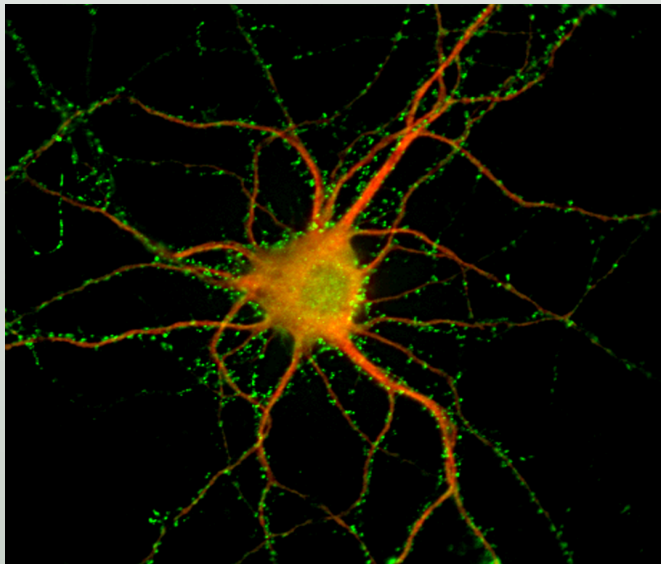
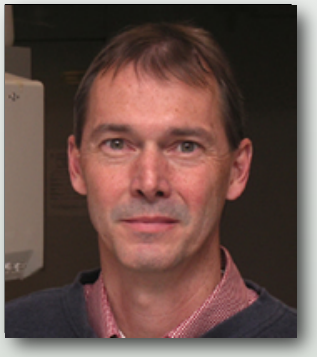
Developing therapies to improve cognitive abilities of Individuals with Down syndrome



Stanford School of Medicine | Down Syndrome Research Center

A program of the Stanford Institute for Neuro-innovation and Translational Neurosciences



Craig Garner, PhD

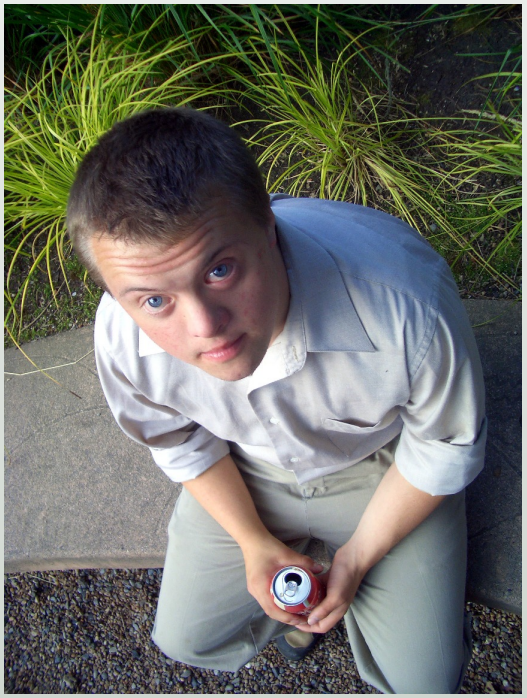
H Craig Heller, PhD

Ahmad Salehi, MD, PhD

Stanford University
Dept. Psychiatry

Web: http://dsresearch.stanford.edu
Facebook: 'Stanford Down Syndrome Research Center'
Twitter: StanfordDS

From research finding to approved drug: translational research and clinical development for Down syndrome



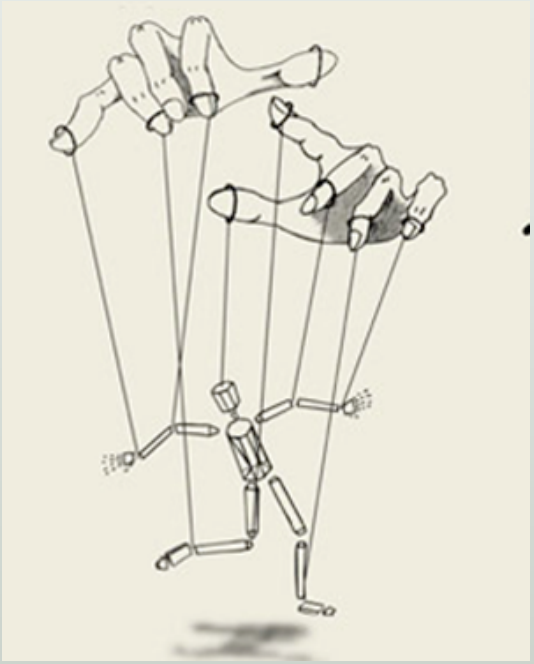
Down Syndrome Outline

- What is abnormal in the DS brain? How do these differences cause cognitive dysfunction?
- Abnormalities in modulatory neurotransmitter signaling contributes to cognitive impairment in DS (Ahmad Salehi)
- Excessive inhibitory tone also suppresses learning and memory function. One strategy to address cognitive dysfunction (Craig Garner)
- Clinical programs in Down syndrome

A new view on neurogenetic cognitive disorders – Brains can be fixed!

To understand what we are doing, it is necessary to have a different concept of the brain than is commonly held even by neurobiologists.

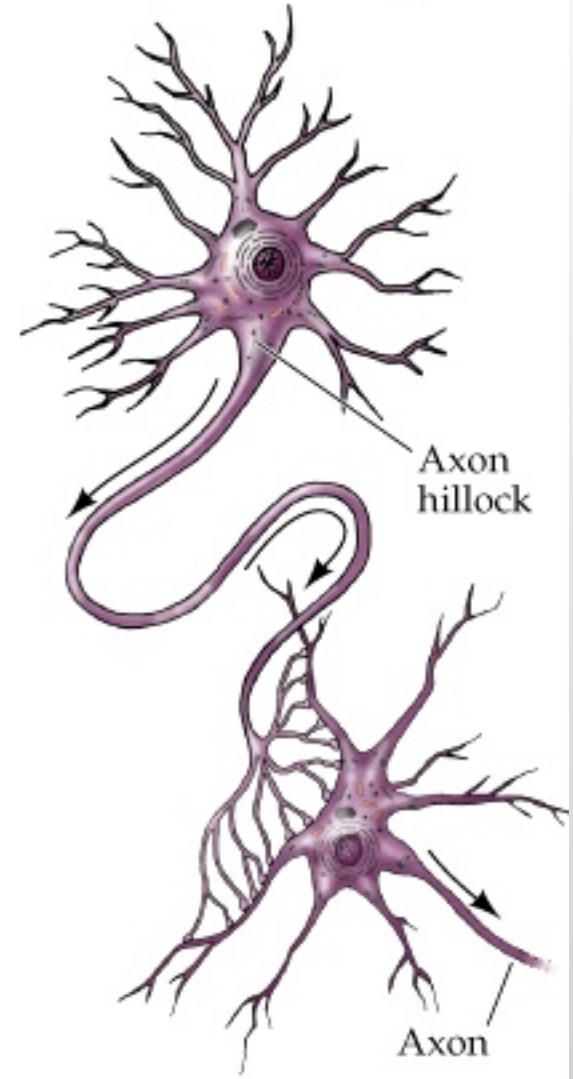
The brain is not like a puppet master just pulling the strings.



The brain is more like a symphony conductor, speeding up, slowing down, making some sections louder and others softer.

How do are brains work?

Short course on Neurobiology.



Brains are made up of billions and billions of nerve cells or neurons.

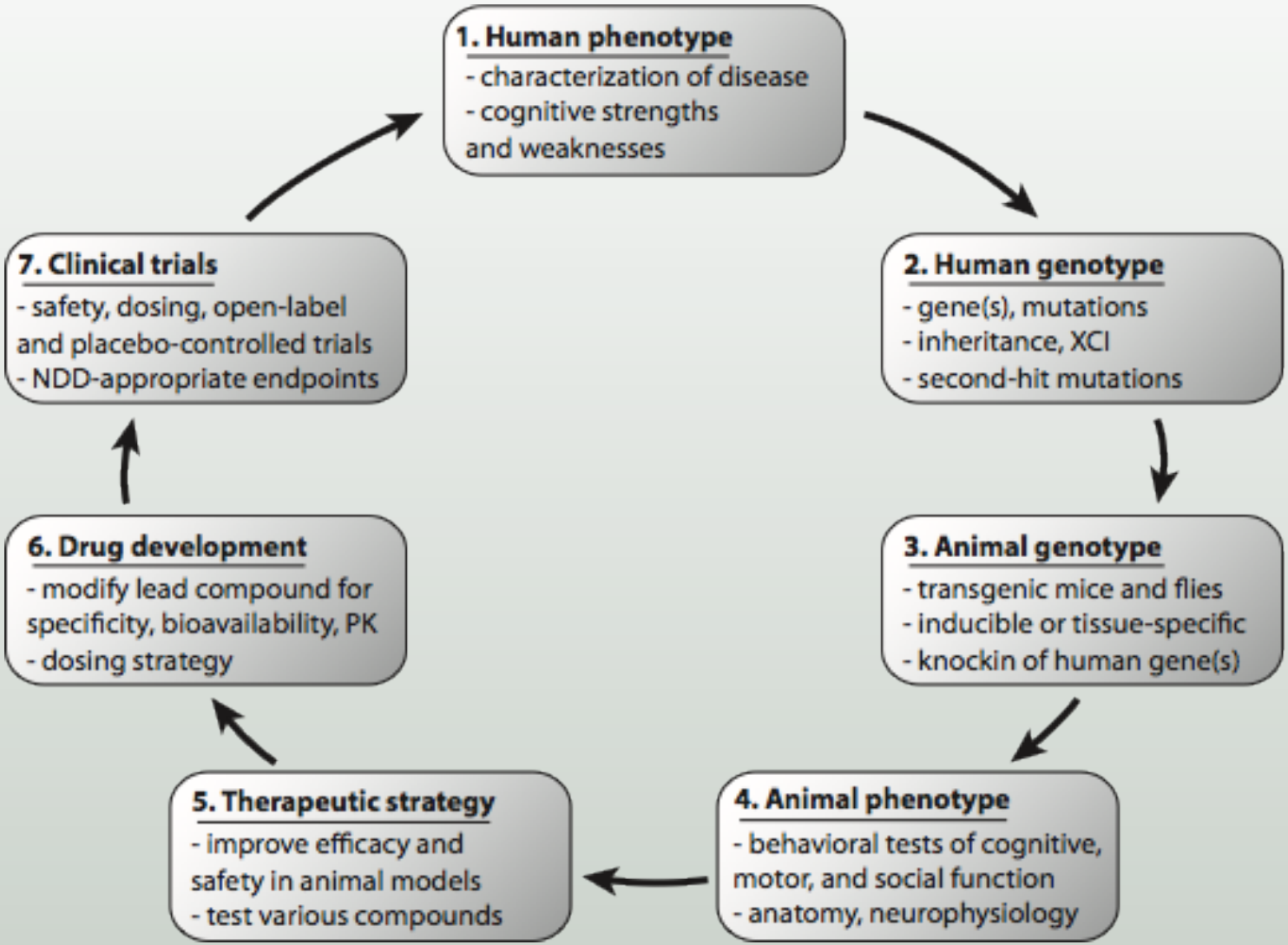
They send information to each other by electrical signals -- nerve impulses -- that travel along extensions of these cells.

At the end of these processes there are connections between the cells called synapses. But, there are gaps between the presynaptic and postsynaptic cells that the electrical signals cannot cross.

The information is carried across the gaps by chemicals called neurotransmitters released by the pre-synaptic cell and received by the post-synaptic cell.

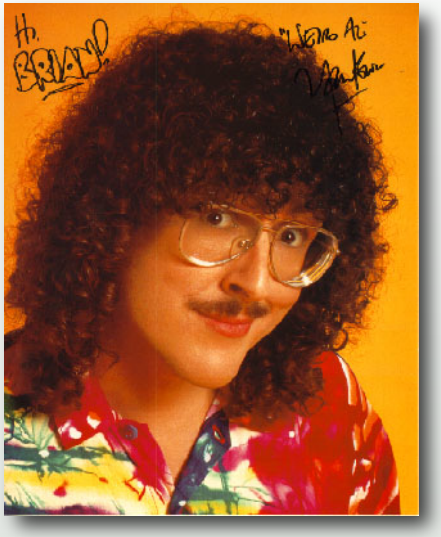
These chemicals are neurotransmitters and they can either excite or inhibit their target cells.

The Translational Cycle



Human phenotype

Zac Efron



Weird Al Yankovic

Arizona
Cognitive
Test
Battery

J Neurodevelop Disord
DOI 10.1007/s11689-010-9054-3

Development and validation of the Arizona Cognitive Test Battery for Down syndrome

Jamie O. Edgin · Gina M. Mason · Melissa J. Allman · George T. Capone · Iser DeLeon · Cheryl Maslen · Roger H. Reeves · Stephanie L. Sherman · Lynn Nadel

Down Syndrome

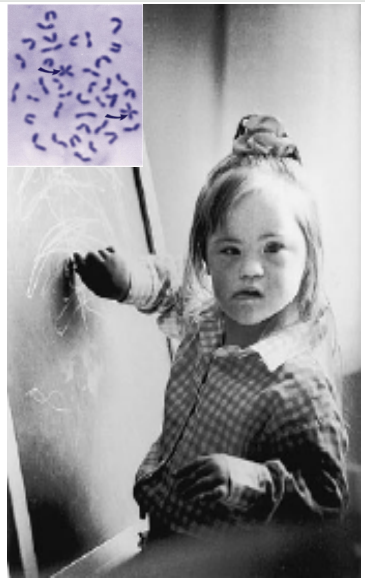
Clinical Assessment

- Caused by the triplication of Chromosome 21 (~250 genes).
- Common Disorder: 1/600 Births: Incidence higher when mothers are over 35
- 350,000 afflicted in US; 500,000 Europe; > 3 Million world wide
- Cognitive impairment, mild-severe (IQ 20-80)
- Progressive cognitive decline
- Deficits in speech and language skills
- Deficits in short- and long-term memory
- Propensity for early onset Alzheimer Disease (~30 years of age)

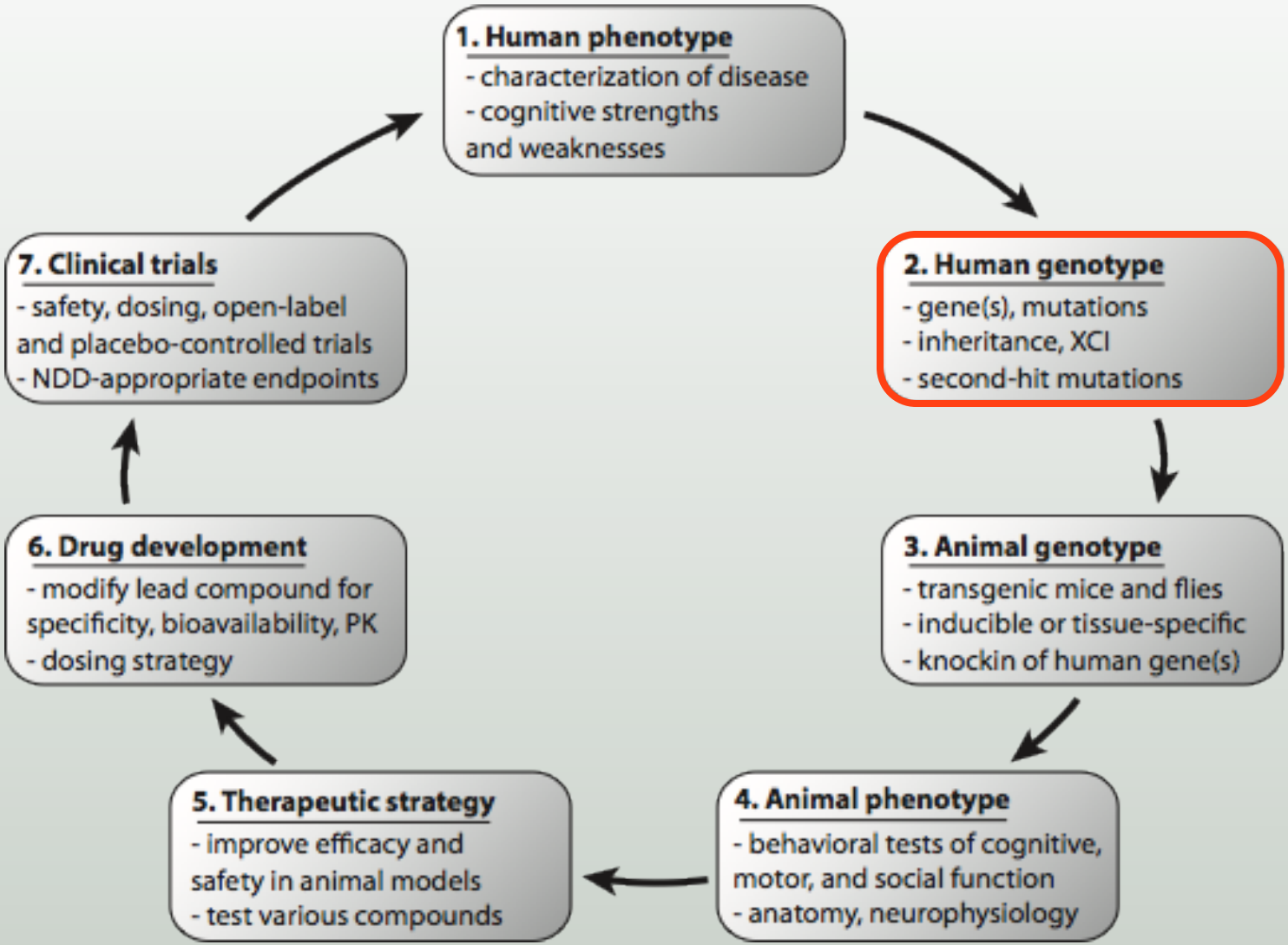
Neuropsychological Assessment of Learning and Memory in Down Syndrome

(see Lynn Nadel, Genes,Brain and Behavior 2:156 2003)

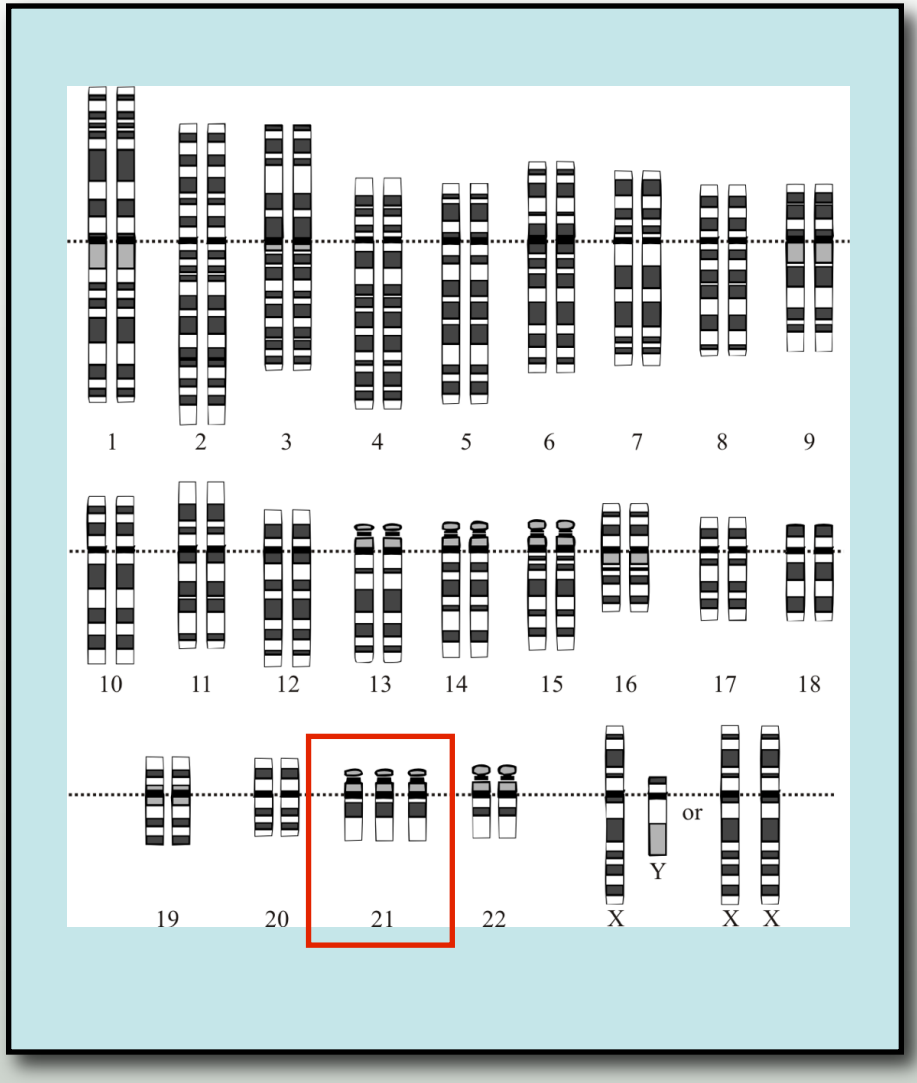
- Learning is normal in very young subjects <6 month, but declines progressively in the first year.
- A second decline occurs in adulthood as the risk of early onset Alzheimer disease takes it toll.
- Impairment is not spread across all learning and memory systems
- Disproportionately affected are the hippocampus and prefrontal cortex.
- Impairment is most robust for explicit or declarative memory, though implicit or procedural memory is also affected.
- These directly affect speech, language and verbal short term memory and IQ.



The Translational Cycle



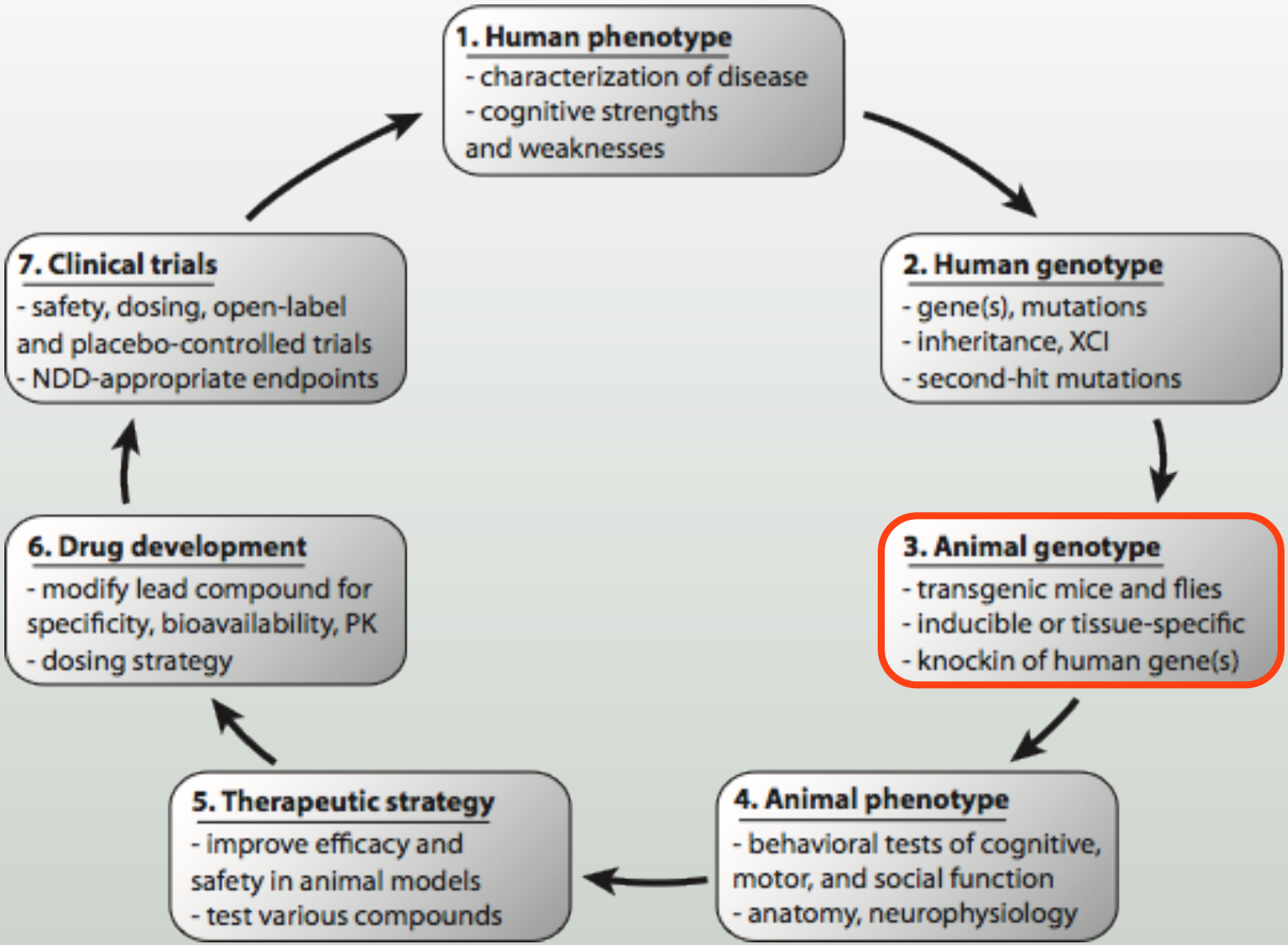
Characterizing human genotype



Lejeune et al 1959

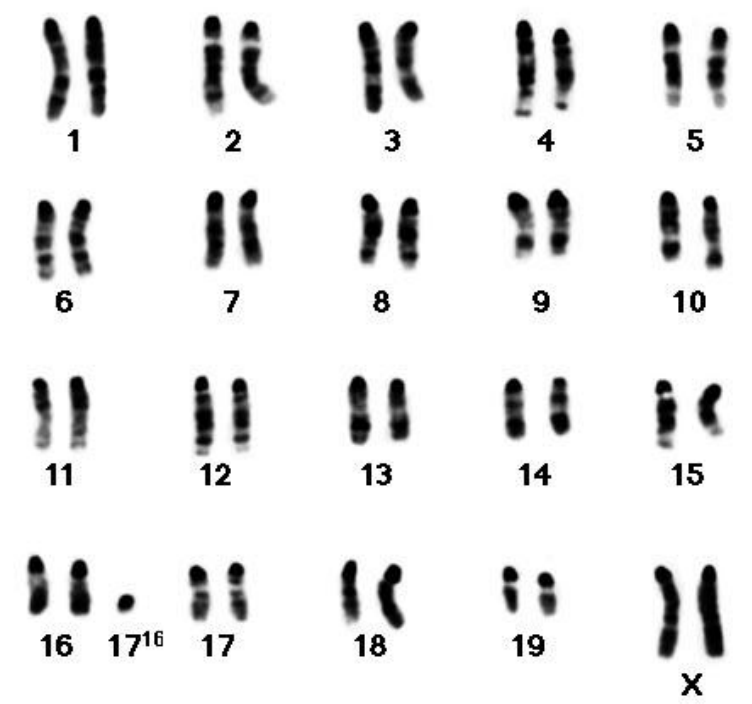
DS cqused by the triplication of Chromosome 21 (~250 genes).

The Translational Cycle



Animal models of genetic disorders

Meet the Ts65Dn Mouse: Our Workhorse, our Hero.



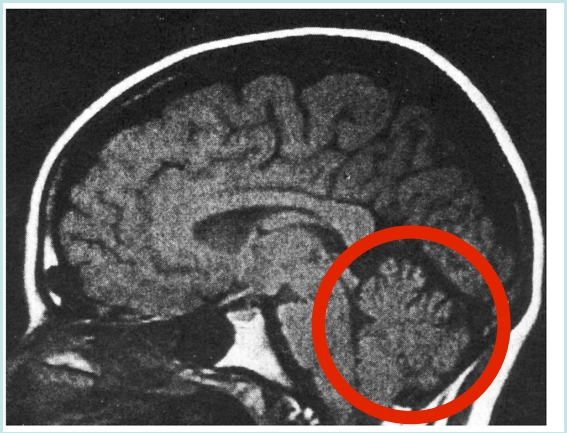
Karyotype analysis

(visual display of the chromosomes grouped by their size, number and shape)

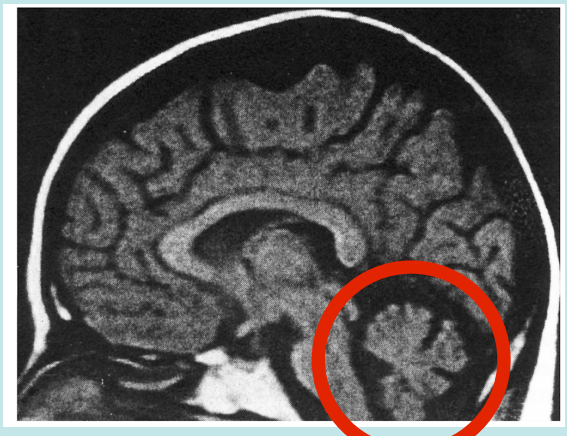
TS Mouse **WT or 2N Mouse**

Anatomy

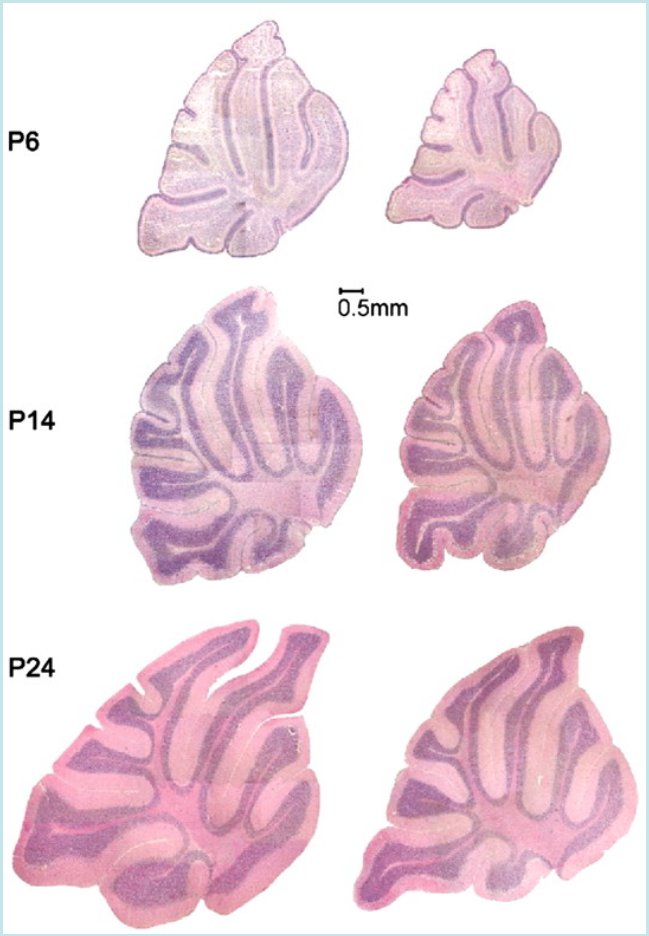
2N



DS



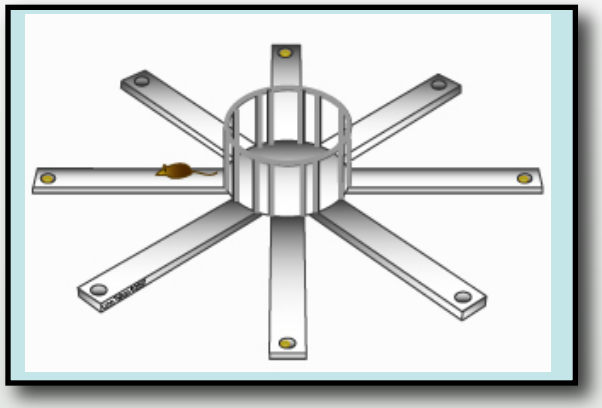
2N Ts65Dn

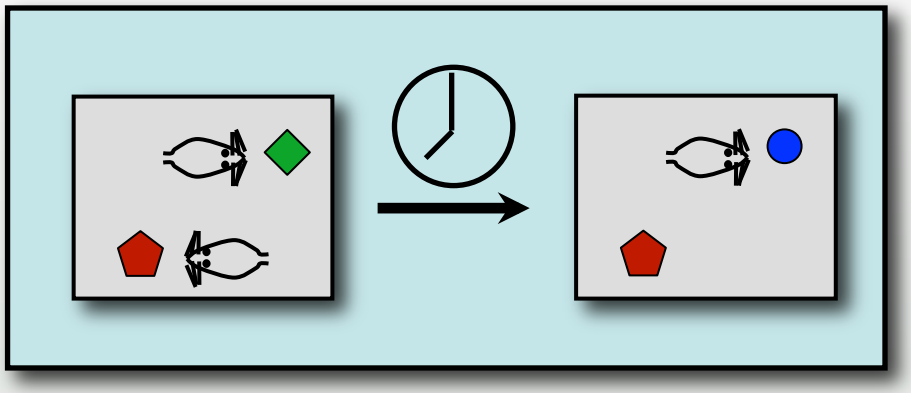


Kesslak et al. *Neurology* 1994; Roper et al. *PNAS* 2006

Behavioral tests

Long-term memory



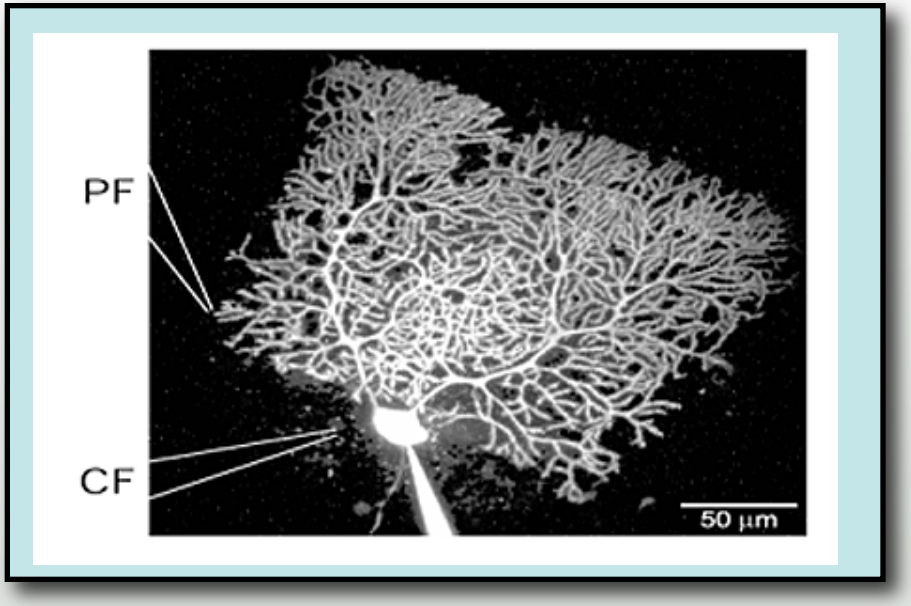


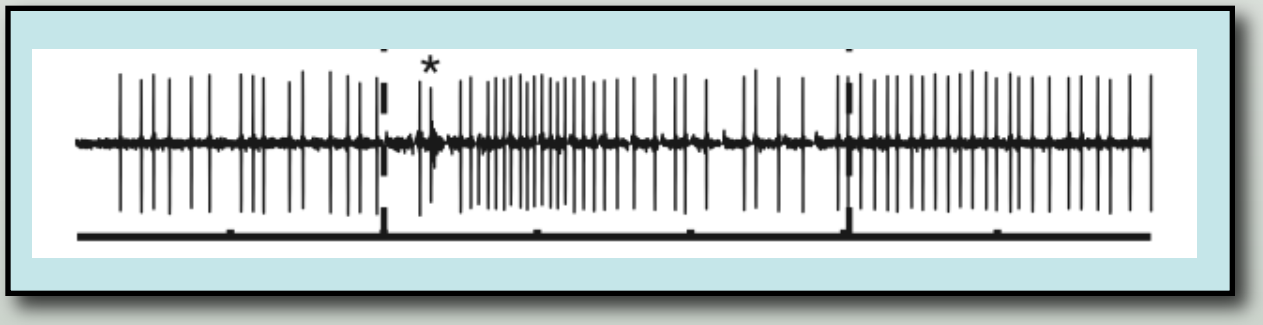
Motor behaviors

Social behaviors

As in humans, Ts mice exhibit learning and memory impairments

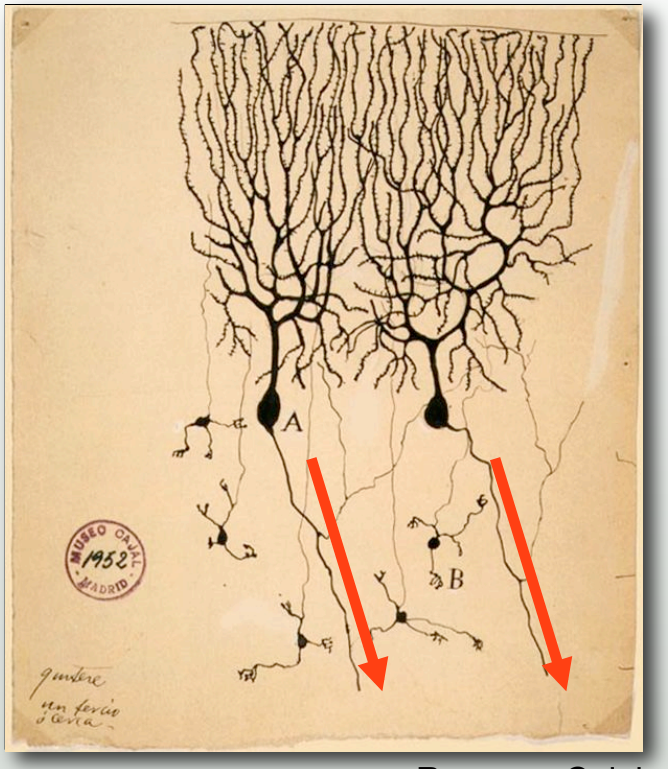
Physiology



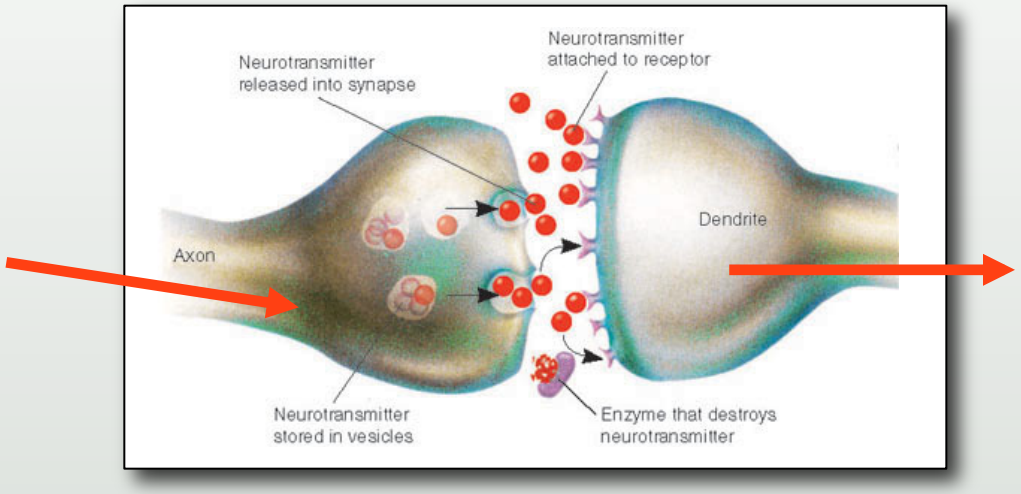


Wang et al., *Nat Neuro* 2000

Neurons and synapses



Ramon y Cajal



Neurons use electrical and chemical signals to communicate: Synaptic transmission is impaired in mouse models of Down syndrome

Synapses and synaptic plasticity in DS mice

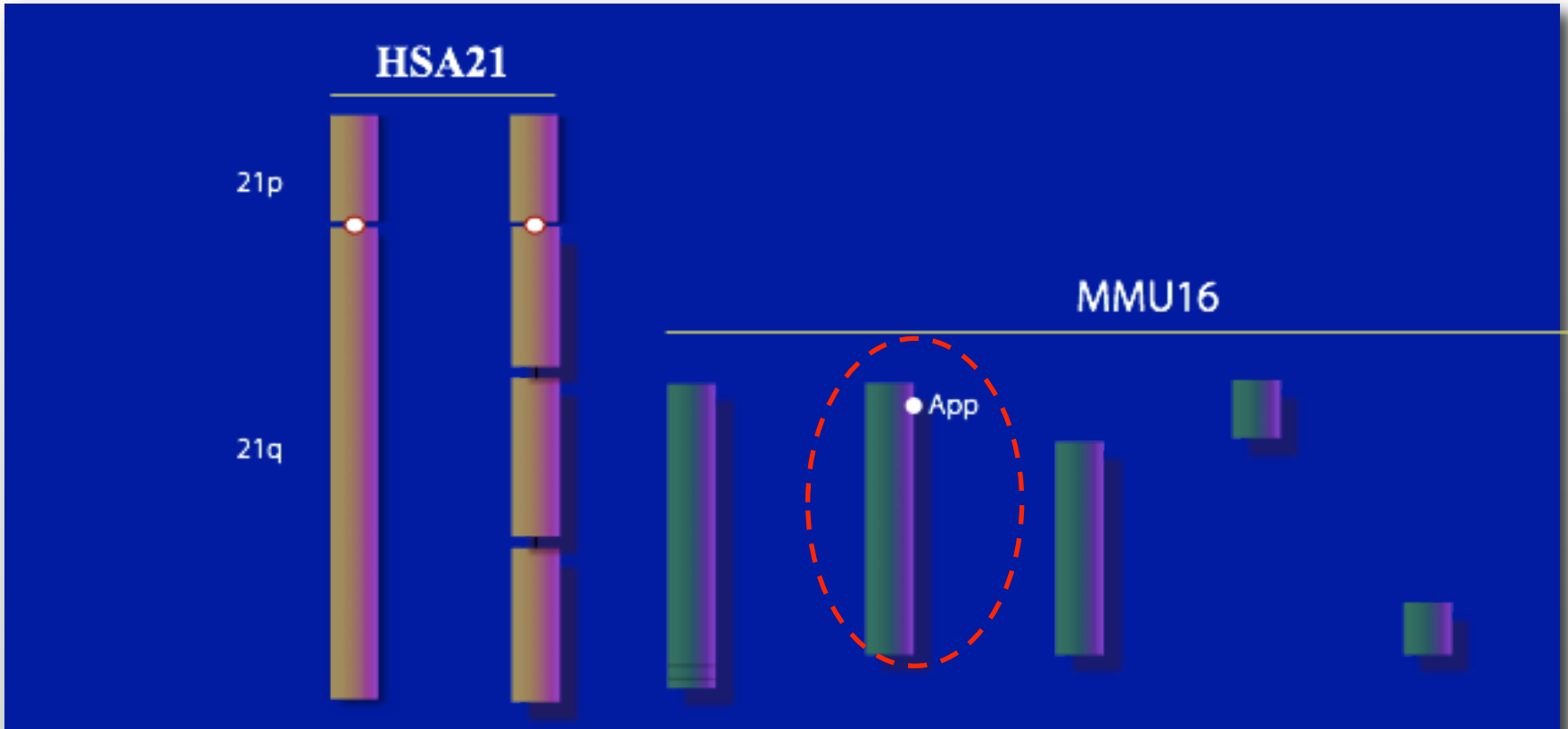
- Brain anatomy is altered.
- Synaptic learning is impaired.
- Inhibitory synapses are too strong
- Excessive inhibition appears to suppress synaptic plasticity in neural circuits critical for memory processing.
- Modulator synapses (cholinergic and noradrenergic) are also too weak.

Data suggest that altered synaptic transmission contributes to impaired learning and memory function in Down syndrome

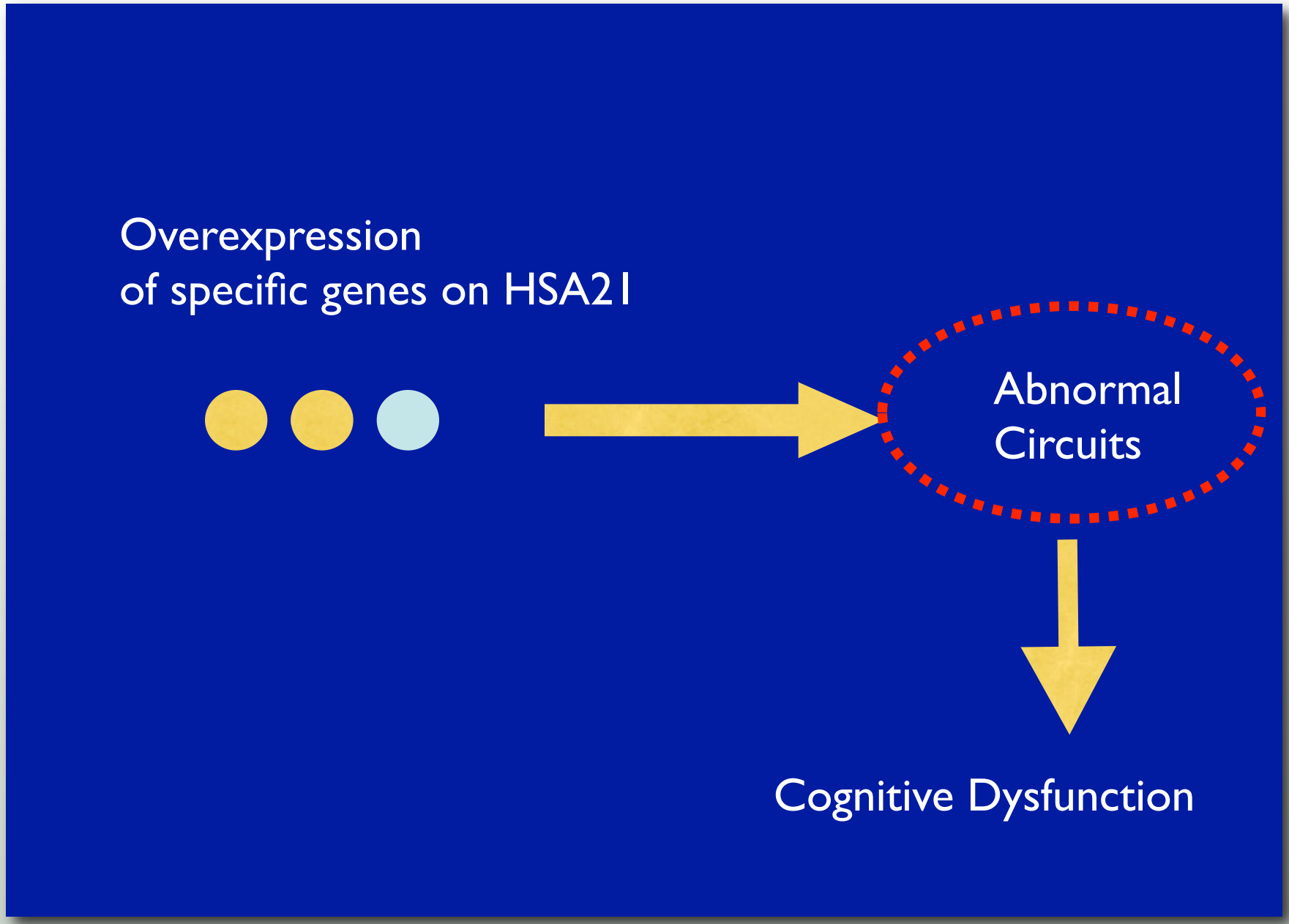
Abnormalities in modulatory neurotransmitter signaling contributes to cognitive impairment in Down syndrome

Ahmad Salehi, M.D., Ph.D
Department of Psychiatry & Behavioral Sciences
VA Palo Alto Health Care System
Palo Alto, California

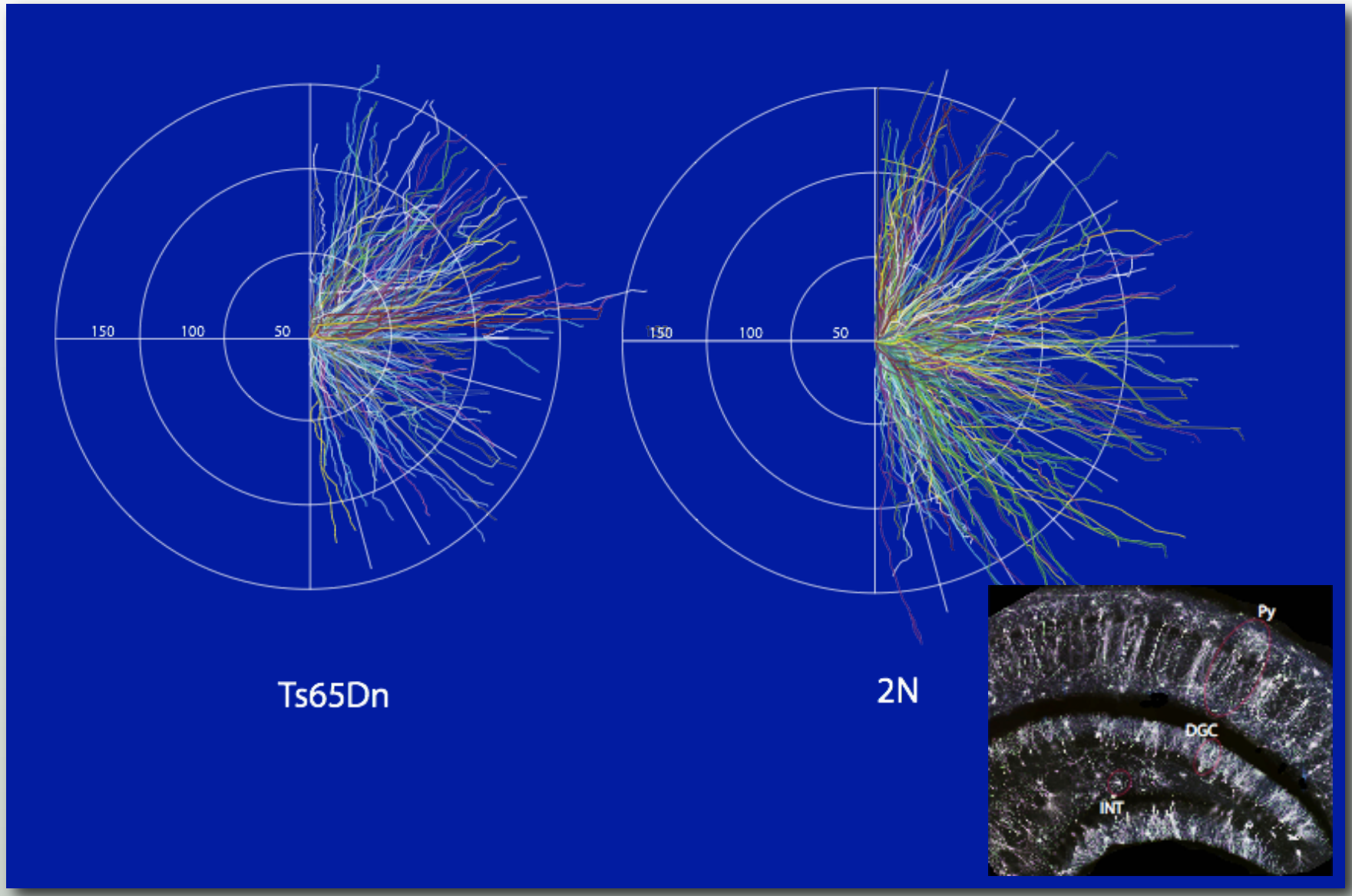
Mouse Models of Down Syndrome



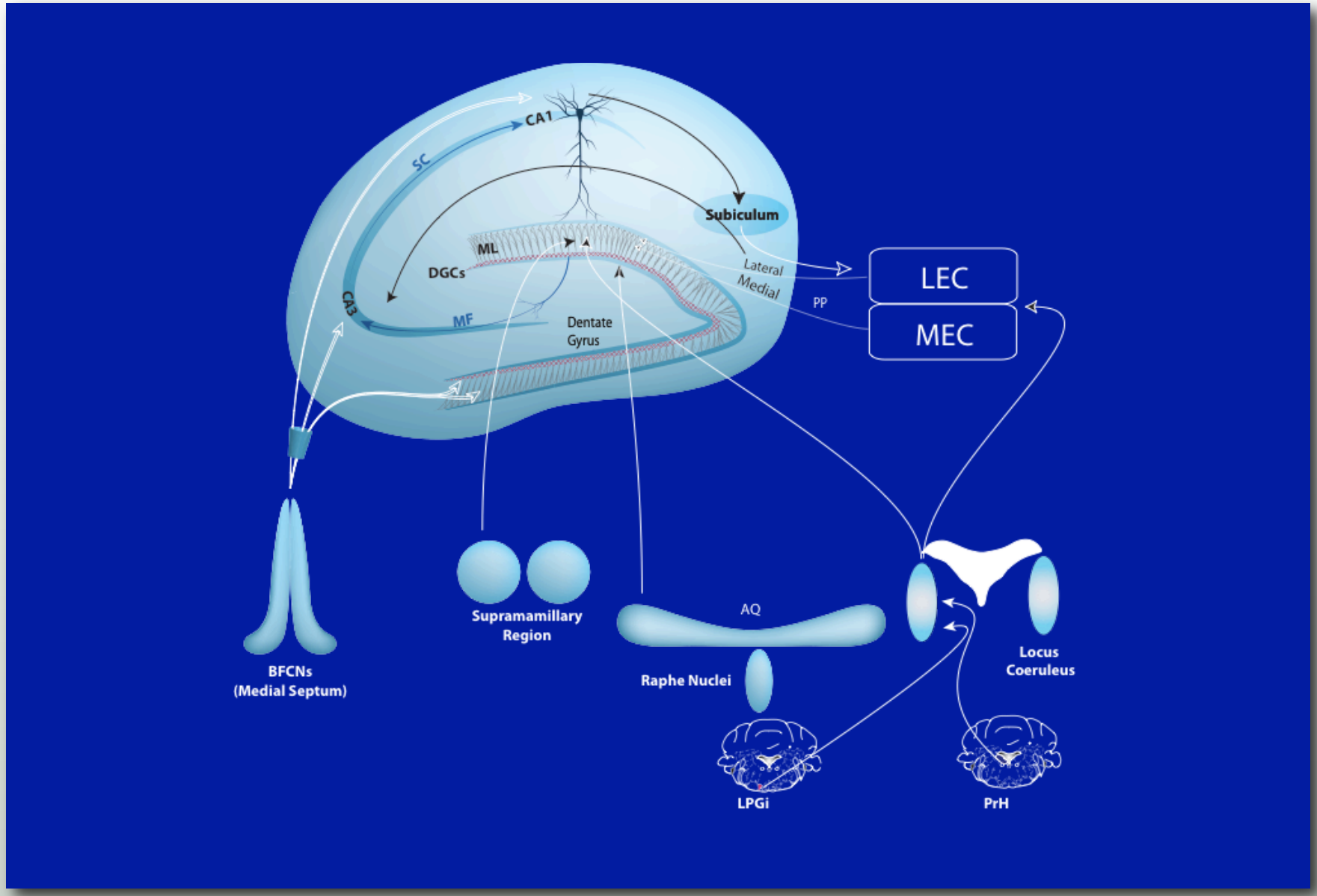
	Down Syndrome	Tc1	Ts16	Ts65Dn	Ts1Cje	Ms1Cje/Ts65Dn	Ts1Rhr
Number of Triplicated Genes	261-364	240-334	731*	104-132	81-85	22-46	33
Viability	+	+	-	+	+	+	+
Cognitive Deficits	Moderate	Severe	ND	Severe	Moderate	Mild	ND
Change in Brain Structure/Function	+	+	+	+	+	ND	ND


Overexpression
of specific genes on HSA21
Abnormal
Circuits
Cognitive Dysfunction

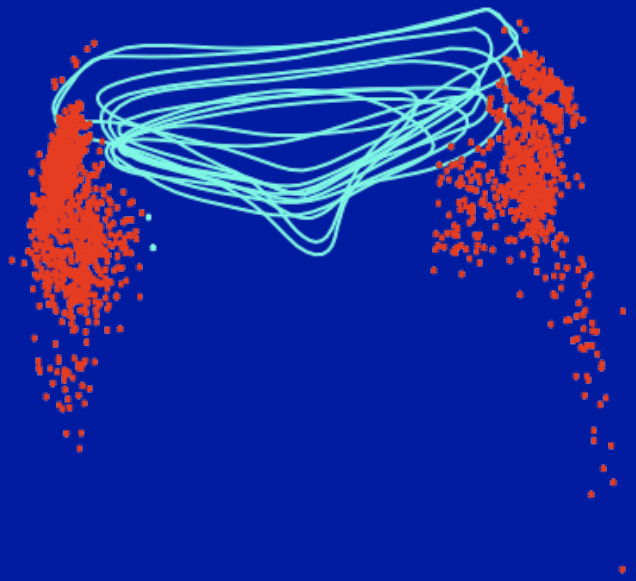
A Significant Loss of Dendritic Arborization in Dentate Gyrus Neurons in Ts65Dn Mice



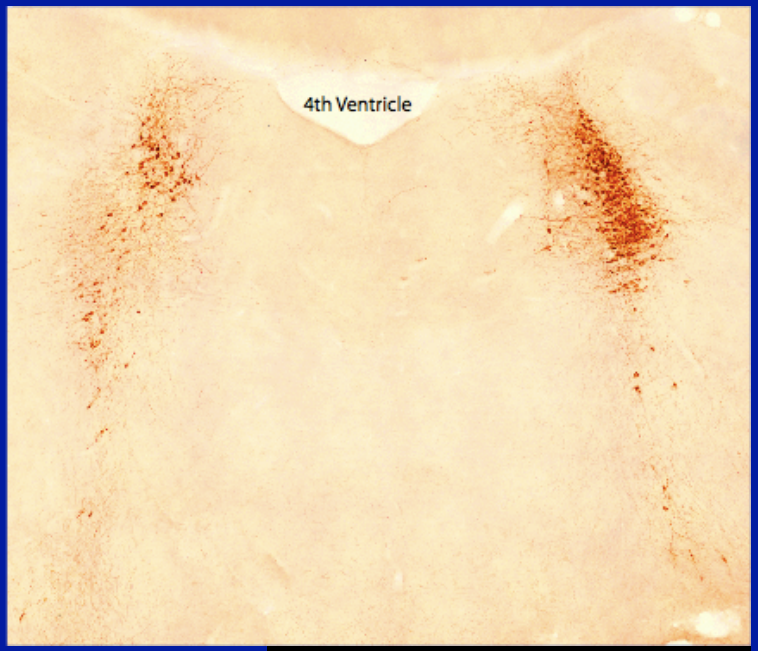
Hippocampal Function is Modulated by Subcortical Regions with Extensive Projections

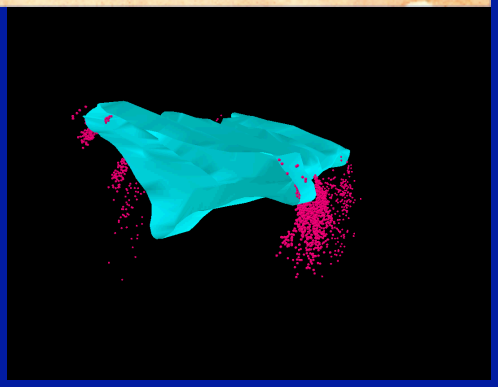


Locus Coeruleus Neurons in the Brainstem Project Extensively to the Hippocampus

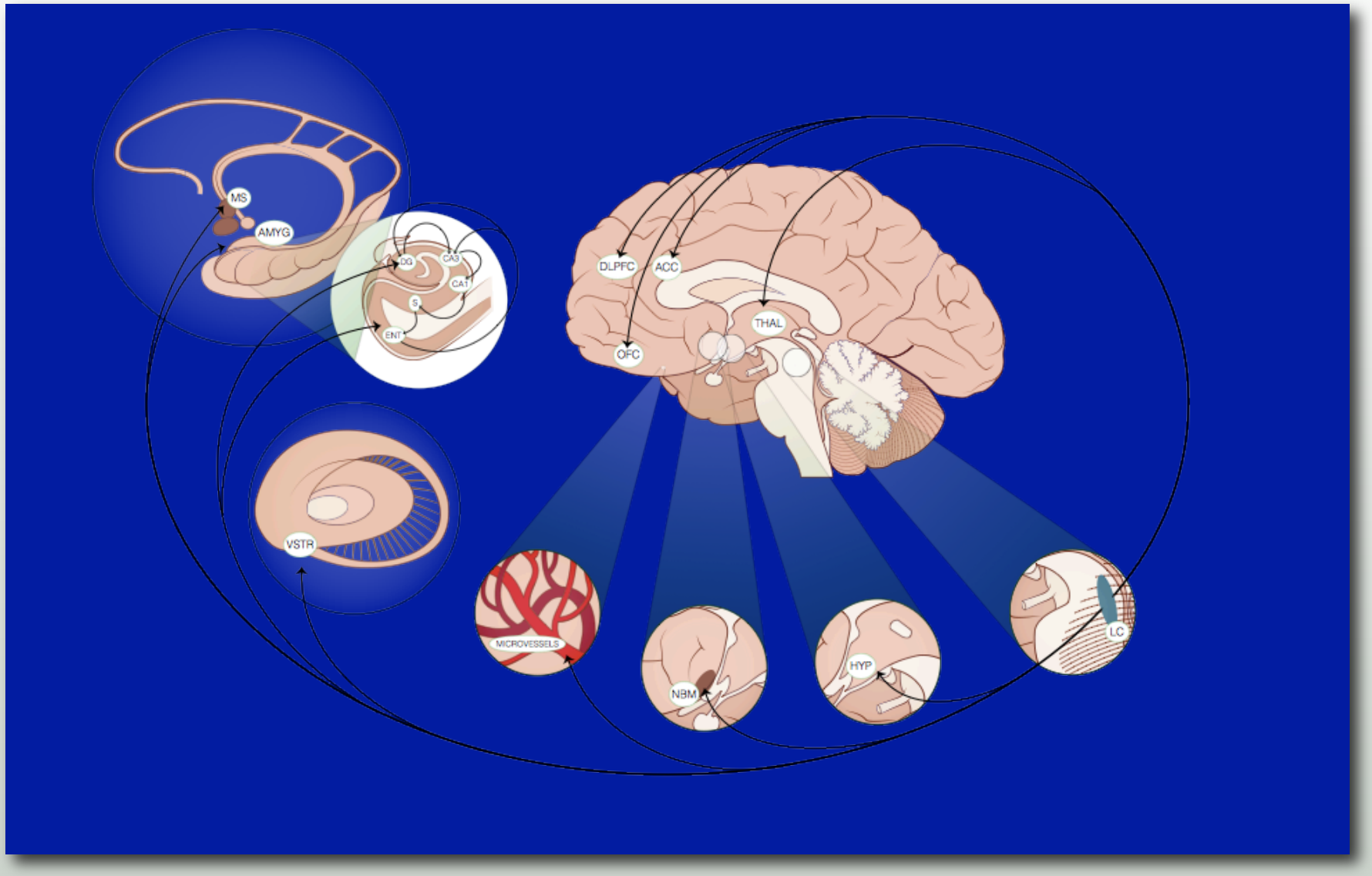


3D LC

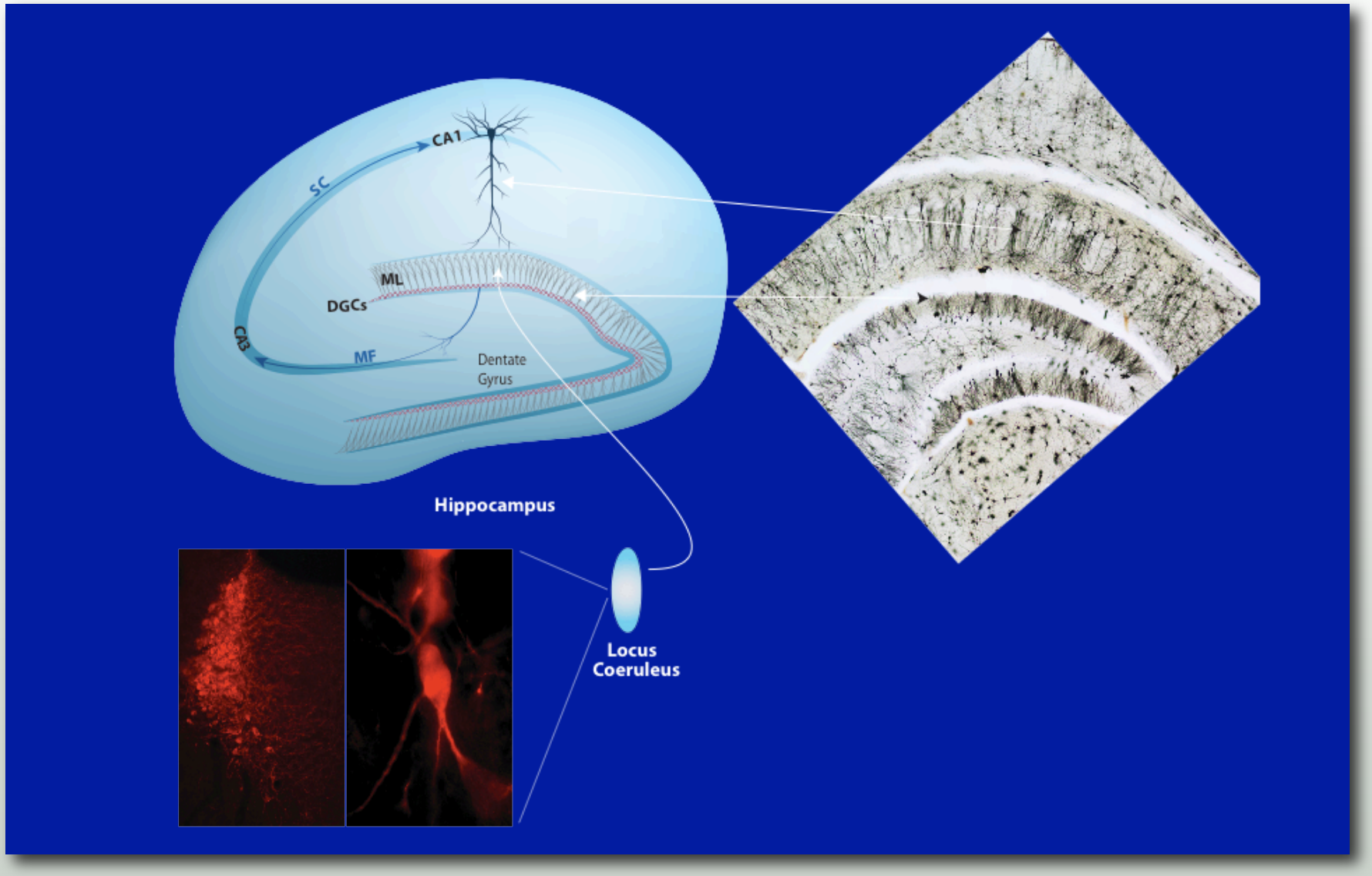




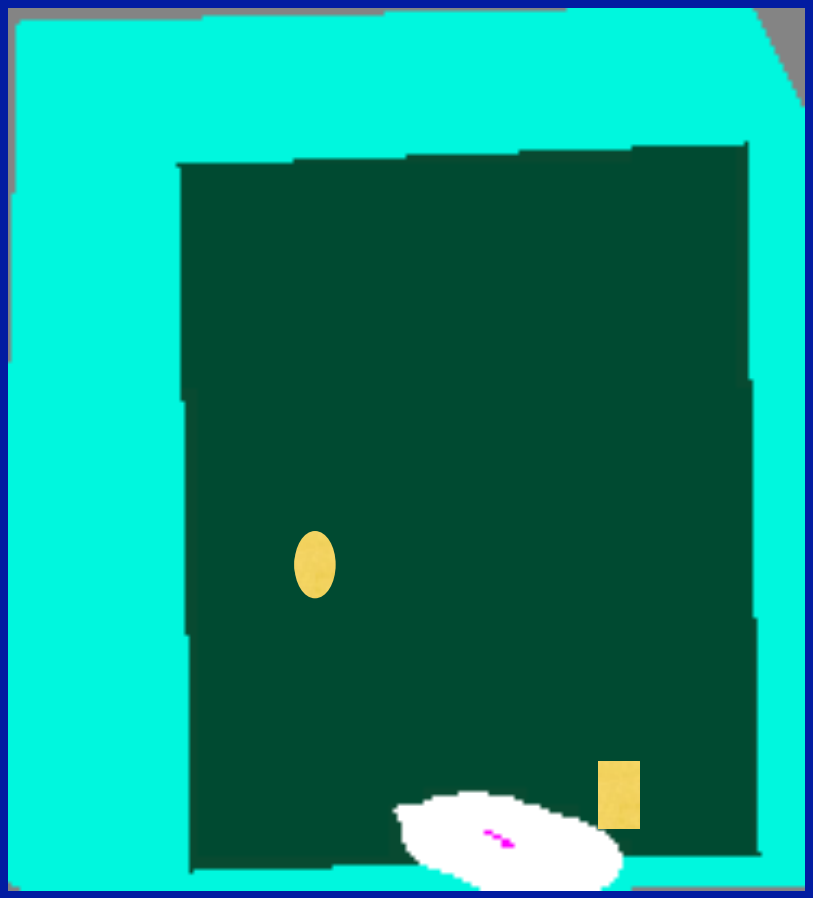
Locus Coeruleus Neurons Send Extensive Projections to the Rest of the Brain



Locus Coeruleus Neurons Are the Sole Source of Norepinephrine for the Hippocampus



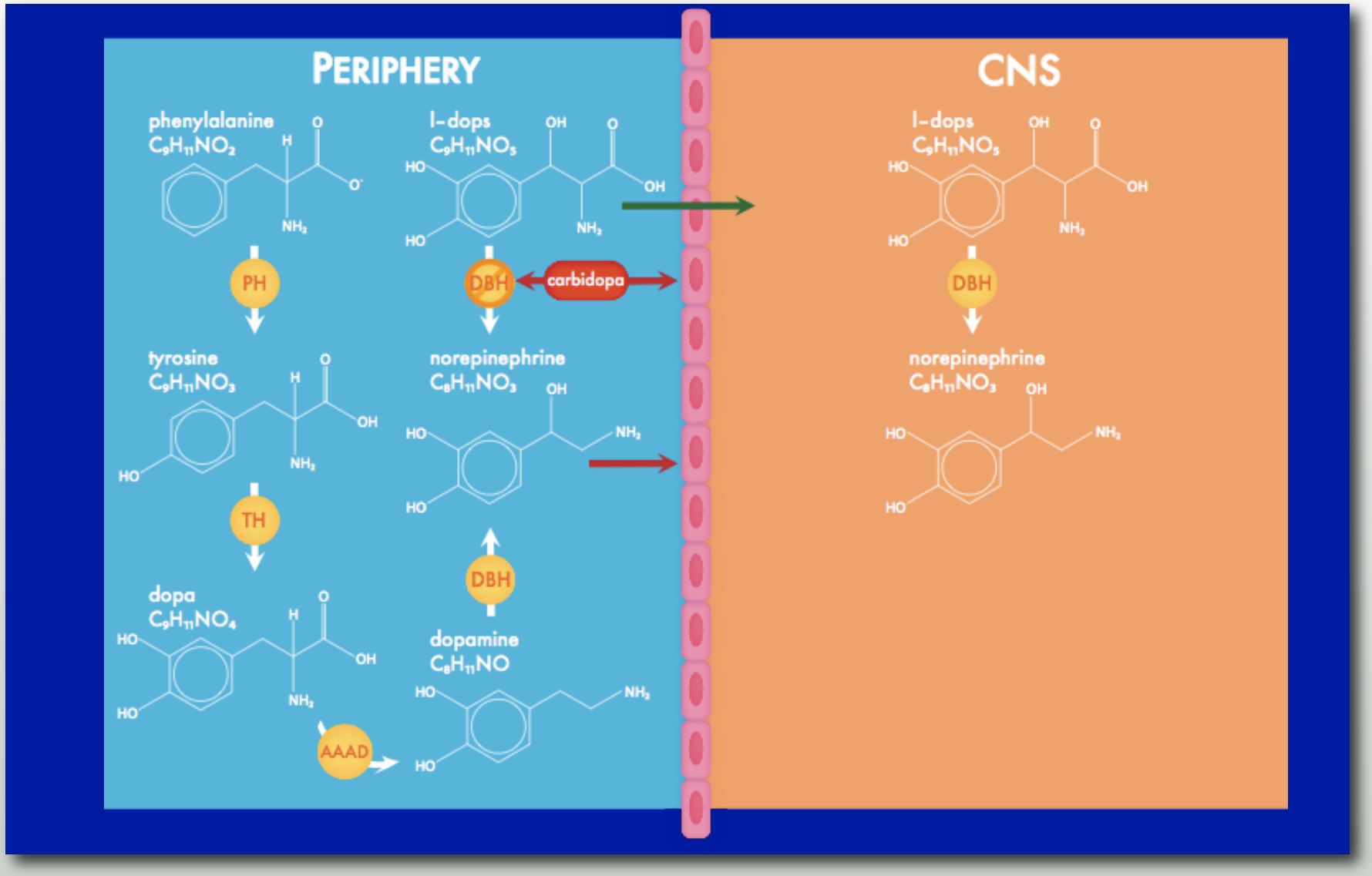
Methods to Study Cognitive Function in Ts65Dn Mice



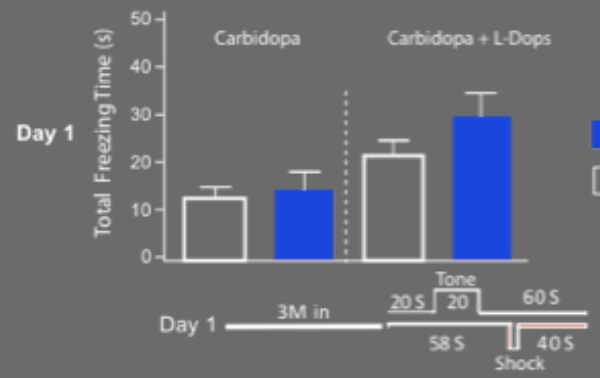
Novel Object Recognition

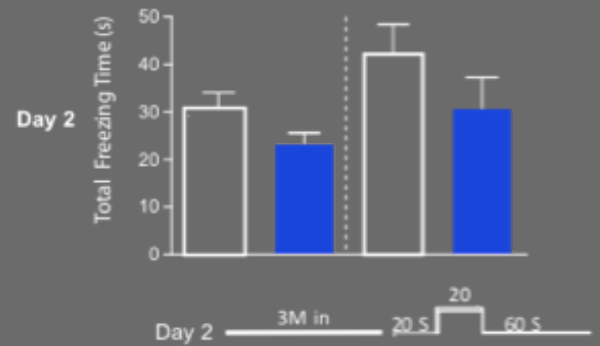
Contextual Learning

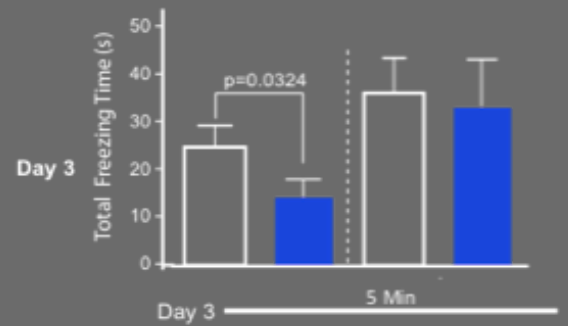
Strategy Used to Increase NE Levels Only in the Brain



Failure in Contextual Learning in Ts65Dn Mice

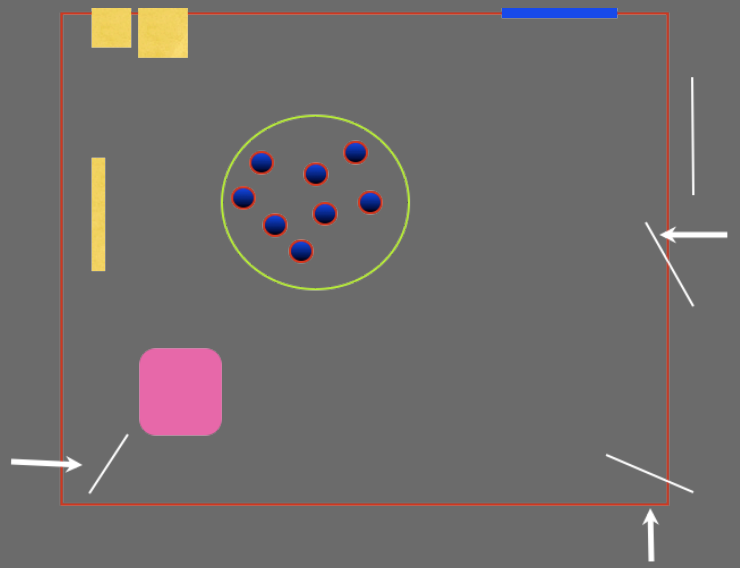






Ts65Dn		2N CD	2N LD
Day 1 CD		0.876	
Day 1 LD			0.150
Day 2 CD		0.182	
Day 2 LD			0.196
Day 3 CD		0.0324	
Day 3 LD			0.595

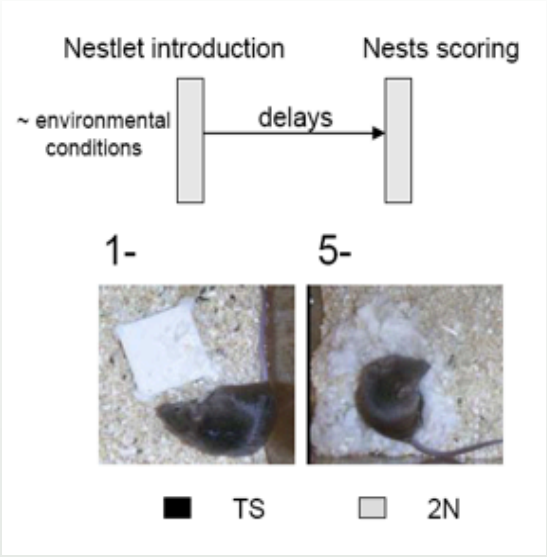
p value- Mann-Whitney U- test

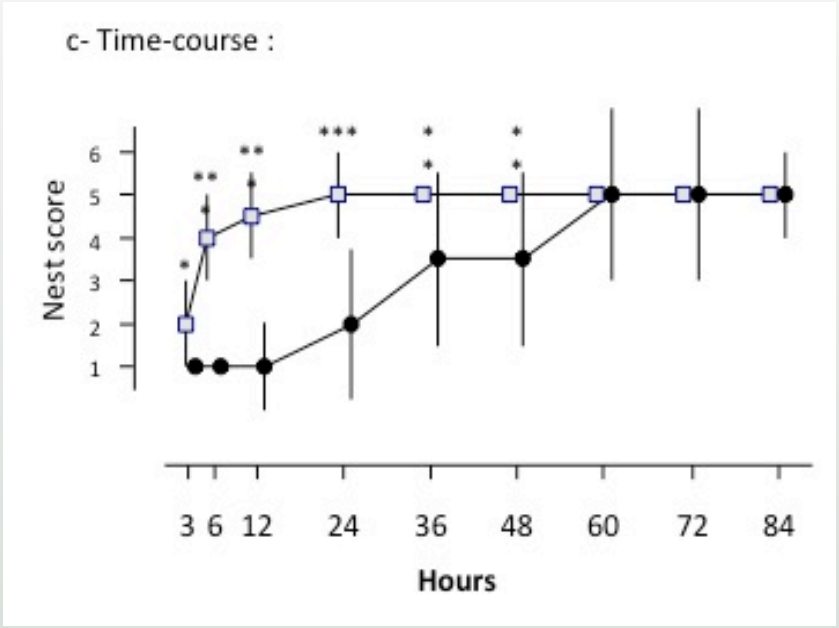


Uecker et al., 1991

Ts65Dn mice show traits of ADHD that are seen in some children with DS.

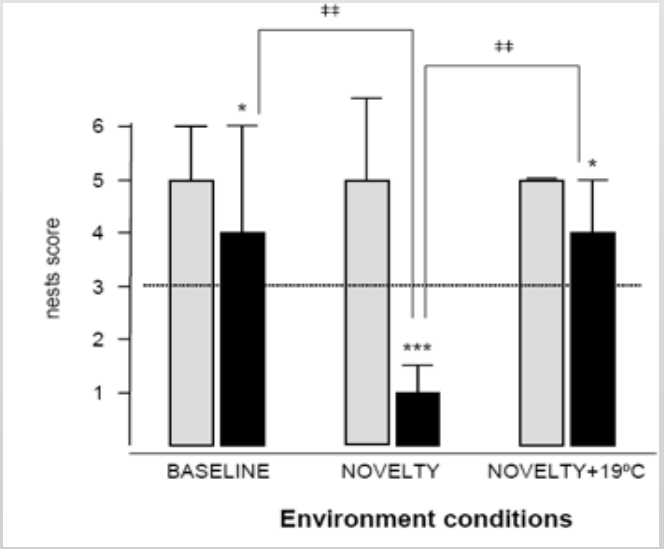
ADHD can be measured by their nest building behavior.





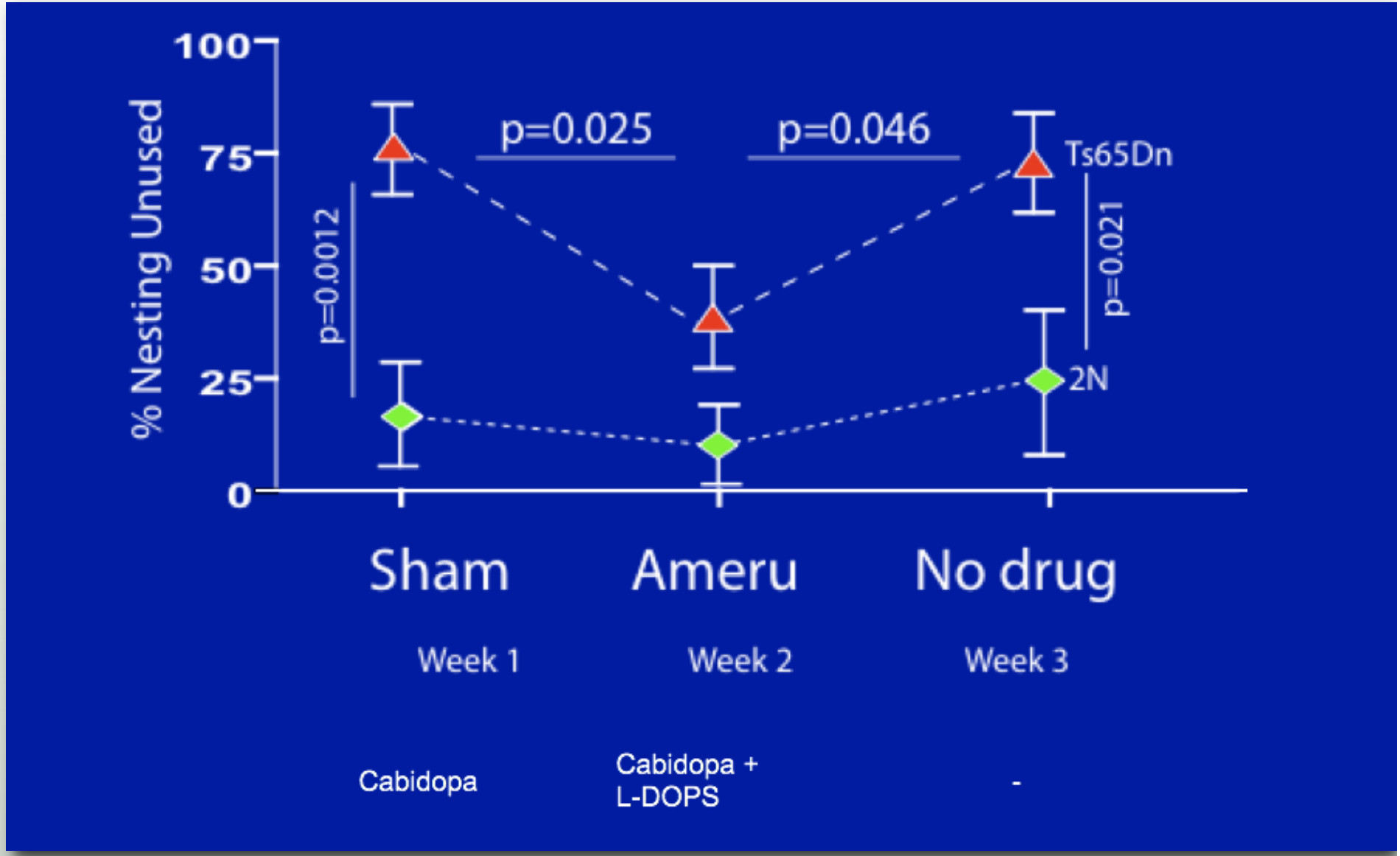
They can build good nests, but it takes more time.

Novelty makes the ADHD worse, motivation (cold) makes it better



PTZ does not treat this trait, but other drugs do.

Increasing Norepinephrine Levels Significantly Improves Nesting in Ts65Dn Mice



Acknowledgments:

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