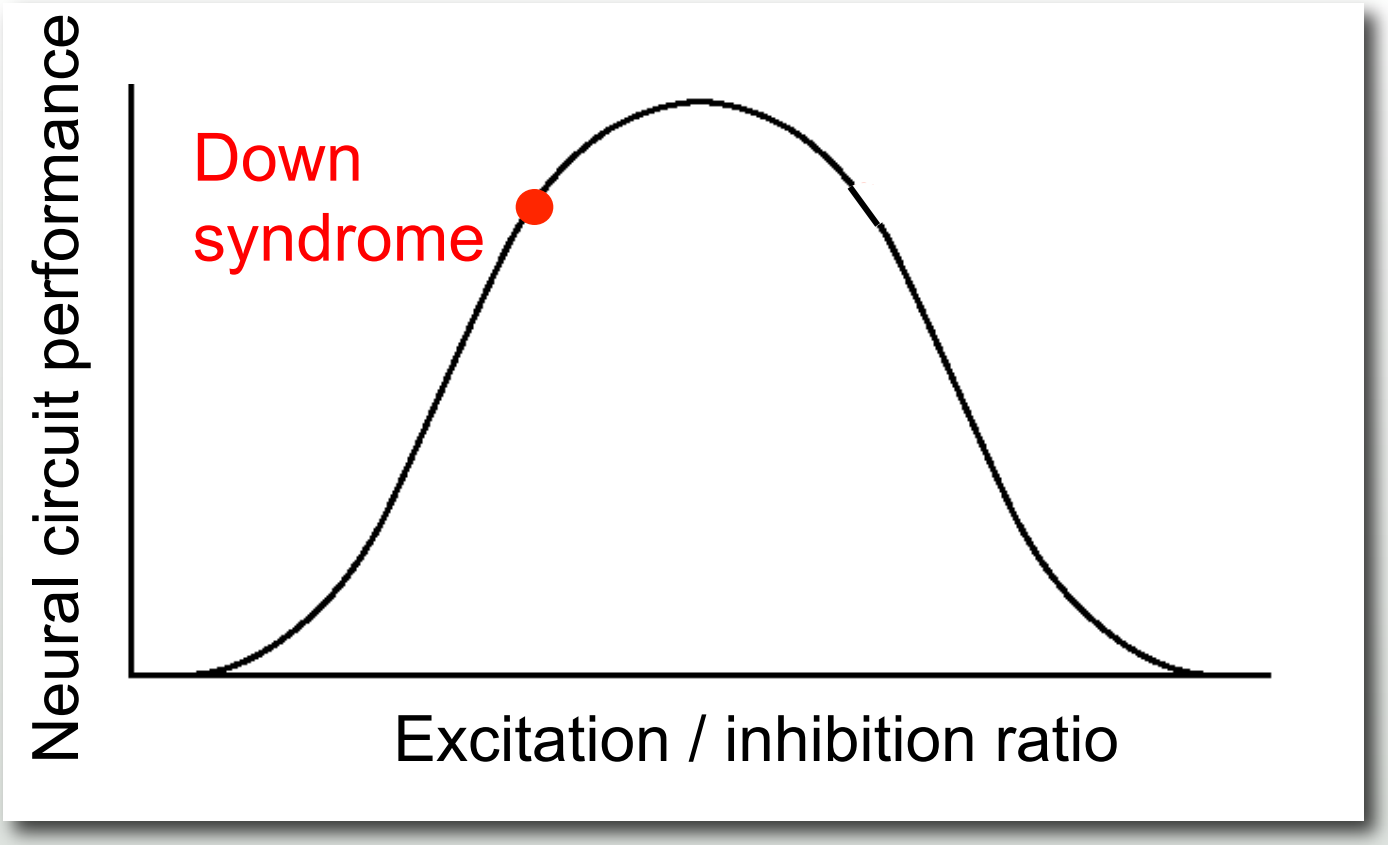
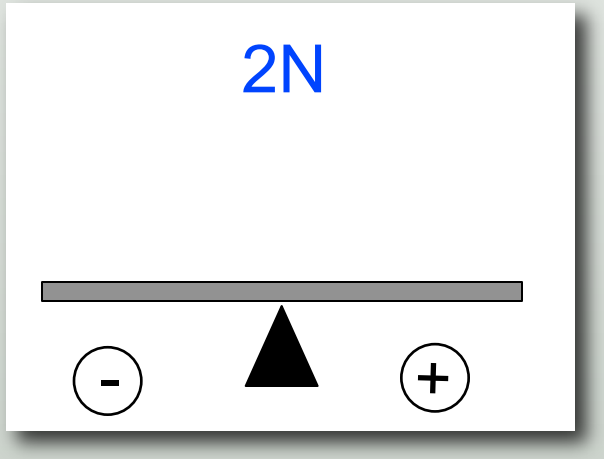
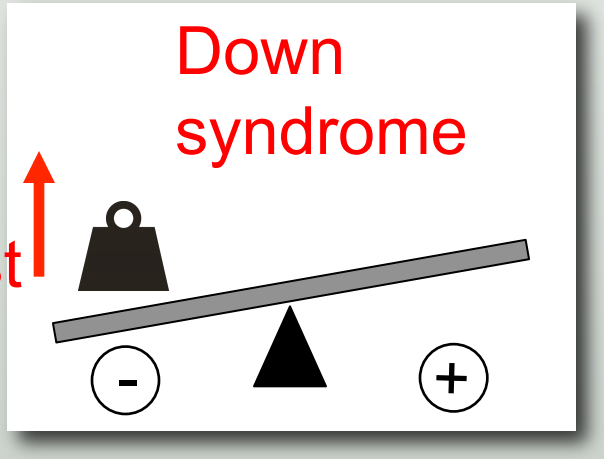
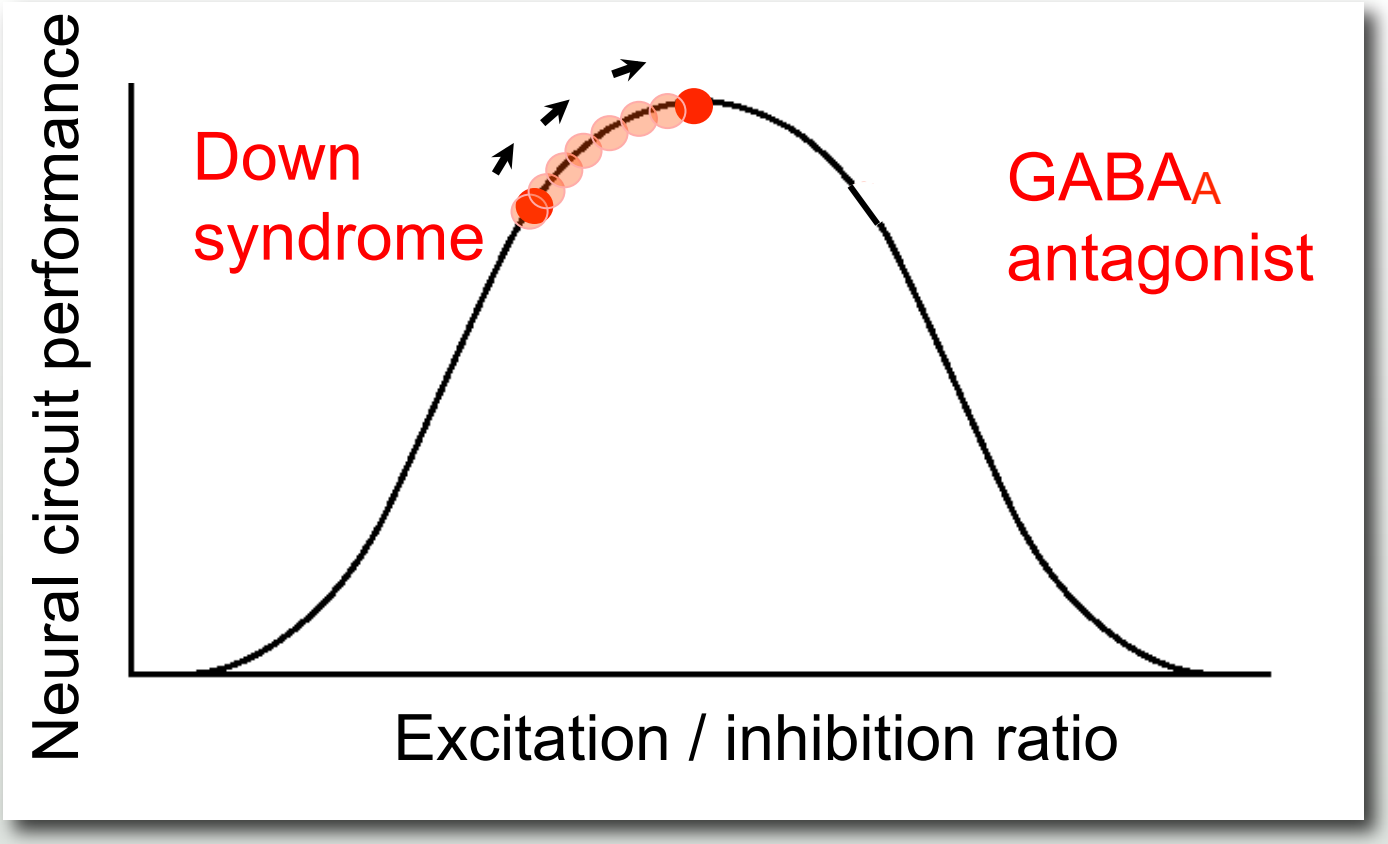

Down
syndrome
-
+

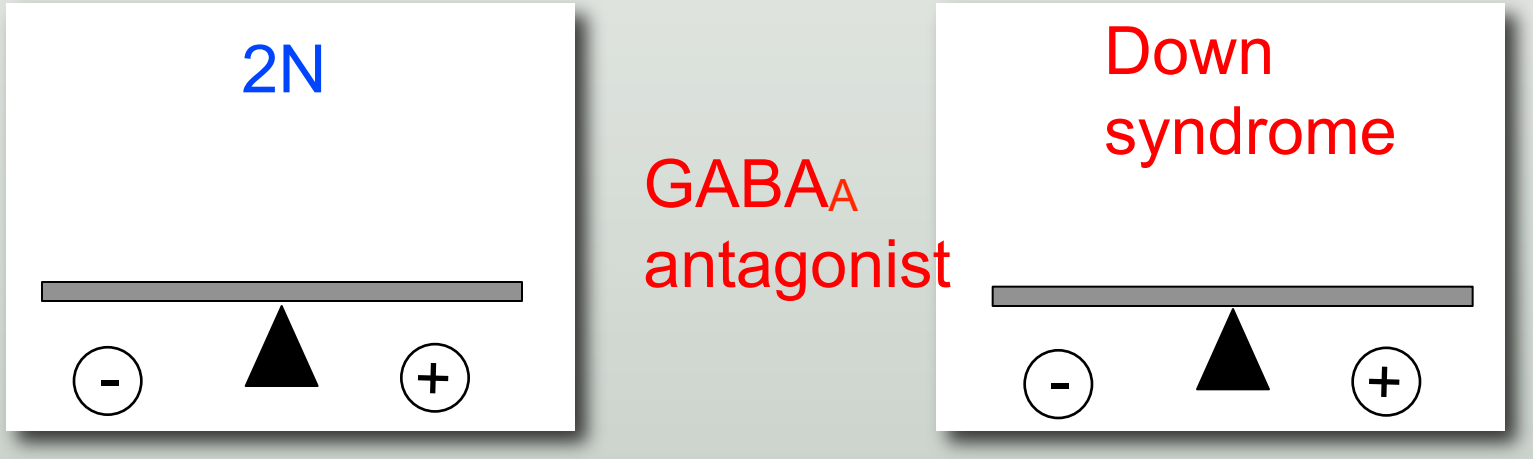




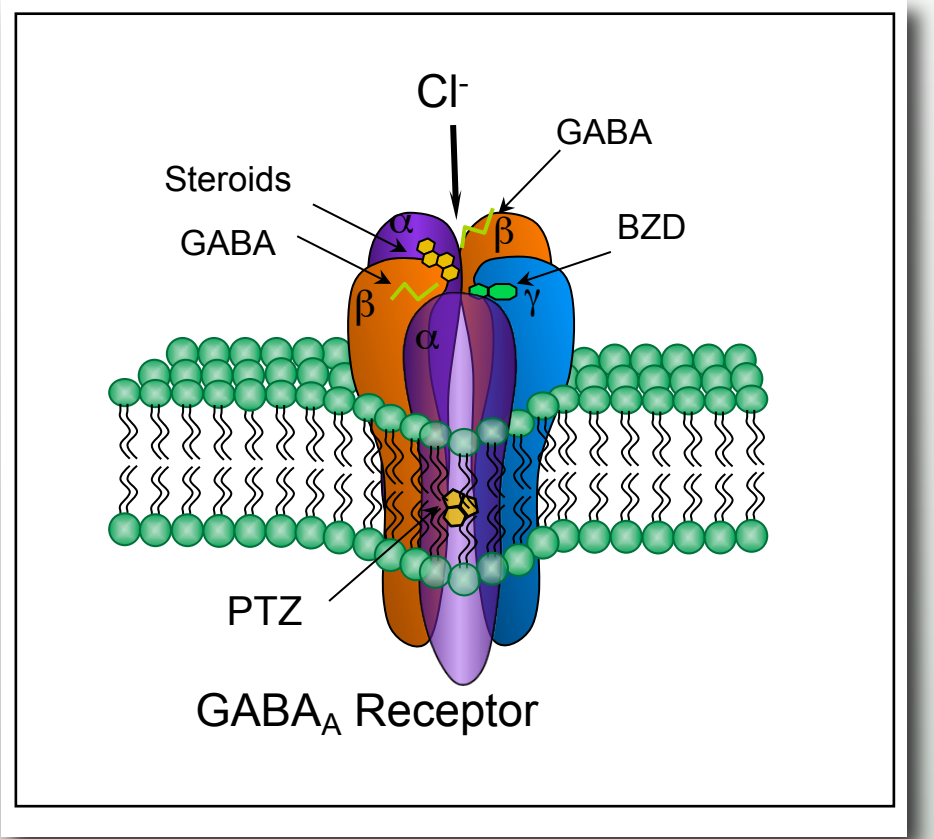
$GABA_A$
antagonist




Neural circuit performance
Down syndrome
GABA$_A$ antagonist
Excitation / inhibition ratio


2N
-
+
GABA$_A$ antagonist
Down syndrome
-
+

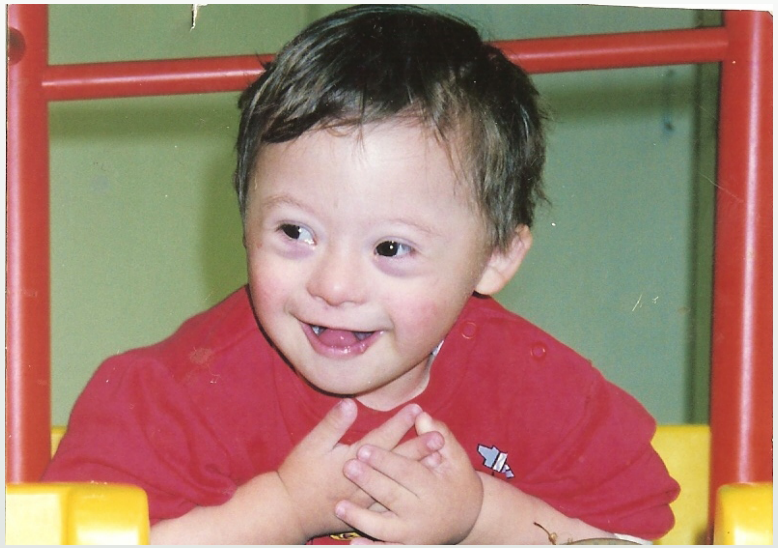
The $GABA_A$ receptor mediates inhibition and has a rich pharmacology

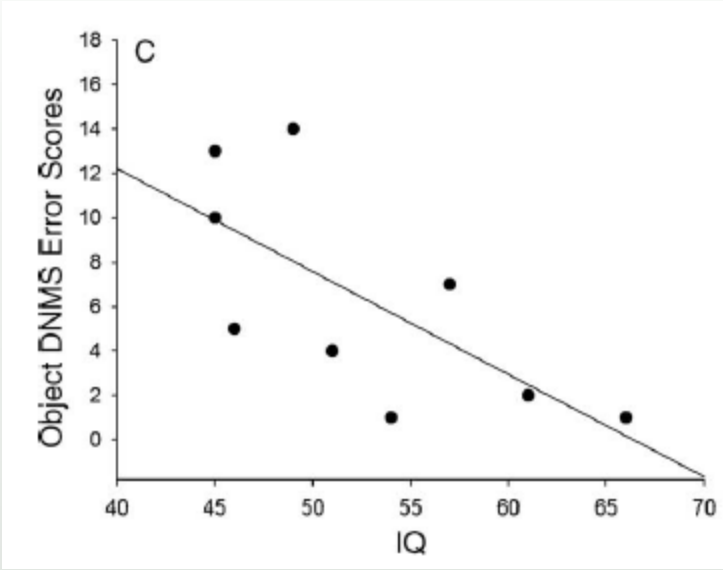


$GABA_A$ Receptor Antagonists Tested and Shown to be Efficacious

- Picrotoxin:
  - Pros: Potent compound (IC50 1uM), excellent bioavailability
  - Cons: narrow therapeutic window
- Bilobalide:
  - Pros: Potent compound (IC50 2uM), excellent bioavailability, good therapeutic window
  - Cons: currently available in plant extract only (Gingko Biloba), difficult synthesis.
- Pentylenetetrazole:
  - Pros: Excellent pharmacokinetic values, oral delivery, excellent bioavailability, good therapeutic window, long history in humans
  - Cons: Currently not approved by FDA
- Alpha5 inverse agonist:
  - Pros: Excellent pharmacokinetic values, oral delivery, excellent bioavailability, good therapeutic window. Specific for a subset of hippocampal $GABA_A$ receptors.
  - Cons: currently not approved by FDA
- Flumazenil:
  - Pros: Excellent pharmacokinetic values, good therapeutic window, approved by FDA for the treatment of benzodiazepine overdose
  - Cons: poor oral bioavailability, acute IV administration

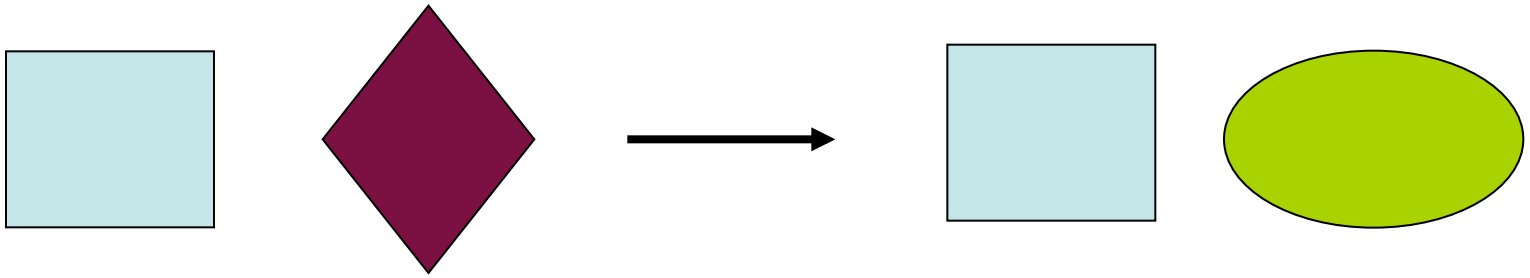
Object recognition in children with Down syndrome





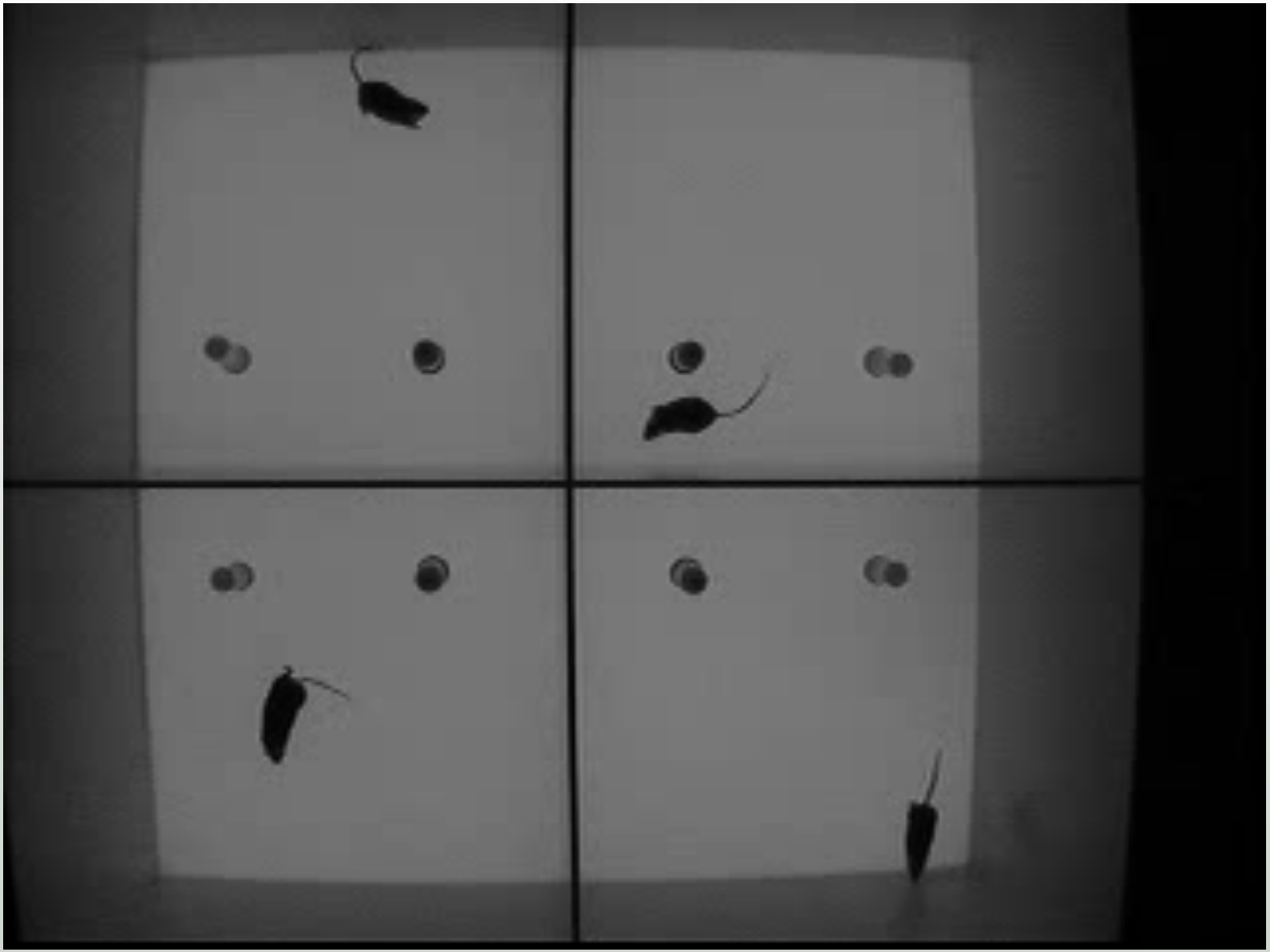
Novel Object Recognition Game

- **Mice are curious:** mice explore new environments and remember what they learn.
- **Learning and memory games for mice:** Games allow us to measure what a mouse learns and how long it remembers. Do therapies improve performance? Short term? Long term?
- **Game rules:**
  - Place mouse in arena with 2 or 3 objects (toys).
  - Mouse explores the objects.
  - At a later time, mouse is placed back in the arena, but one object has been changed. Can it identify the novel object?

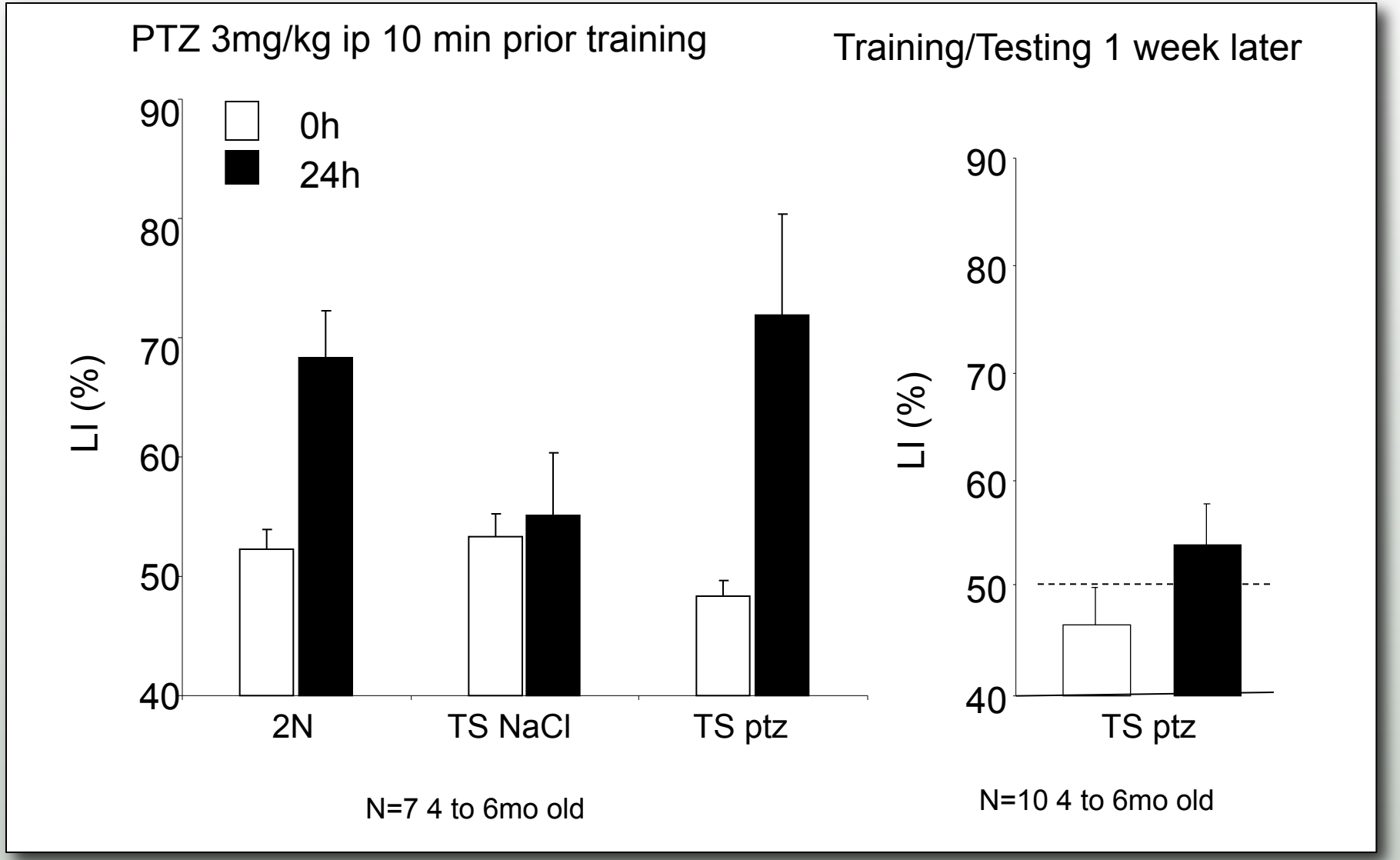


Two Different Familiar Objects **One Familiar Object + One Novel Object**

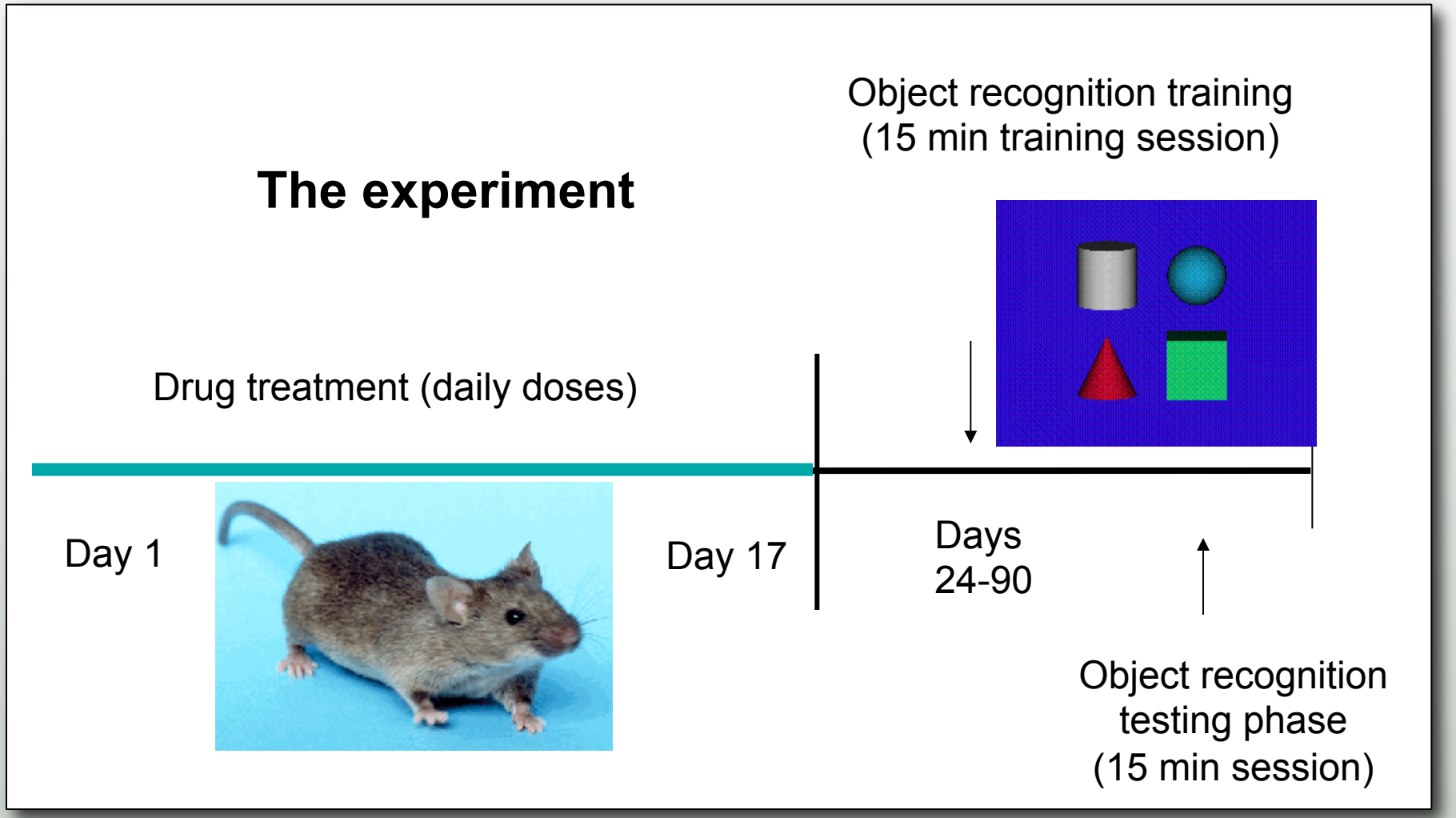
Playing the Game



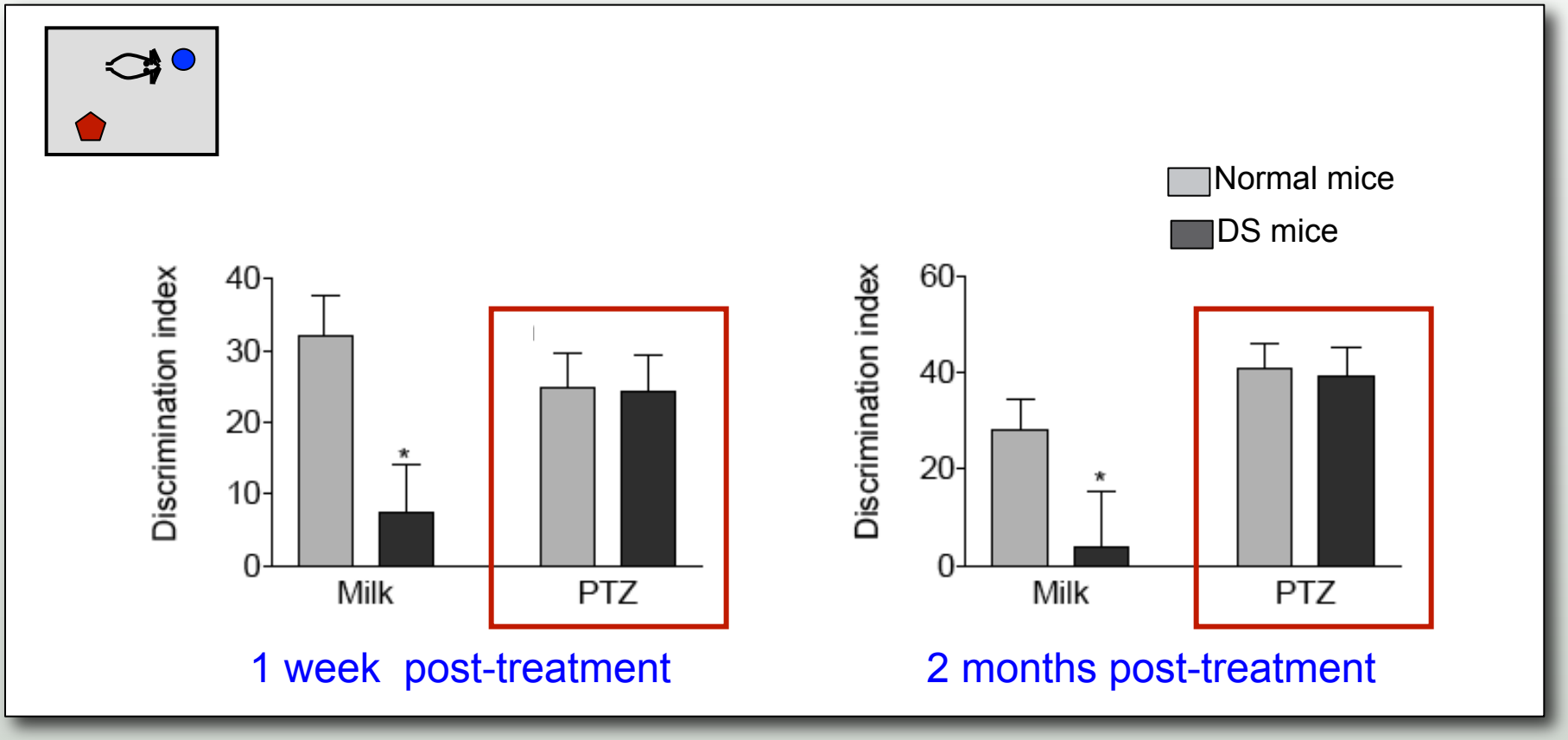
Single doses of GABA antagonist, Pentylenetetrazole improves learning in TS mice, but effects do not last.



It gets better! Short-term chronic treatment with PTZ at low doses induces a very long lasting improvement in learning and memory.



Memory improvement is long-lasting after daily pentylenetetrazole (PTZ) dose



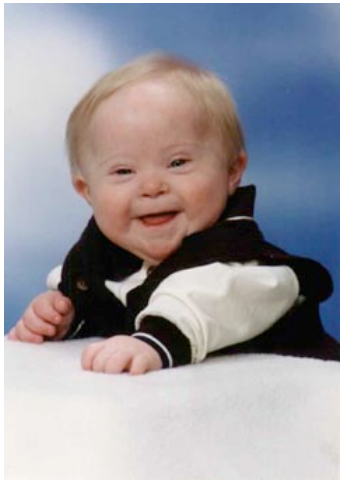
Fernandez & Garner, 2007

Goals of recent studies

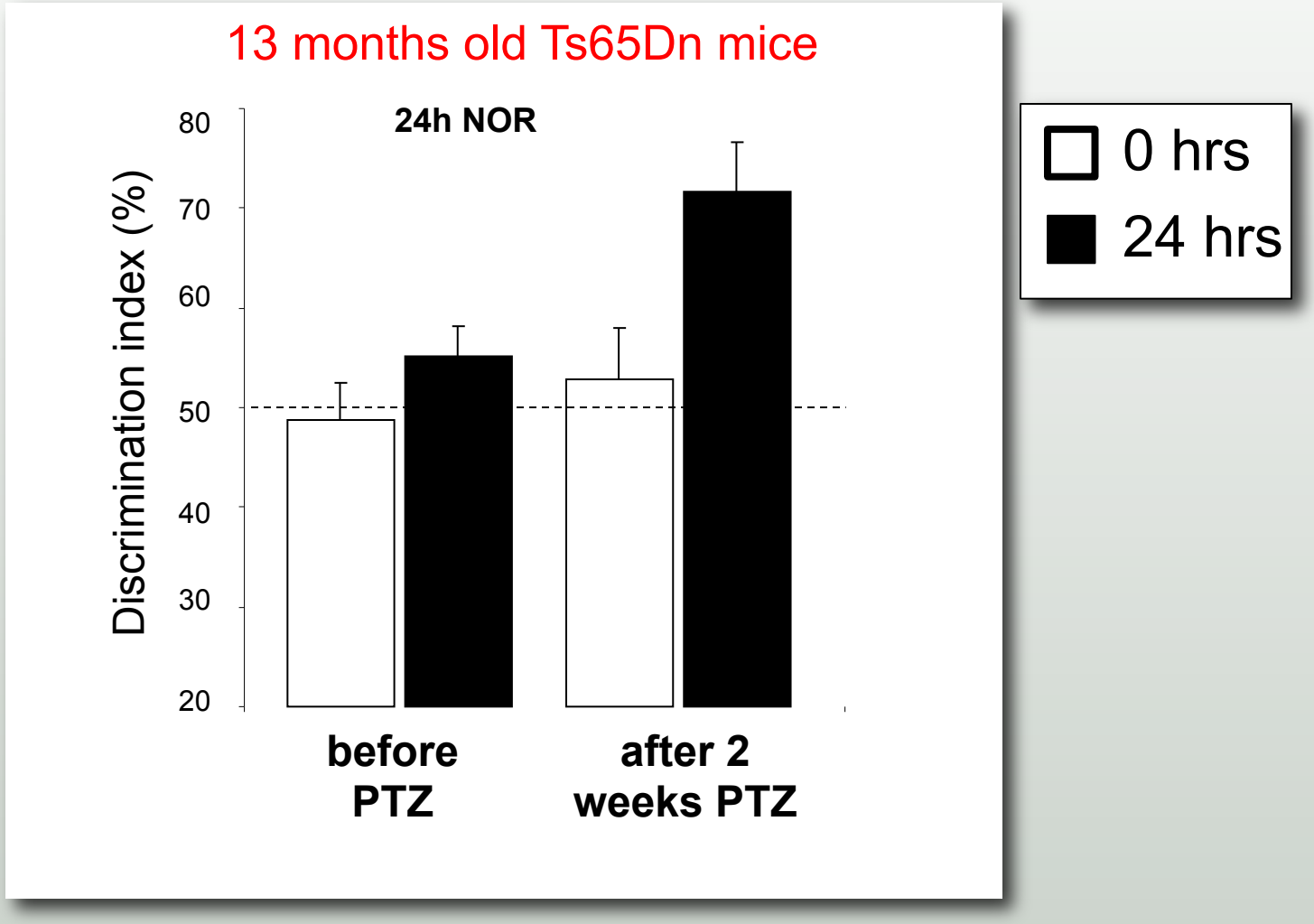
- Preclinical development of PTZ
  – Dose, safety, age, pharmacokinetics

- Investigation of mechanism of drug therapy
  – Dosing strategy
  – Developing New Biometrics
  – Understand Mechanism

- Initiate Clinical Trials
  – FDA approval to move forward
  – Design clinical trial

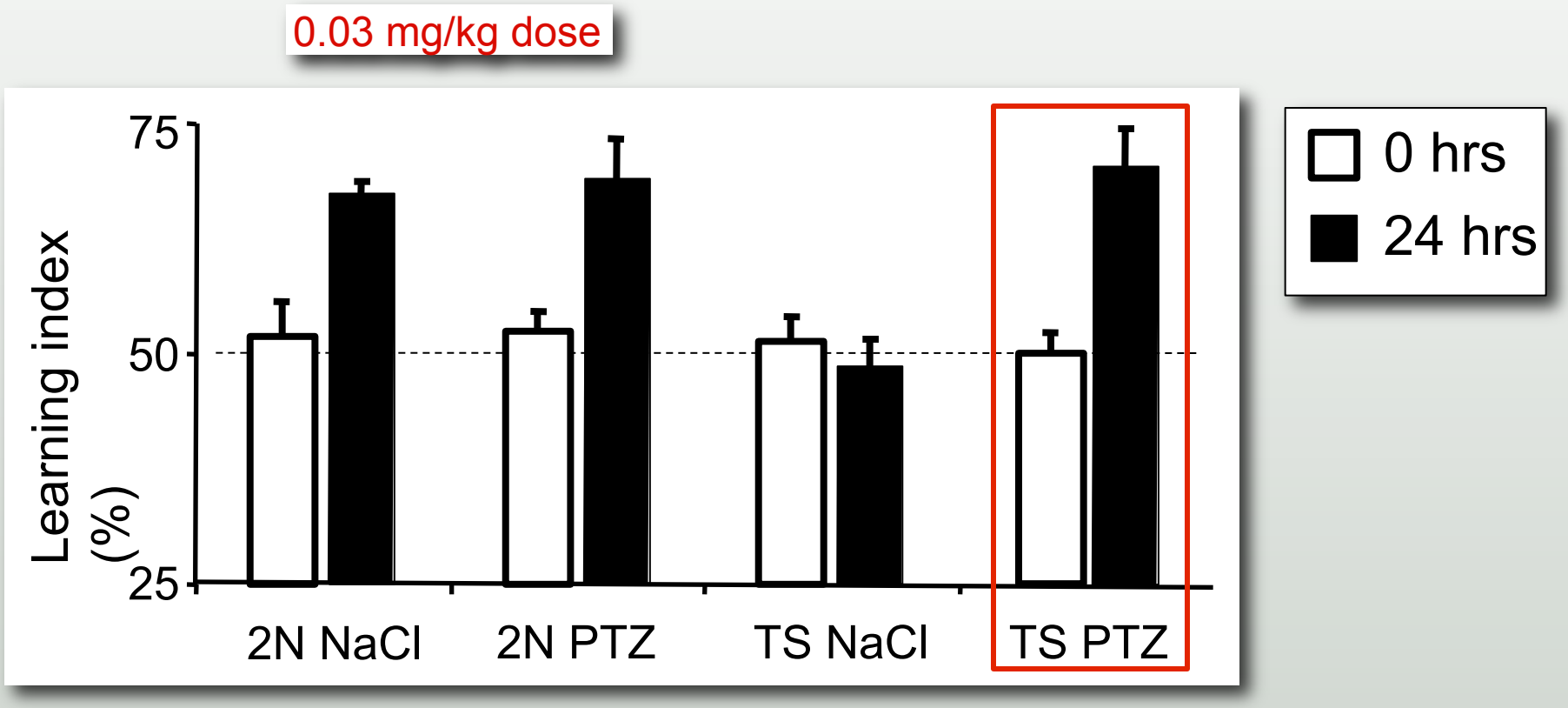


Is PTZ effective in young (2m) and older mice?



Colas & Chuluun

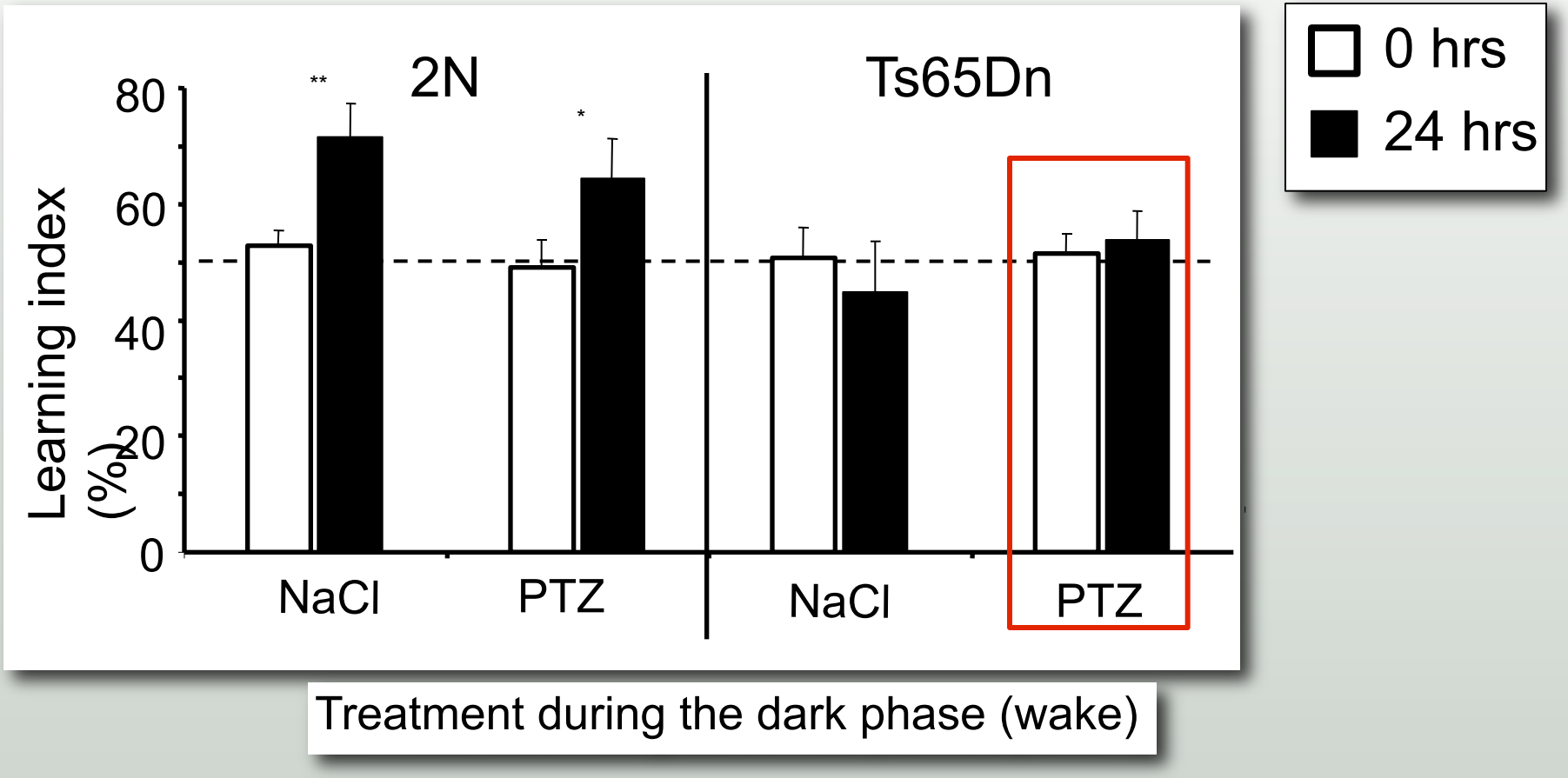
A **100 fold lower dose** of PTZ (0.03mg/kg once-a-day for two weeks) normalizes Long-term Memory in 3mo old Ts65DN mice



Conclusion: drug therapy is very safe.

Colas & Chuluun

$GABA_A$ receptor antagonist effects are circadian phase dependent

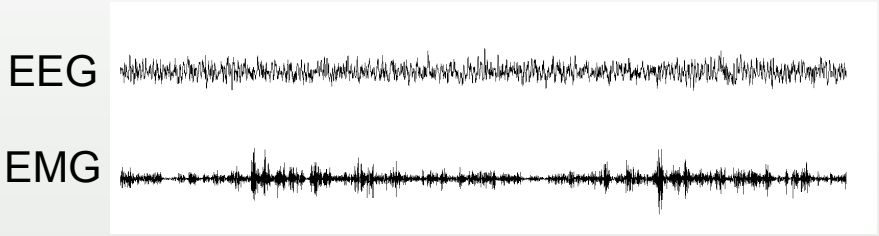


They are most affective during sleep

Colas & Chuluun

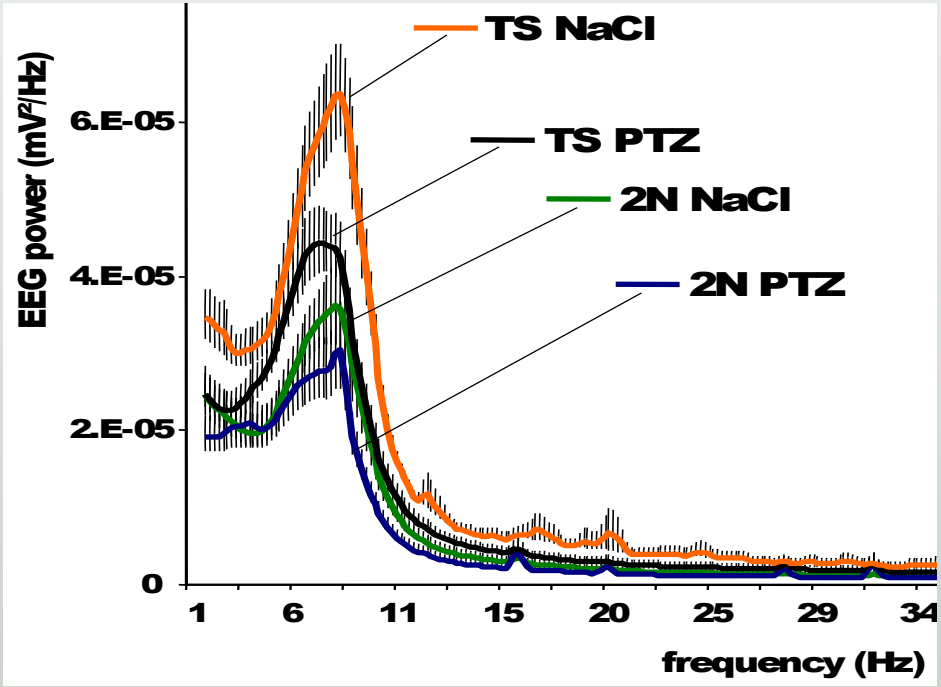
Learning and memory processes occur during sleep
Is sleep different in DS mice, and can it be improved?

We record the EEG and EMB of Ts mice



And, we find differences in comparison to wild-type mice that are partially remediated by PTZ treatment.

But, what do these differences mean?



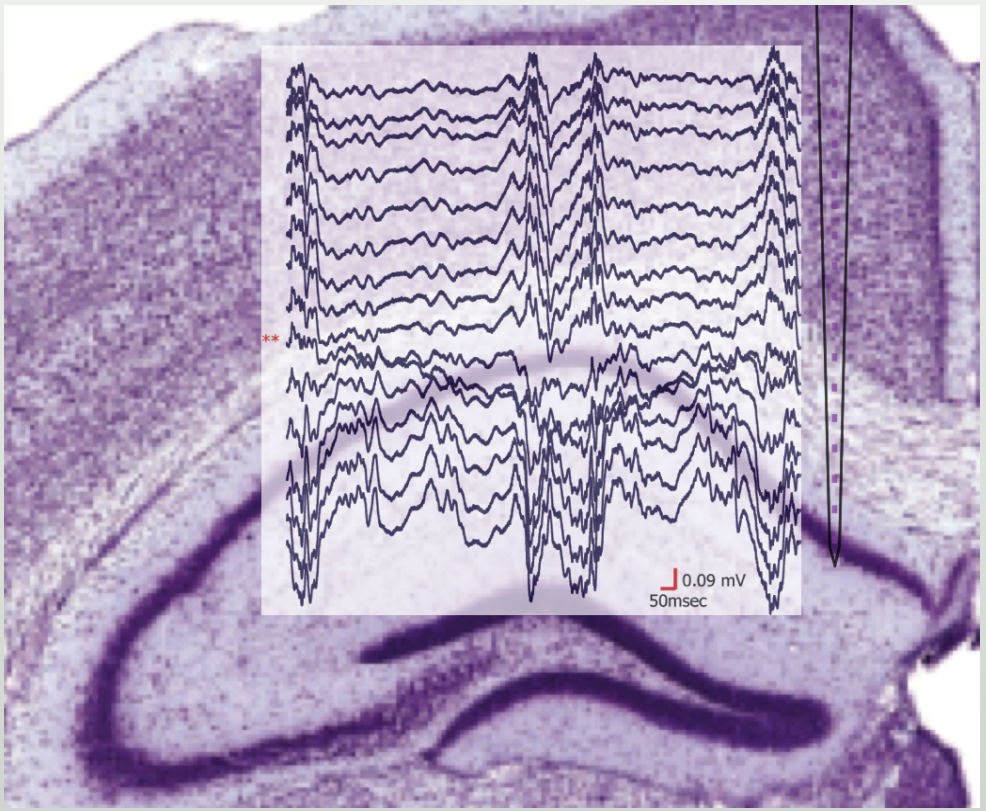
One current goal is to understand how the brain processes of memory consolidation during sleep are altered in DS, and then to fix them.

During wake, information is acquired through our senses and is placed in short term storage.

During sleep, some of the information in short term storage is transferred to long term storage.

These events are organized by specific brain electrical oscillations that we can measure.

Which ones are abnormal in DS, and how can we fix them?



Summary of PTZ characteristics

Pharmacokinetics of PTZ are consistent with expectation of short half-life (~1-2 hours).

Is effective at extremely low doses 0.03-3mg/kg

Long history of safe use in humans

- Chronic: 6-8 mg/kg orally, three-four times daily for weeks to 10 years. No epileptogenesis reported

Effective in young and aged animals

Time-of-day dosing influences effectiveness of therapy

GABA drugs act to normalize sleep architecture

Conclusions

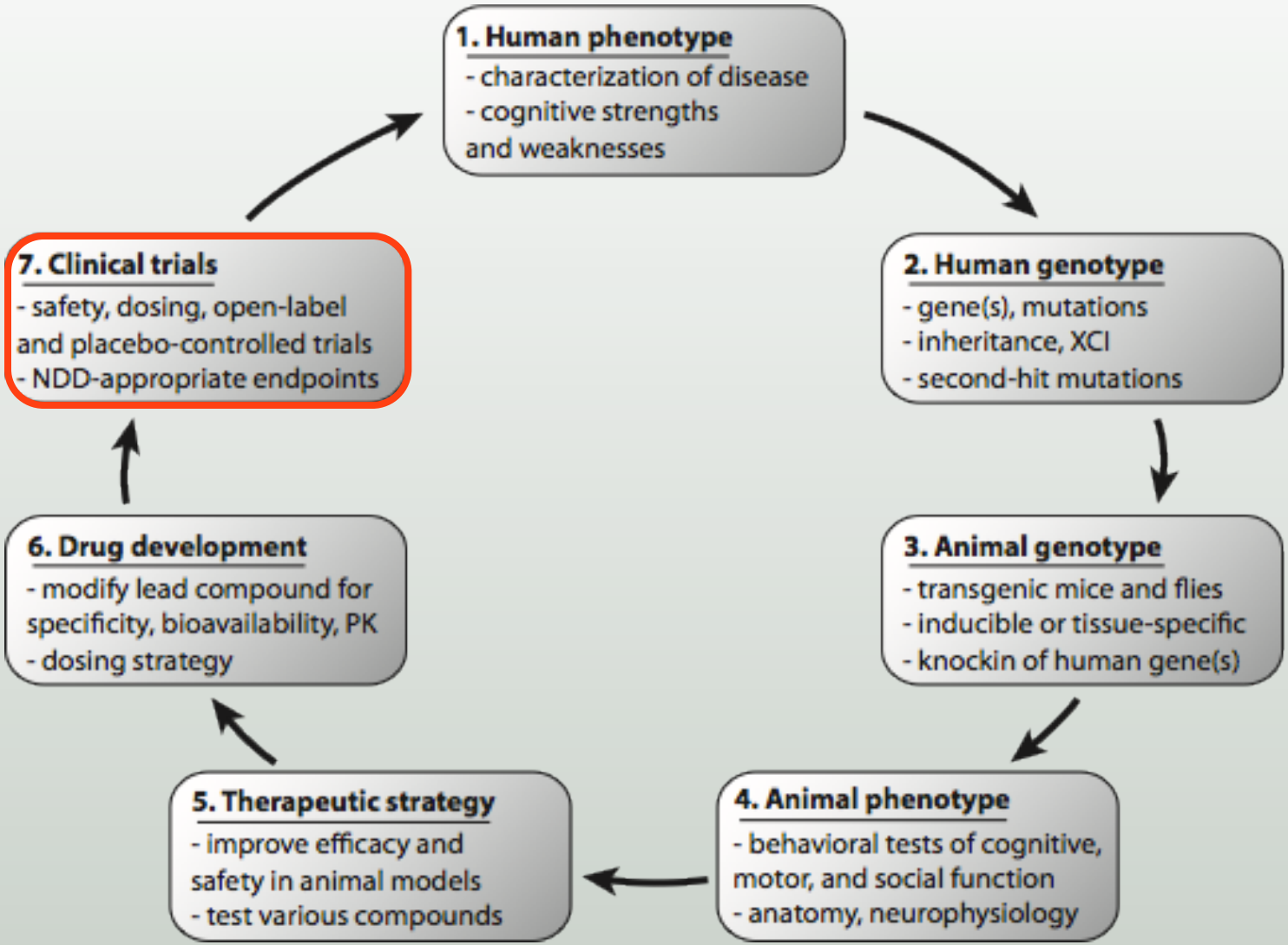
Over-inhibition contributes to memory deficits in Ts65Dn mice

$GABA_A$ antagonism with PTZ is a promising therapy

Other drugs could be effective or complementary

- Other $GABA_A$ drugs (e.g. flumazenil or alpha5IA's)
- L-DOPS or risperidone for ADHD-like behaviors
- Fluoxetine & NAC for hippocampal neurogenesis defects
- Rapamycin for over-activation of mTOR pathways

The Translational Cycle



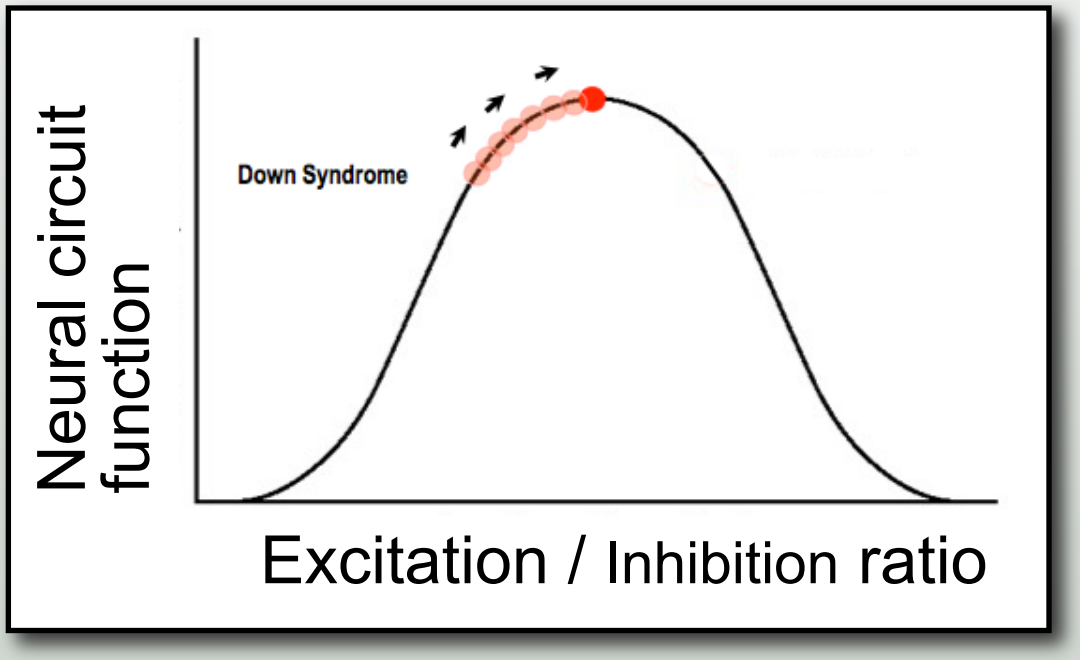
Current Treatment Strategies for Cognitive Impairment in DS

Drug	Description	Trial	Outcome	Adverse
Vitamin supplement	Antioxidants, folinic acid, vitamins A, C, E… and more	Numerous, including placebo-controlled	No significant benefit	
Vasopressin	Peptide hormone	One trial: short, placebo-controlled	No significant benefit	N/A
Piracetam	Nootropic, GABA derivative. Site of action unknown.	One trial: placebo-controlled	No significant benefit	Various, common
Donepezil	Acetylcholinesterase inhibitor	Various. DS + AD, adults, children. Large trial ongoing	Mixed. No clear significant benefit for non-AD.	Various, common
Rivastigmine	Cholinesterase inhibitor.	2 trials: DS + AD placebo-controlled; adolescents open label	No benefit DS + AD, small improvement adolescents	7/11 in adolescents
Mementin	NMDA-R inhibitor	1 placebo-controlled Trial in DS	No significant benefit	Various

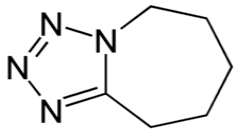
None have been shown to be effective

Findings in animal models suggest therapies to address dysfunction

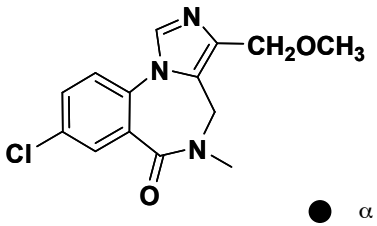
1. Overinhibition addressed with $GABA_A$ antagonist



Fernandez & Garner 2007



Pentylenetetrazole
Bilobalide
Balance Therapeutics



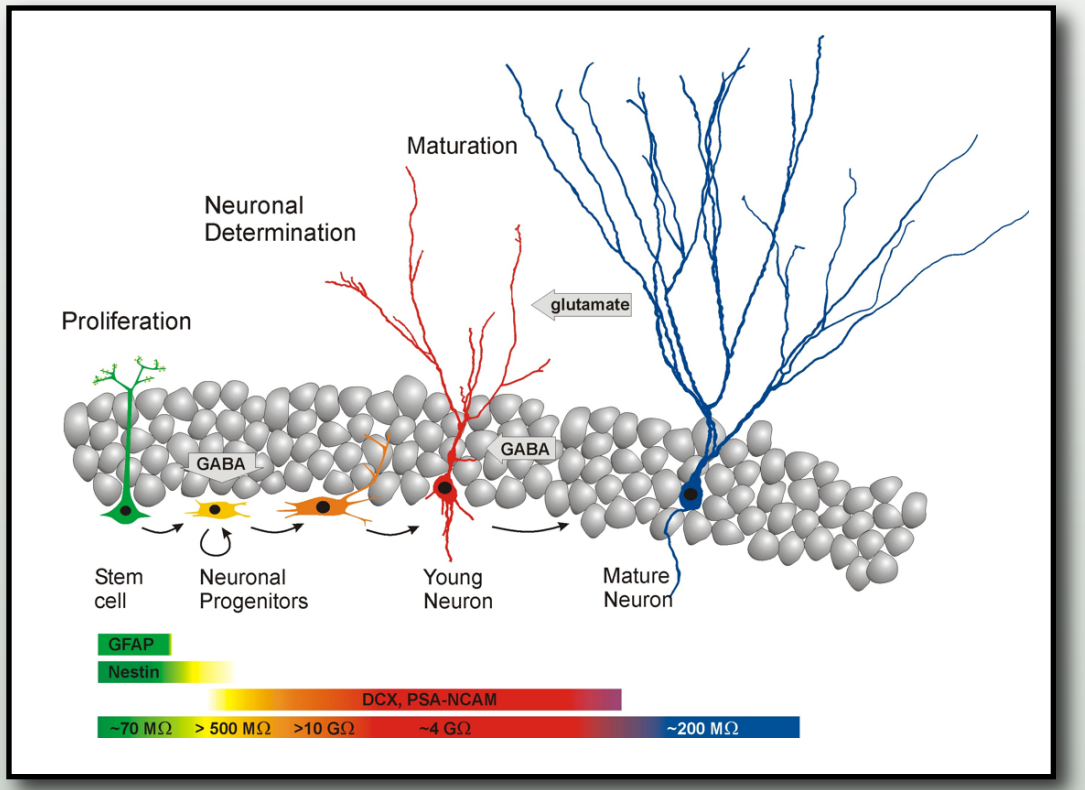
Alpha5 inverse agonist
Roche, Merck

Compose Study
(**Co**gnition and **M**emory in **P**eople with D**o**wn **S**yndrom**e**)

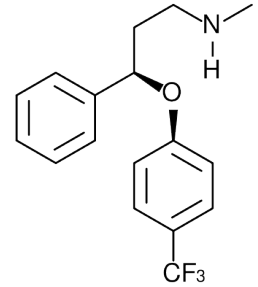
- Phase II placebo controlled study to evaluate safety and tolerability of BTD-001 in adolescents and young adults with Down Syndrome (13-35 yrs)
- Study will also assess improvements in cognitive processes (memory, reaction time and language), daily activities and behavior.
- Study is currently enrolling at 4 sites in Australia.
- For more info see Http://compose21.com
- PI: Dr Robert Davis, Monash University
- Sponsored By Balance Therapeutics Inc

Findings in animal models suggest therapies to address dysfunction

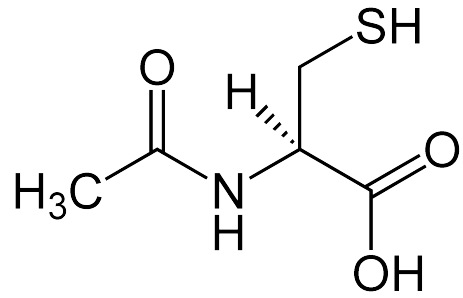
2. Reduced neurogenesis, increased cell death and memory impairment can be addressed with SSRIs or drugs that reduce ROS



Bischofberger lab website



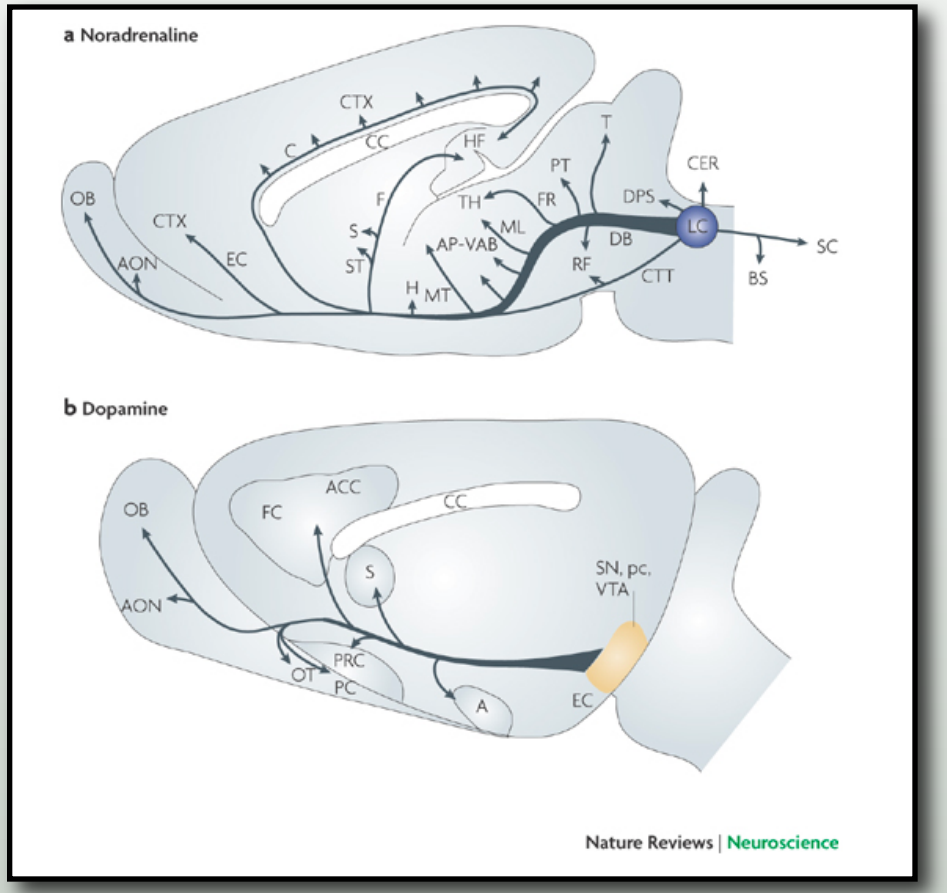
Fluoxetine (prozac)



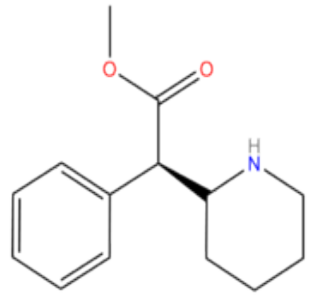
N-AcetylCisteine (NAC)

Findings in animal models suggest therapies to address dysfunction

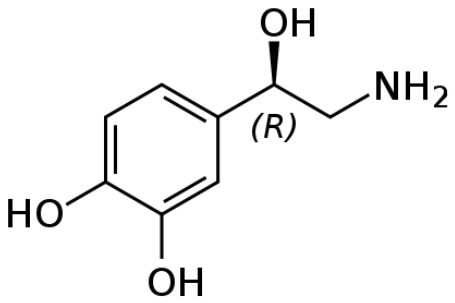
3. Reduced neuromodulatory function addressed with various drugs, e.g. ADHD medications



Sara 2009 Nat Rev Neuro



Focalin



Norepinephrine
L-Dops

Key points to take home:

- The development of approved drug therapies is slow and expensive. The Translational Cycle defines the steps in this process.
- Research in animal models improves our understanding of brain function and permits principled design of therapies.
- Significant progress is being made for drug therapies for neurodevelopmental disorders such as DS.
- We believe investment in basic research is the best value for advancing the Translational Cycle.

DS Clinical Research at Stanford

STANFORD
SCHOOL OF MEDICINE
Stanford University Medical Center

Learn more about your child's sleep!

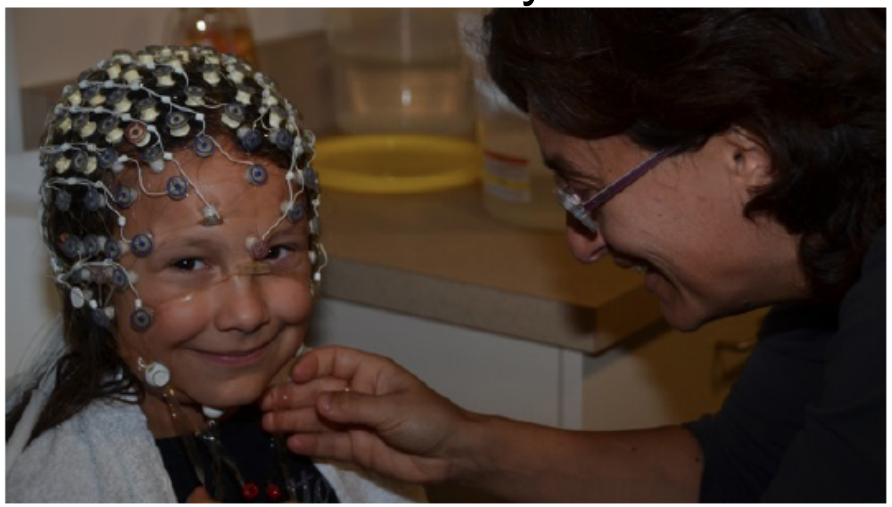
We are looking for families interested in taking part in a Stanford University study investigating sleep in children.

Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Study Coordinator: Sean Berquist
Phone: 650-723-2795

DS Clinical Research at Stanford

Stanford Vision and Neurodevelopment Lab

Vision in Down Syndrome



Vision in typically developing infants and children

Using vision to understand general properties of brain development in special populations

Professor Tony Norcia, Director
650-736-2793 Svndl.stanford.edu

DS Clinical Research at Stanford

STANFORD UNIVERSITY

Children Needed for Intellectual/Developmental Disorder Research Study

Does your child have an intellectual disorder or developmental delay and a significant language delay?

Researchers at Stanford University are currently recruiting children to participate in a research study examining the effectiveness of Pivotal Response Treatment (PRT) in targeting language skills in children with intellectual disorders or developmental delay.

Professor Antonio Hardan
650 736-1235

Lucile Packard Children's Hospital

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Bayara Chuluun

Damien Colas

Fanuel Muindi

Normal Ruby

Asya Rolls

Grace Hagiwara

Salehi Laboratory

Van Dang

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