

Therapeutic Strategies for Cognitive Dysfunction in People with Down Syndrome



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Down Syndrome: A Malady of Angels

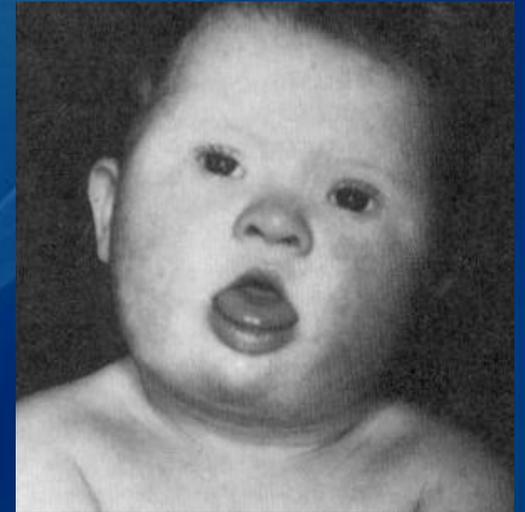


Adoration of the Christ Child, 1515 AD, Source: Met Museum of Arts

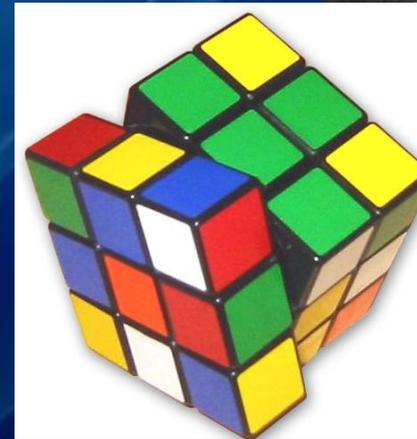
Characteristics of Down Syndrome

Physical Features:

- Dysmorphic facial features
- Growth retardation



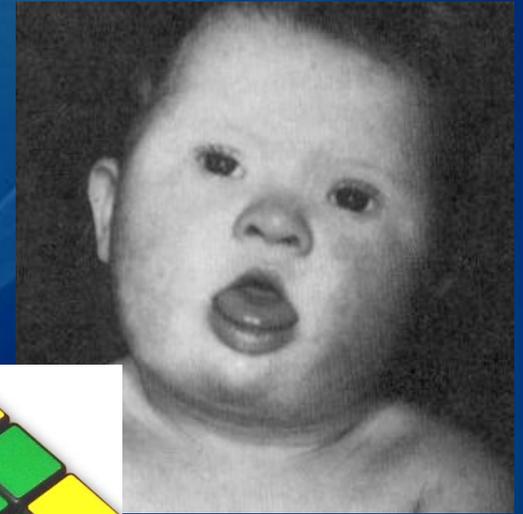
Characteristics of Down Syndrome



Central Nervous System:

- Intellectual disability (I.Q. 35-70)
- Cognitive dysfunction
- Attention deficit & hyperactivity (ADHD)

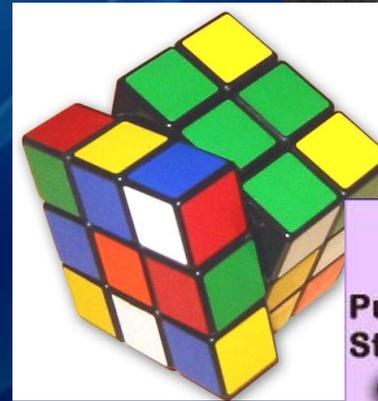
Characteristics of Down Syndrome



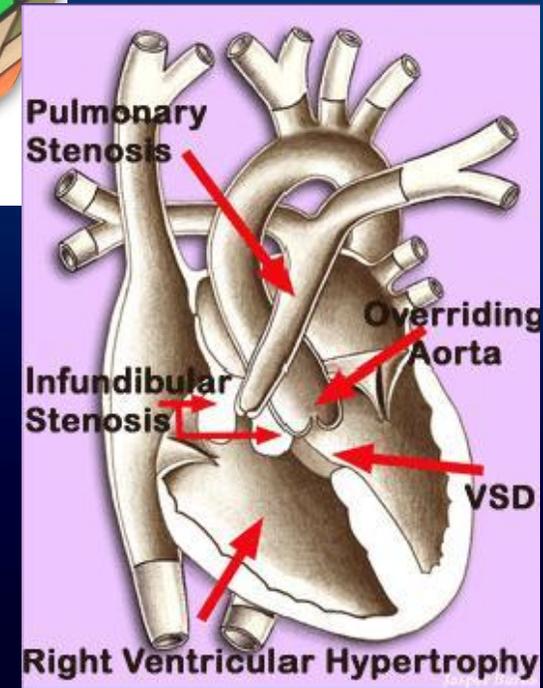
Cardiovascular System:

Cardiac malformations

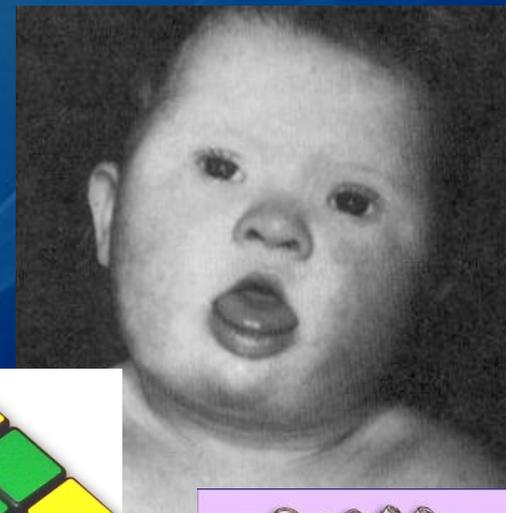
- Septal defects
- Tetralogy of Fallot
- Patent ductus arteriosus



Leading cause of mortality in Down syndrome

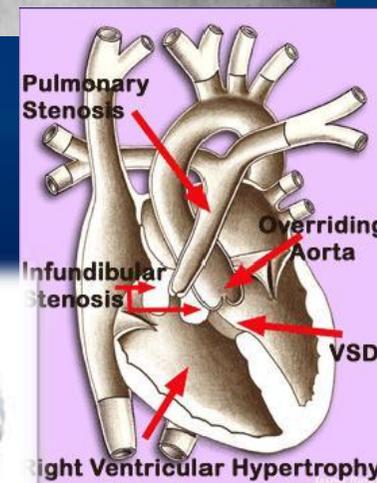
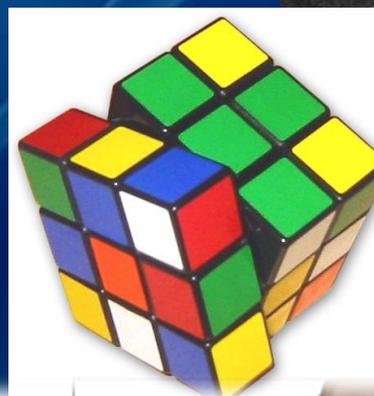


Characteristics of Down Syndrome

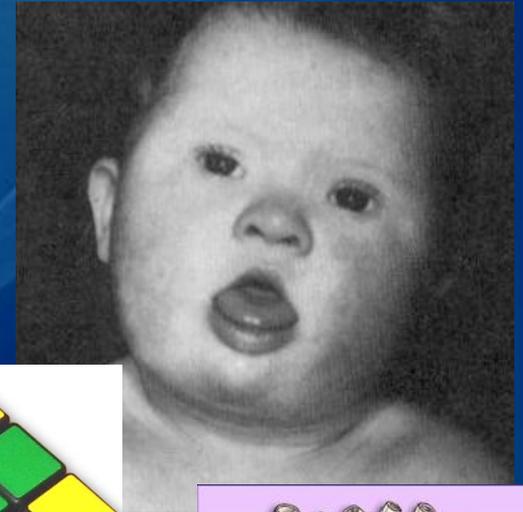


Musculoskeletal System:

- Dysplasia of the pelvis
- Hypotonia

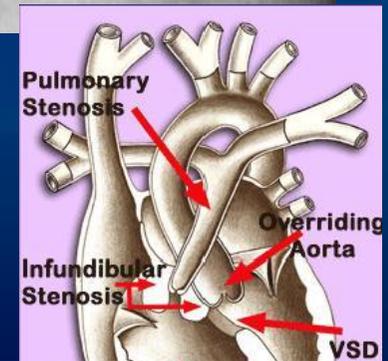
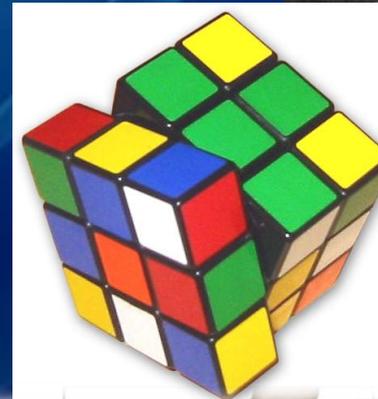


Characteristics of Down Syndrome

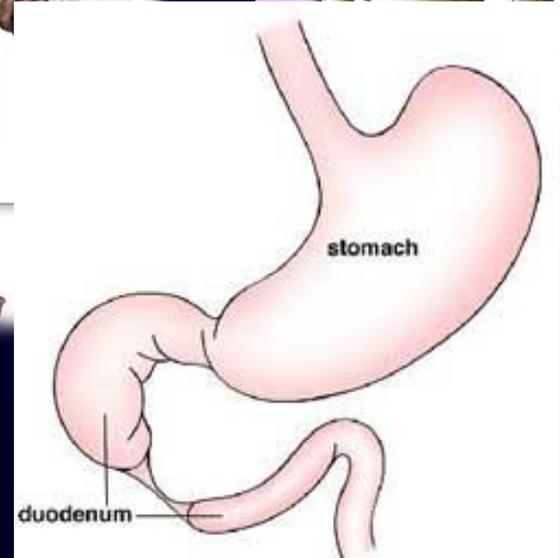


Gastrointestinal System:

- Intestinal atresia
- Abnormalities of anus
- Hirschsprung's disease (absence of nerve cells in bowel-wall)

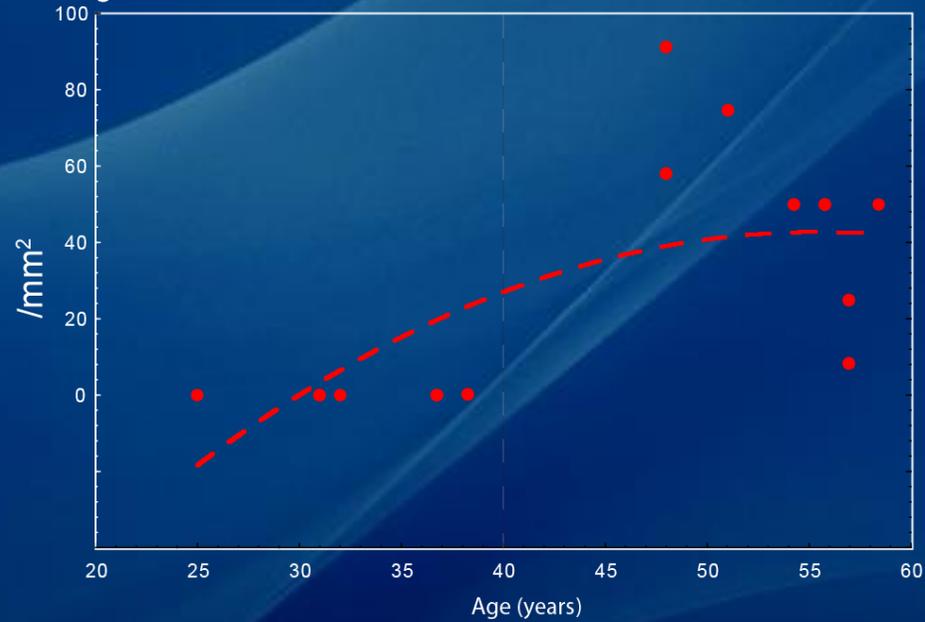


Hypotonia
(decreased
muscle tone)

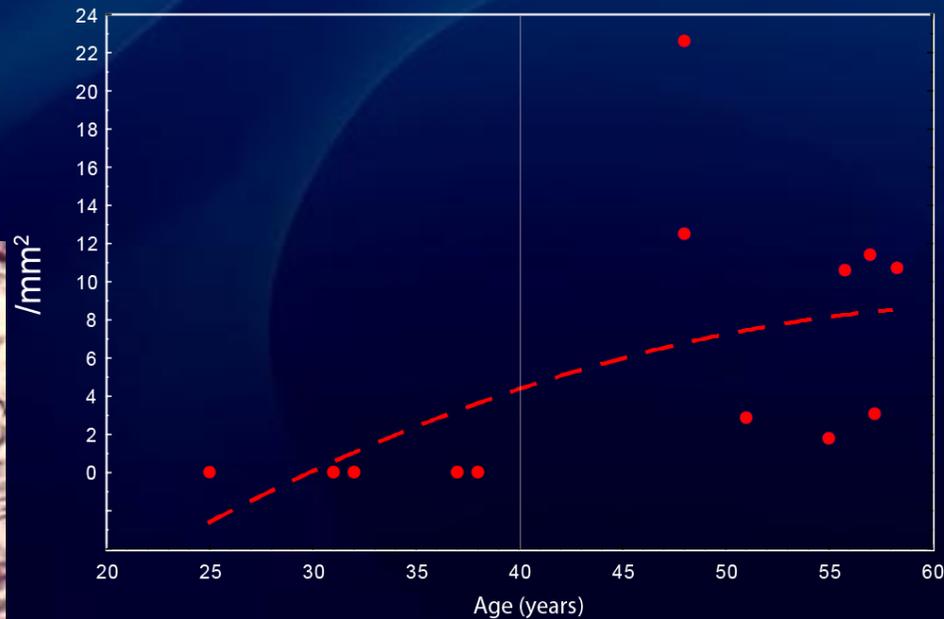


Alzheimer's Disease Pathology in Adults with Down Syndrome

Neurofibrillary tangles



Plaques



Process of Drug Development

Define the problems



Discover genes and mechanisms



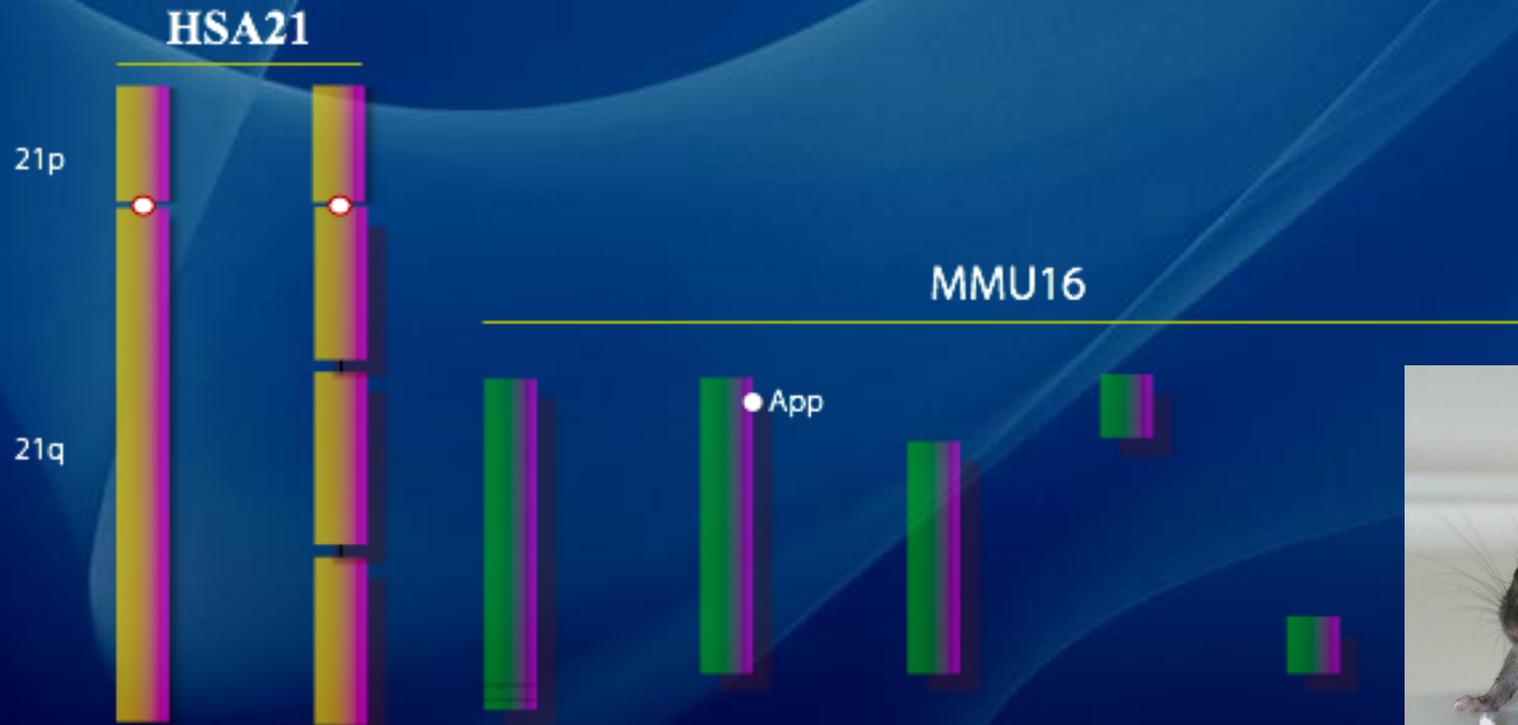
Discover treatments



Deliver treatment



Mouse Models of Down Syndrome



	Down Syndrome	Tc1	Ts16	Ts65Dn	Ts1Cje	Ms1Cje/Ts65Dn	Ts1Rhr
Number of duplicated 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

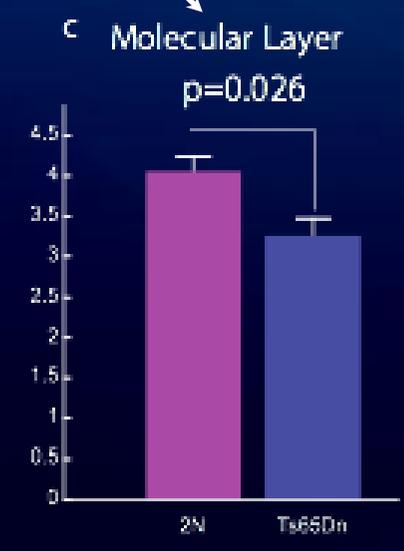
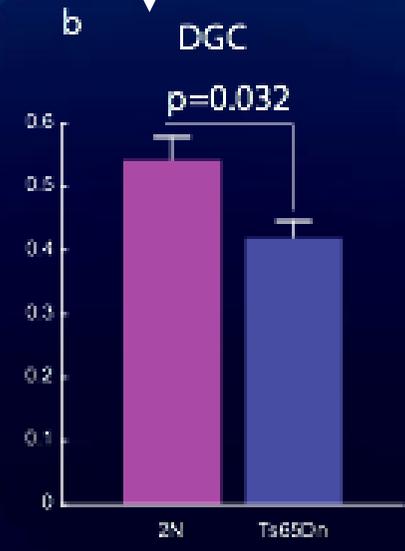
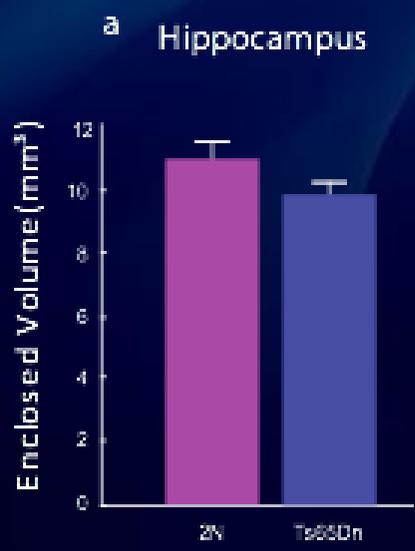
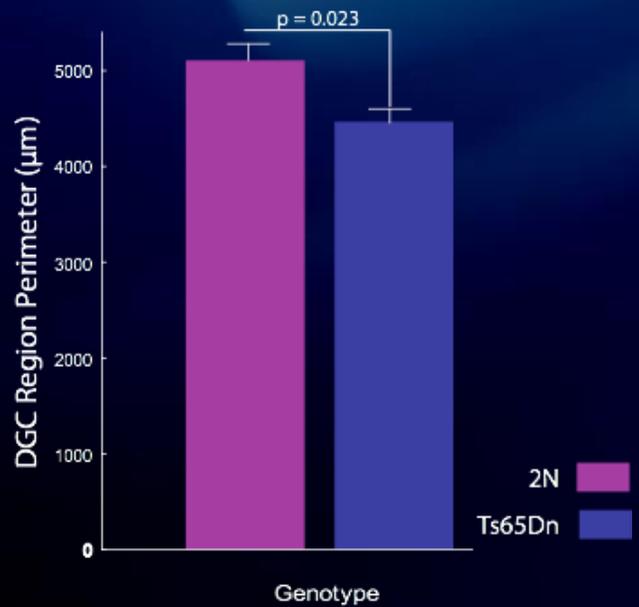
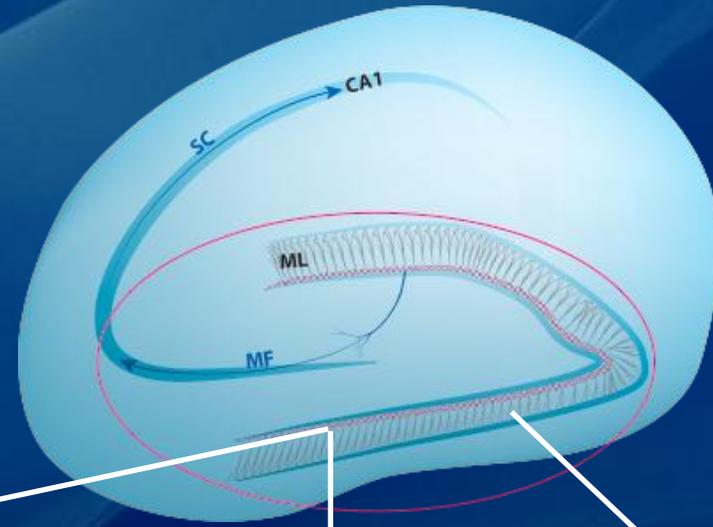
Target Abnormal Circuits

Overexpression
of specific genes on
HSA21

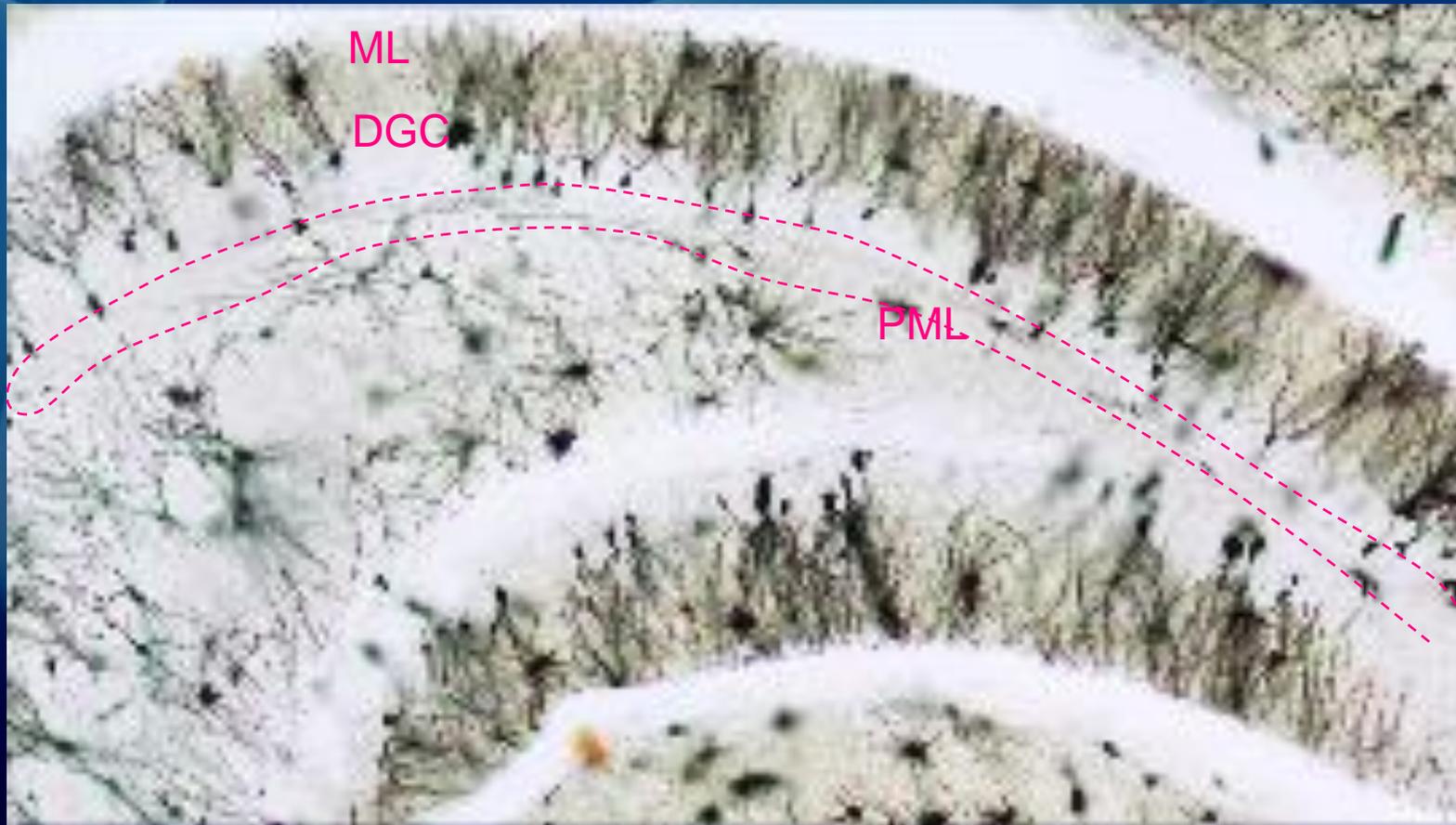


Cognitive Dysfunction

Dentate Gyrus Undergoes Significant Atrophy in Ts65Dn Mice

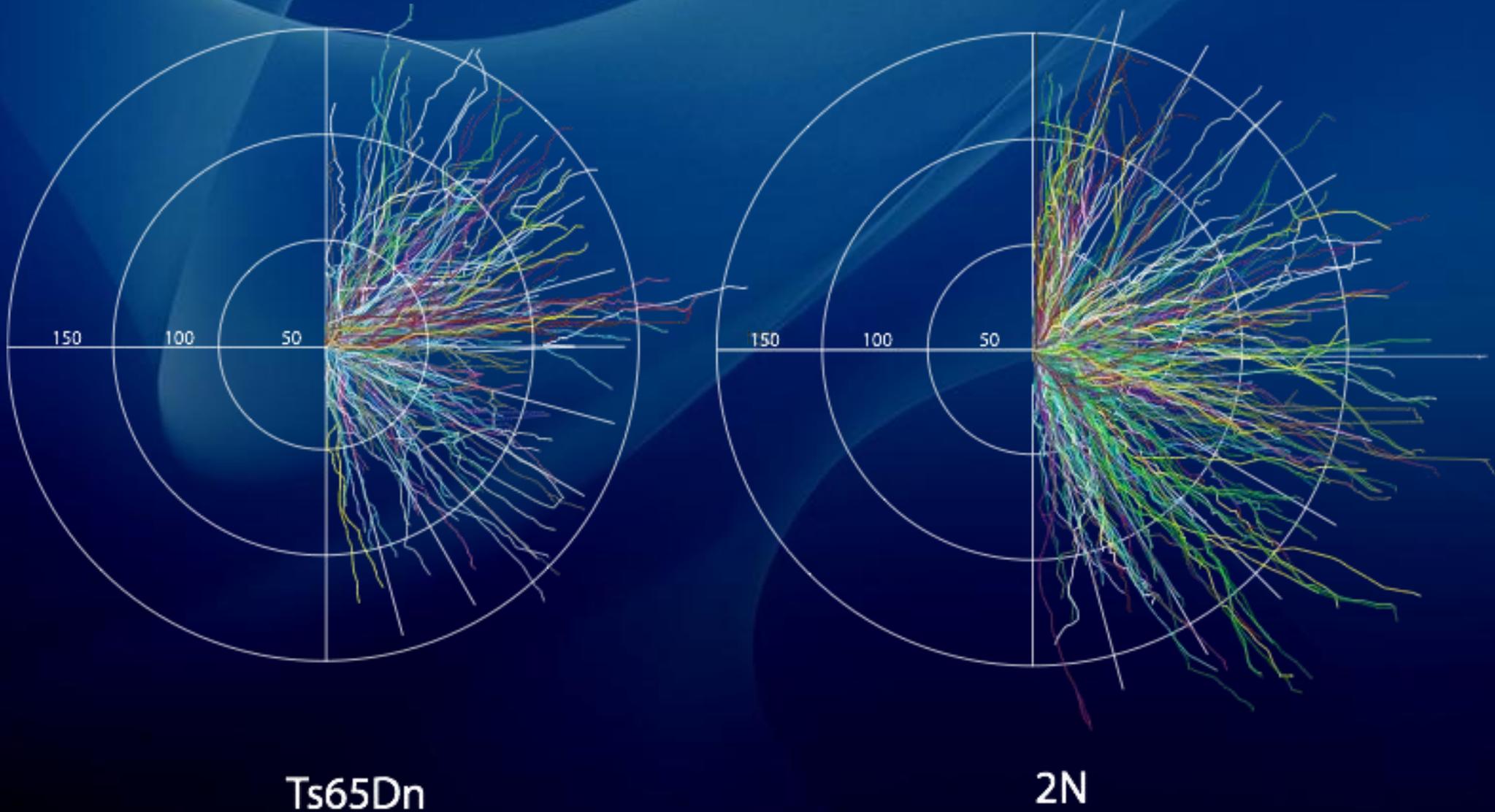


Quantification of Dendritic Tree in DGCs

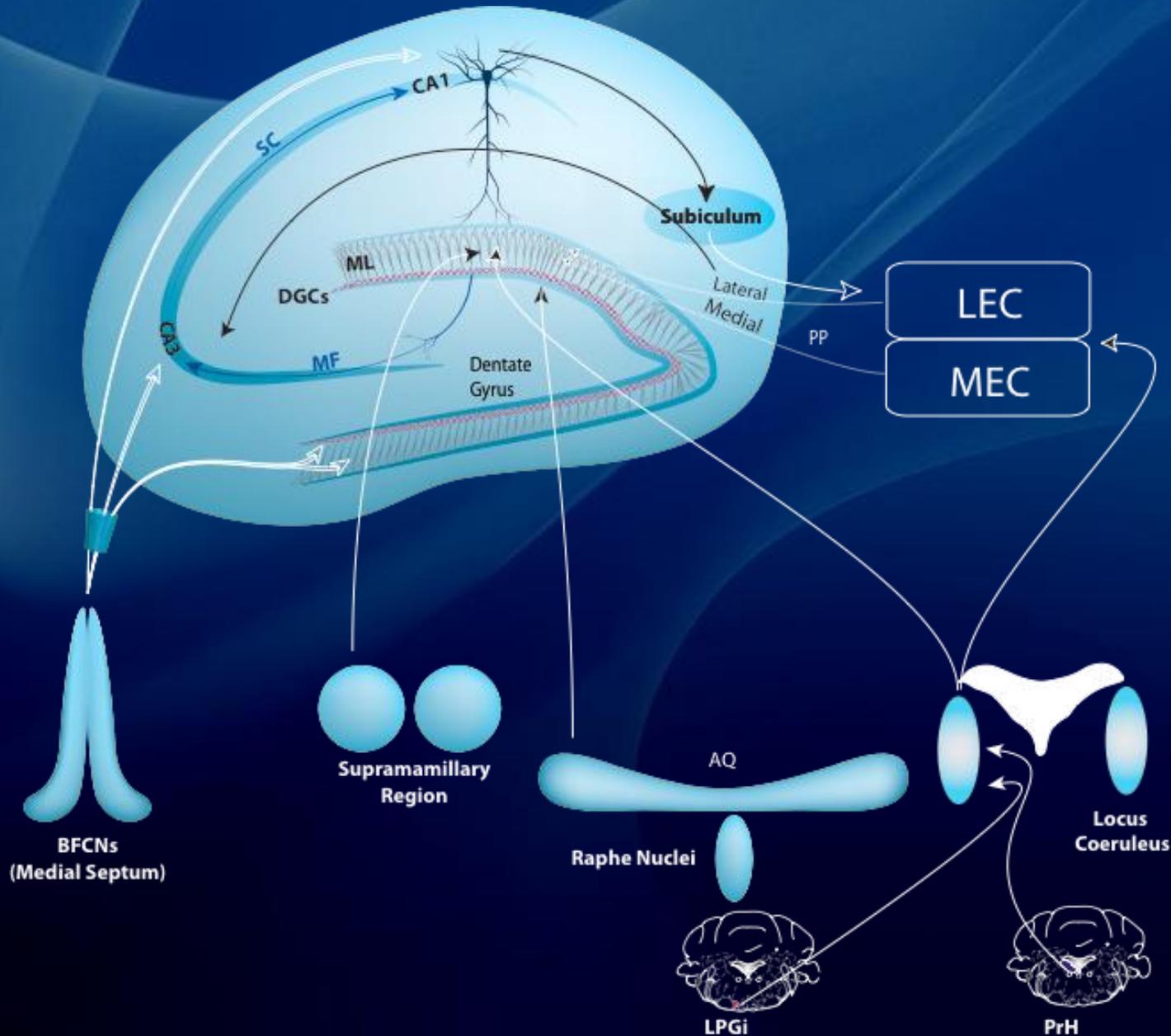


Dentate Gyrus

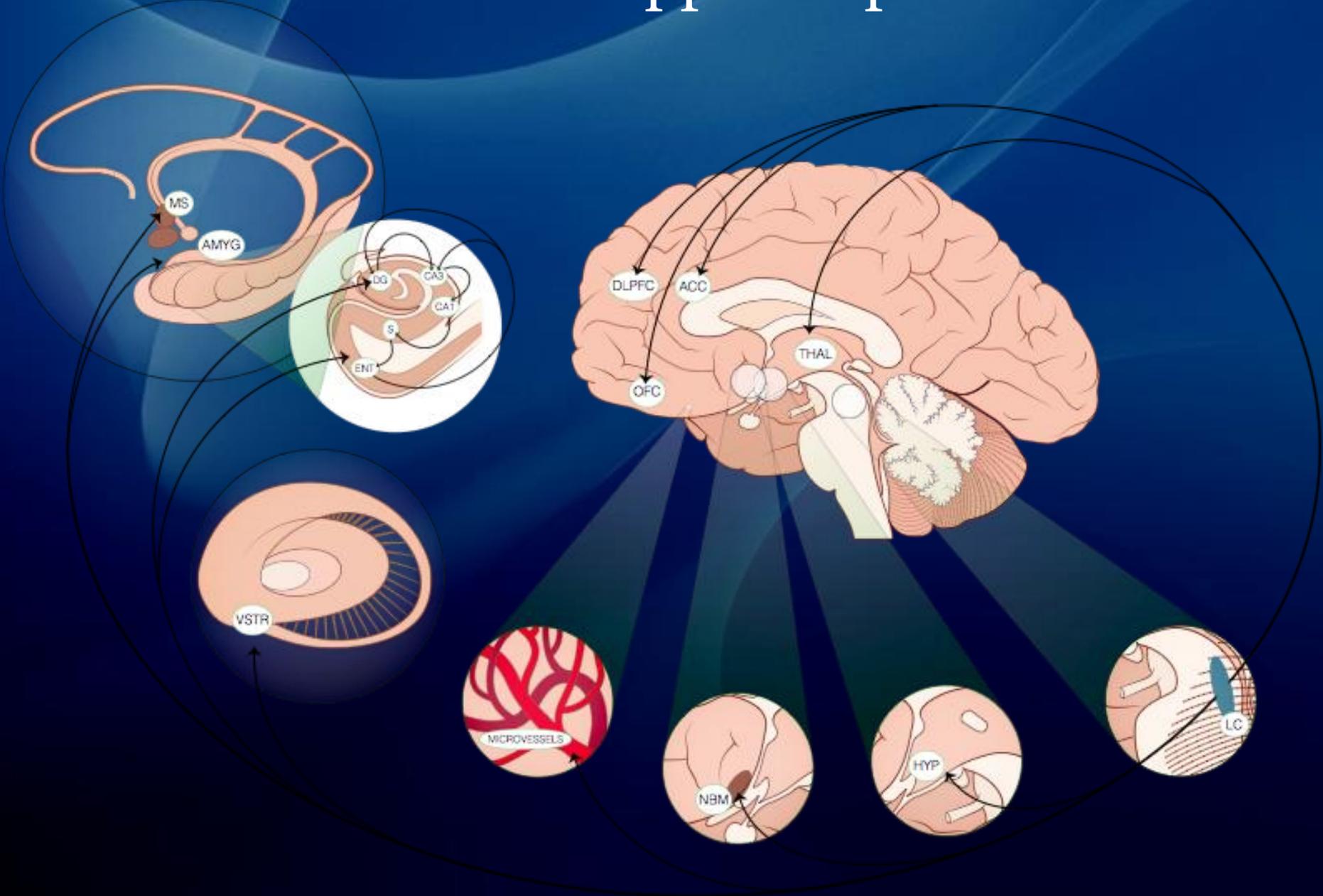
A Significant Loss of Dendritic Arborization in DGCs in Ts65Dn Mice



Hippocampal Function is Modulated by Subcortical Regions with Extensive Projections



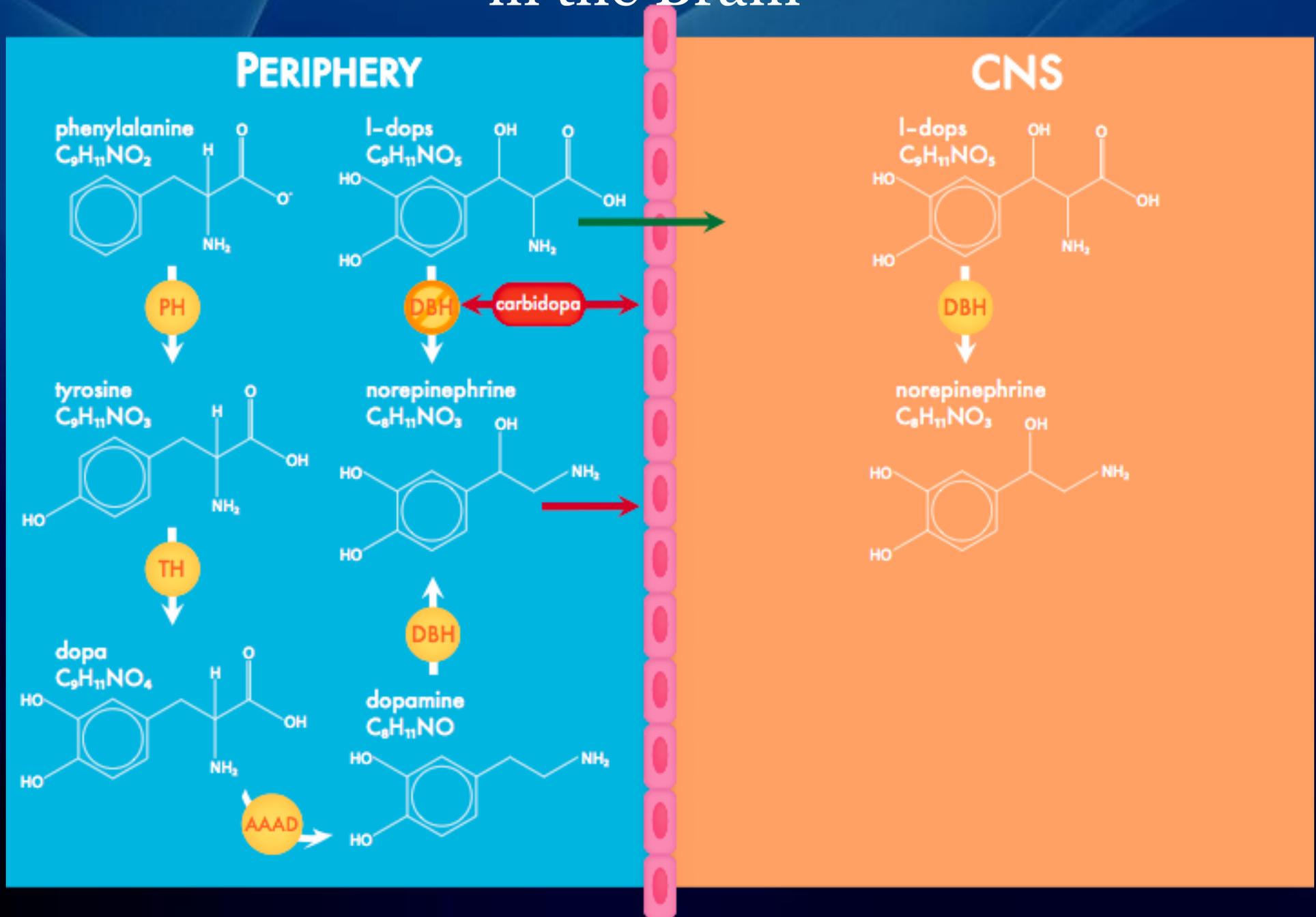
Locus Coeruleus Neurons Send Extensive Projections to the Rest of the Brain Particularly the Hippocampus



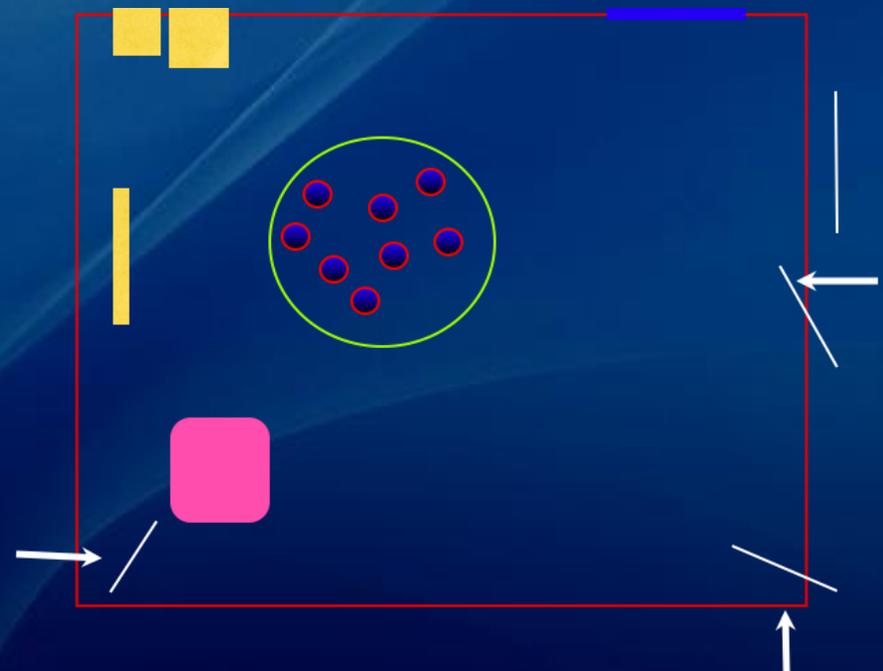
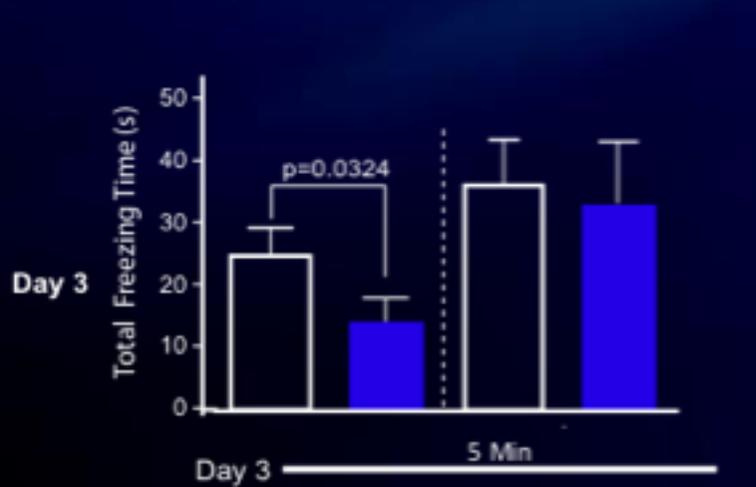
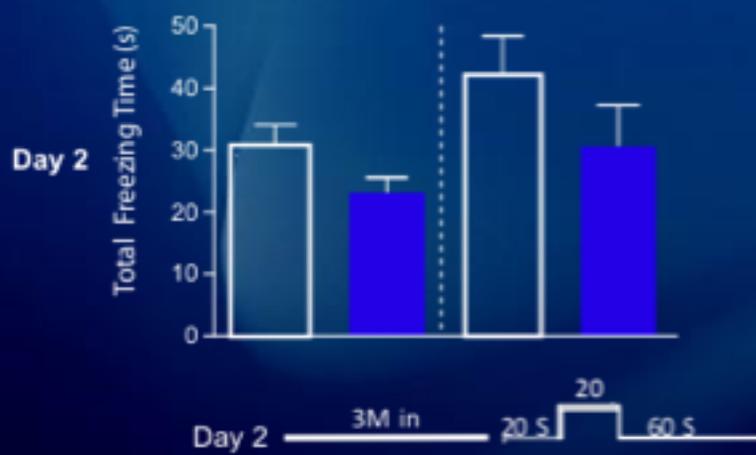
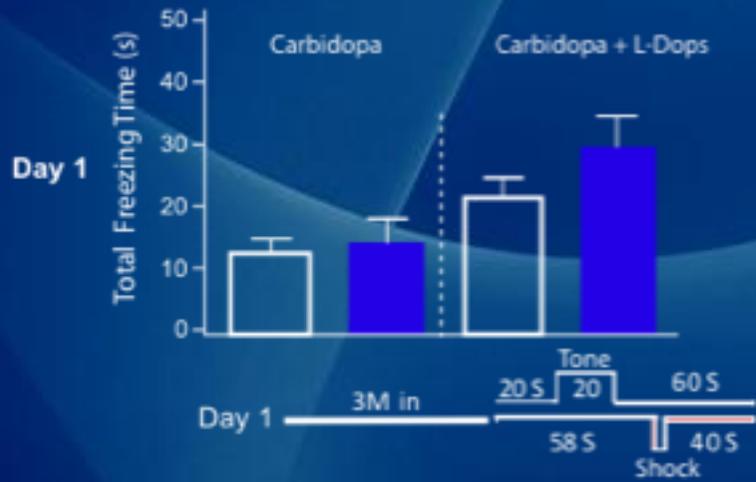
Strategies to Increase Norepinephrine (NA) Levels in Ts65Dn Mice

- 1) Increasing brain NE levels.
- 2) α adrenergic agonists.

Method of Increasing Norepinephrine Levels in the Brain



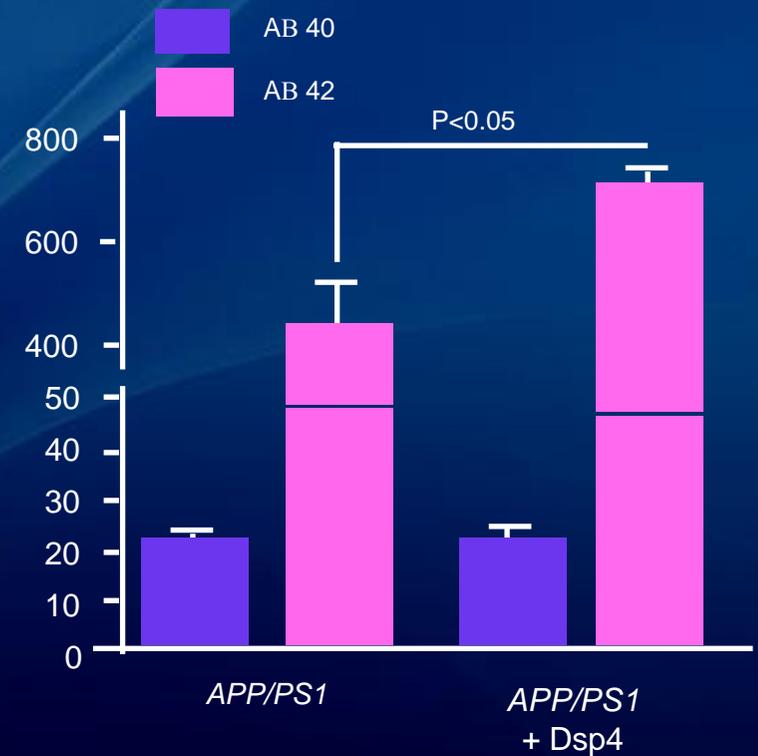
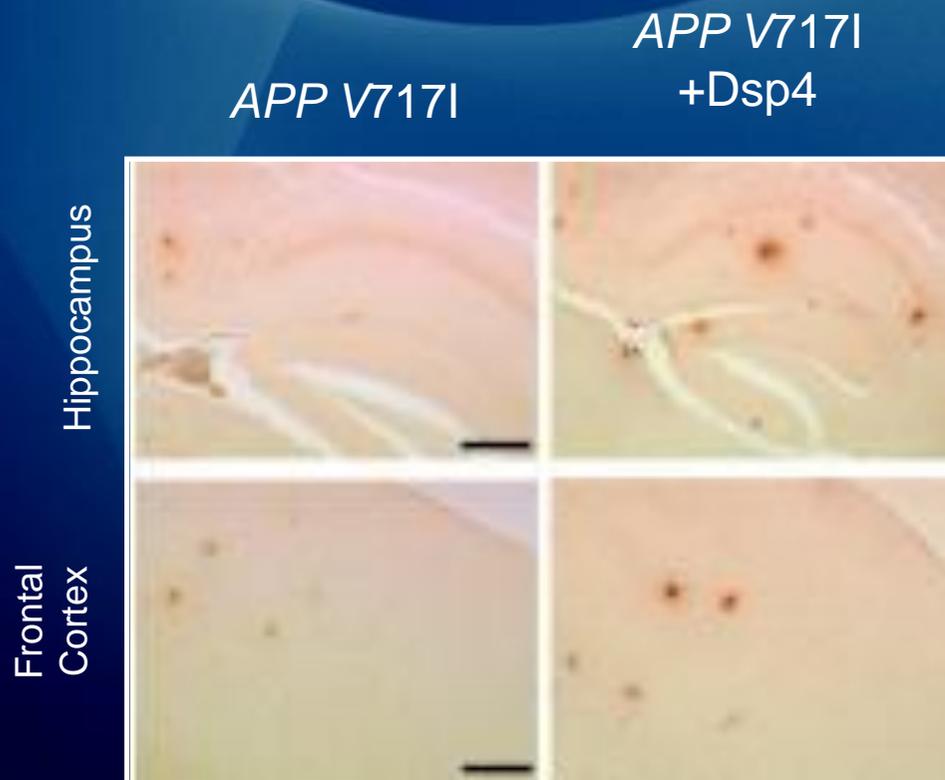
Failure in Contextual Learning in Ts65Dn Mice



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

p value- Mann-Whitney U- test

Loss of Locus Coeruleus Neurons in Mouse Models of AD

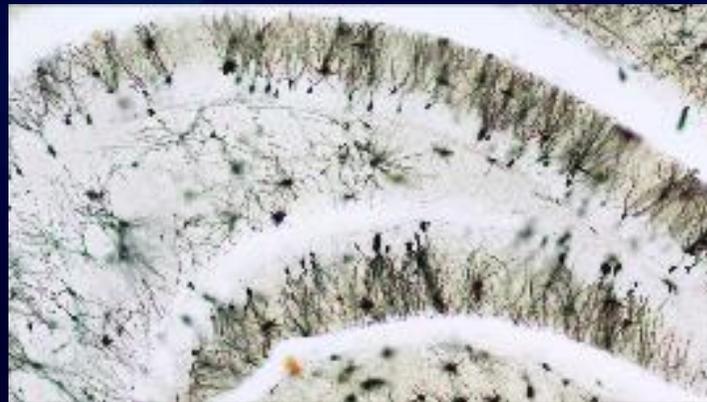
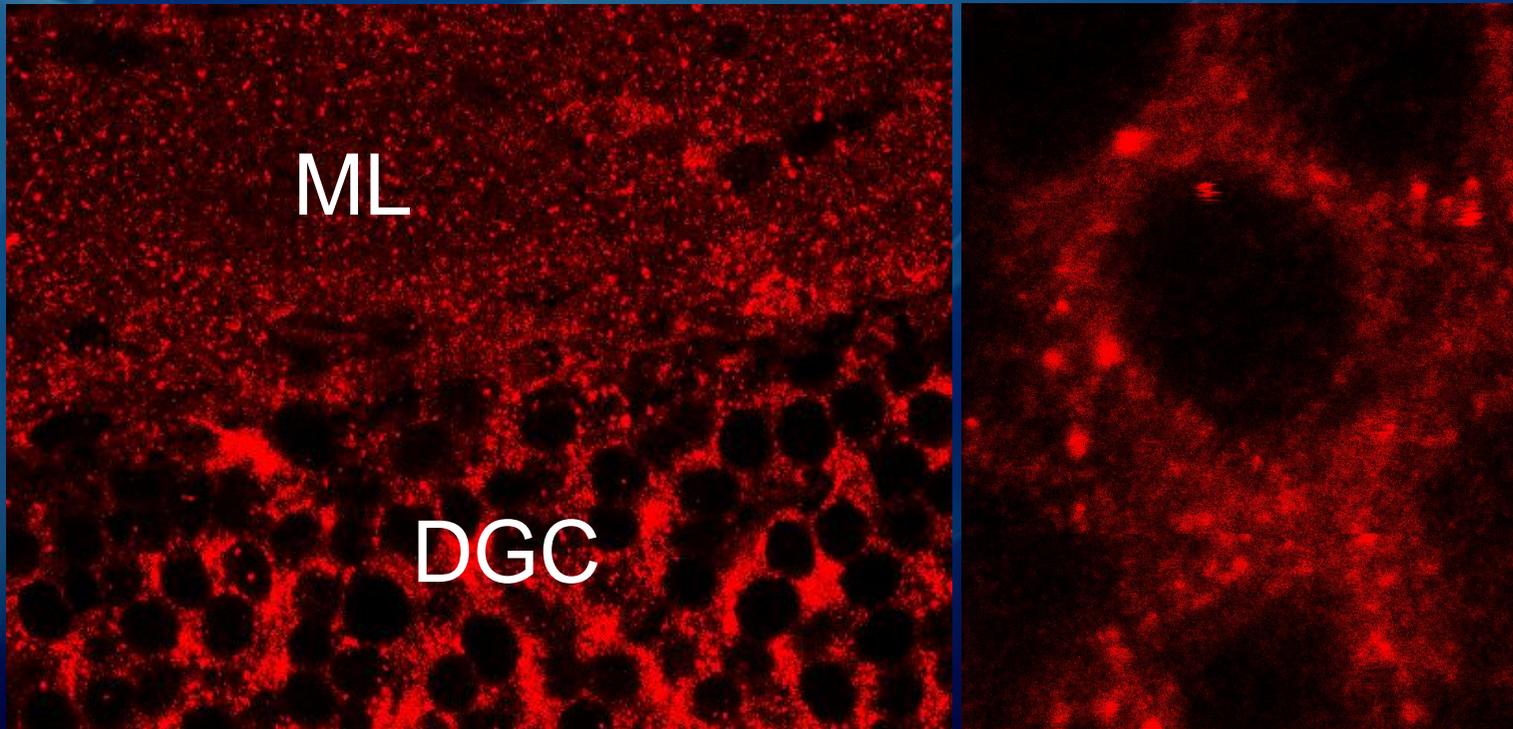


L-DOPS is able to restore cognitive function in the Ts65Dn mouse model of Down syndrome but it is yet to be approved by the FDA

Targeting β_1 or β_2 Adrenergic Receptors?

- 1) Cardiovascular complications are the most common cause of death in DS.
- 2) β_2 gene expression is more than beta1 in DGCs
- 3) Effects of NE on LTP is mediated by β_2 .
- 4) β_2 mediates the effects of NE on ADE.
- 5) β_2 polymorphism has been linked to dementia of AD.
- 6) β_2 mediates the positive effects of NE on neurogenesis.

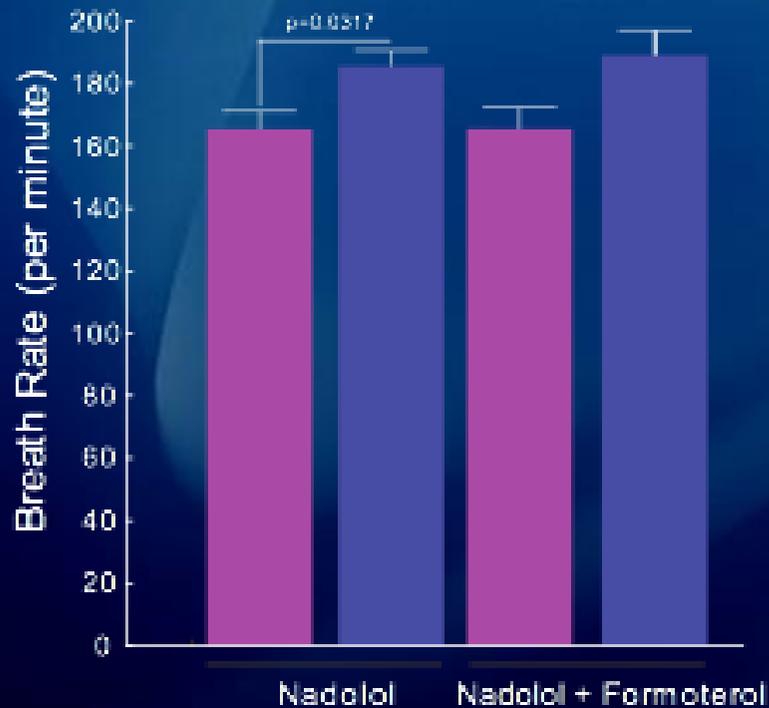
β_2 Adrenergic Receptors in Dentate Granule Cells



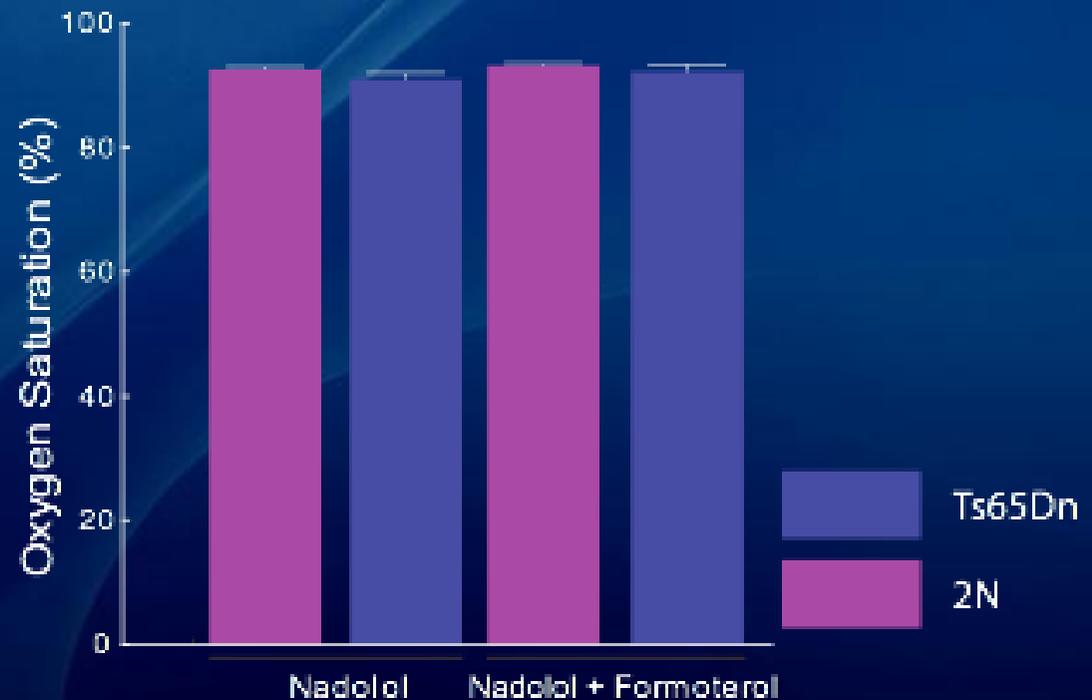
Formoterol (FORM) is a long-acting specific β_2 -adrenergic receptor agonist used for the treatment of asthma.

No Adverse Effects of Formoterol on Respiratory System

The Effects of Formoterol Treatment on Respiratory System



Genotype: $F=10.67$, $p=0.003$, Treatment: $F=0.06$, $p=0.809$



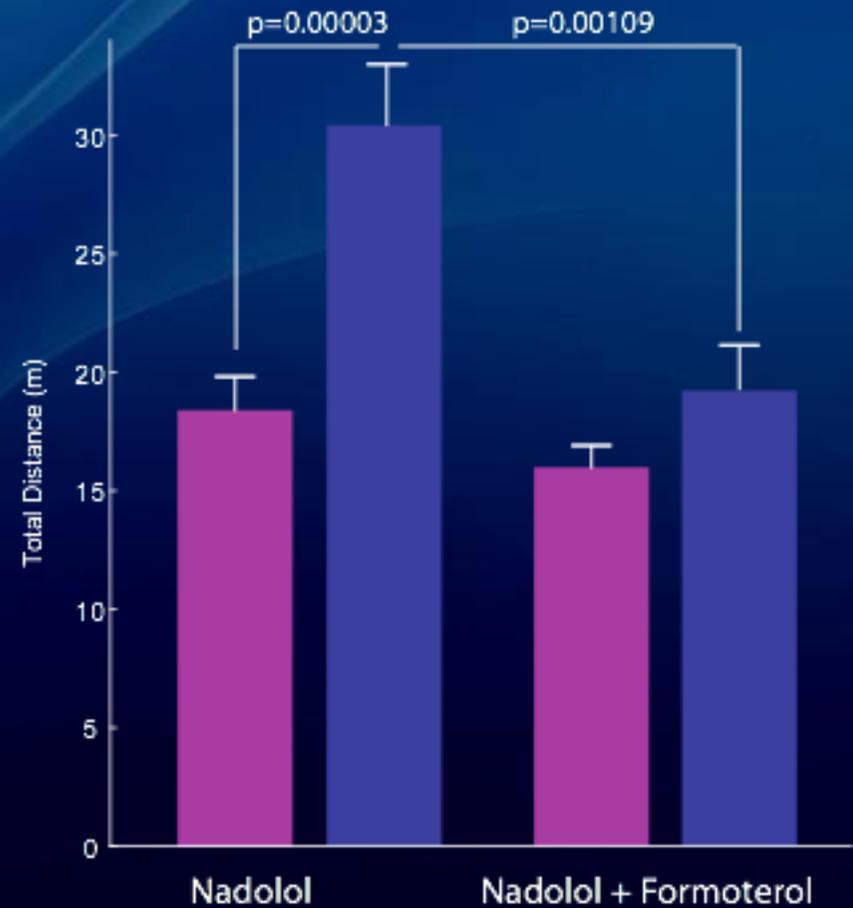
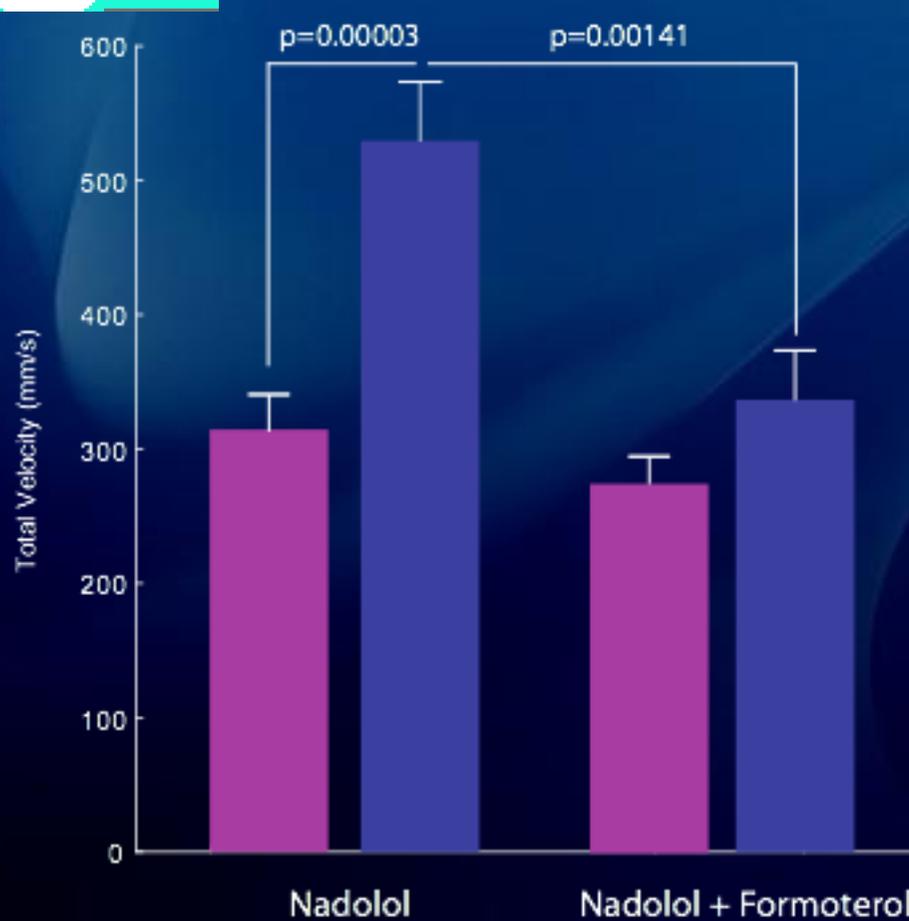
Genotype: $F=2.595$, $p=0.120$, Treatment: $F=1.325$, $p=0.259$

Formoterol Reduces Open Field Activity in Ts65Dn Mice

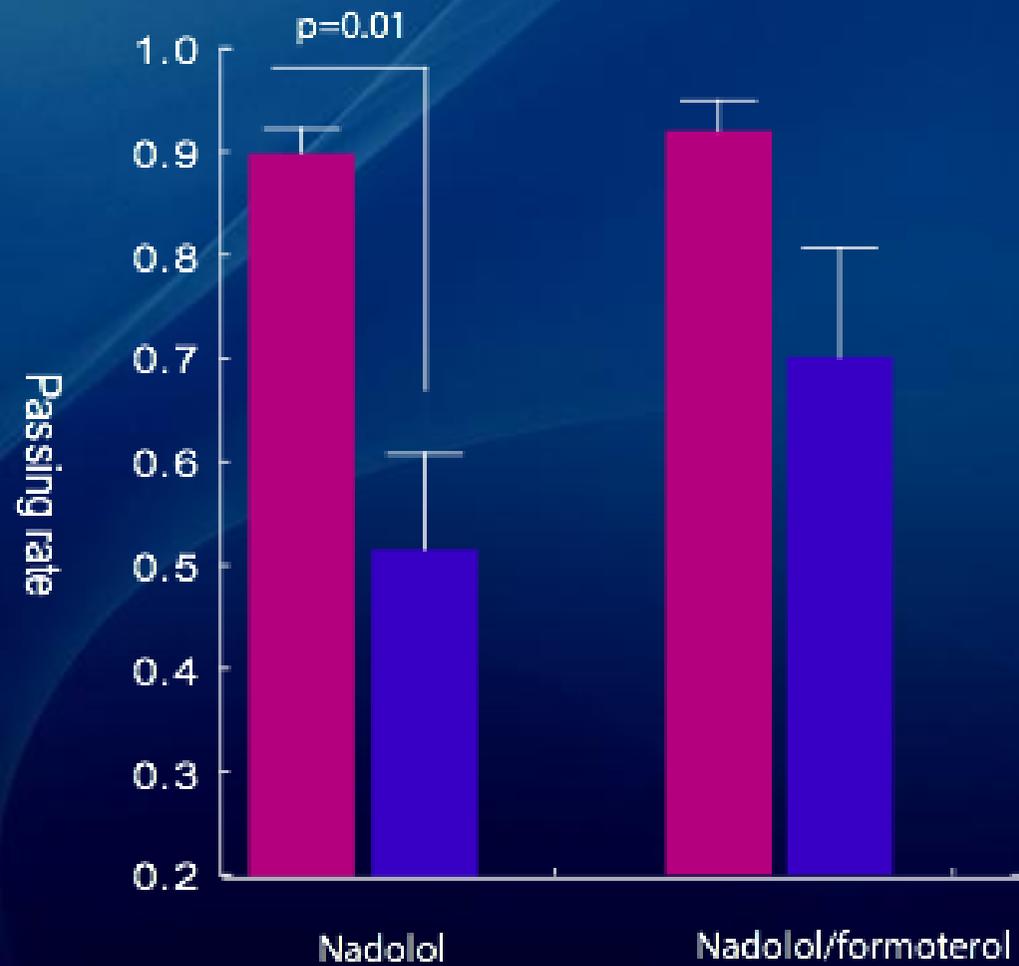
Velocity

Total Distance Travelled

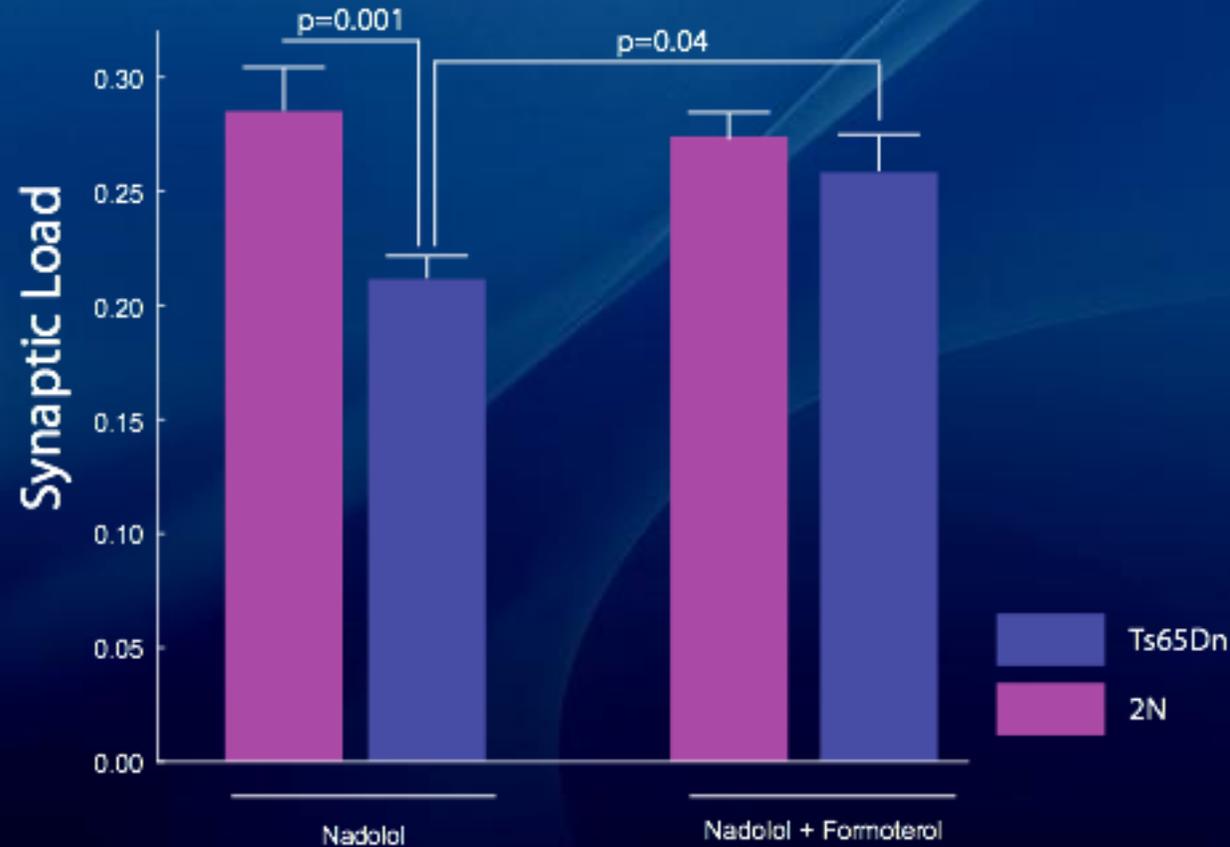
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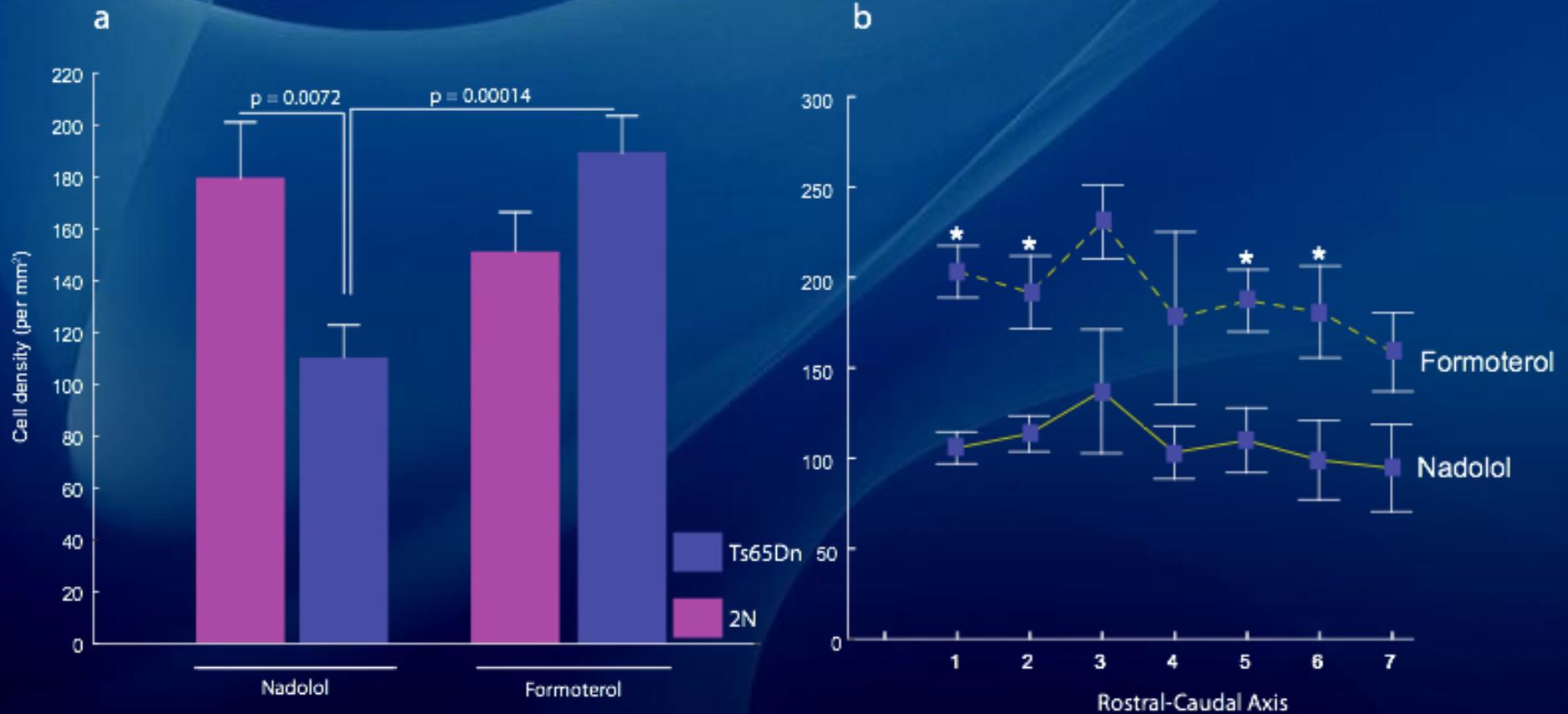
Formoterol Improves Spatial Learning in Ts65Dn Mice



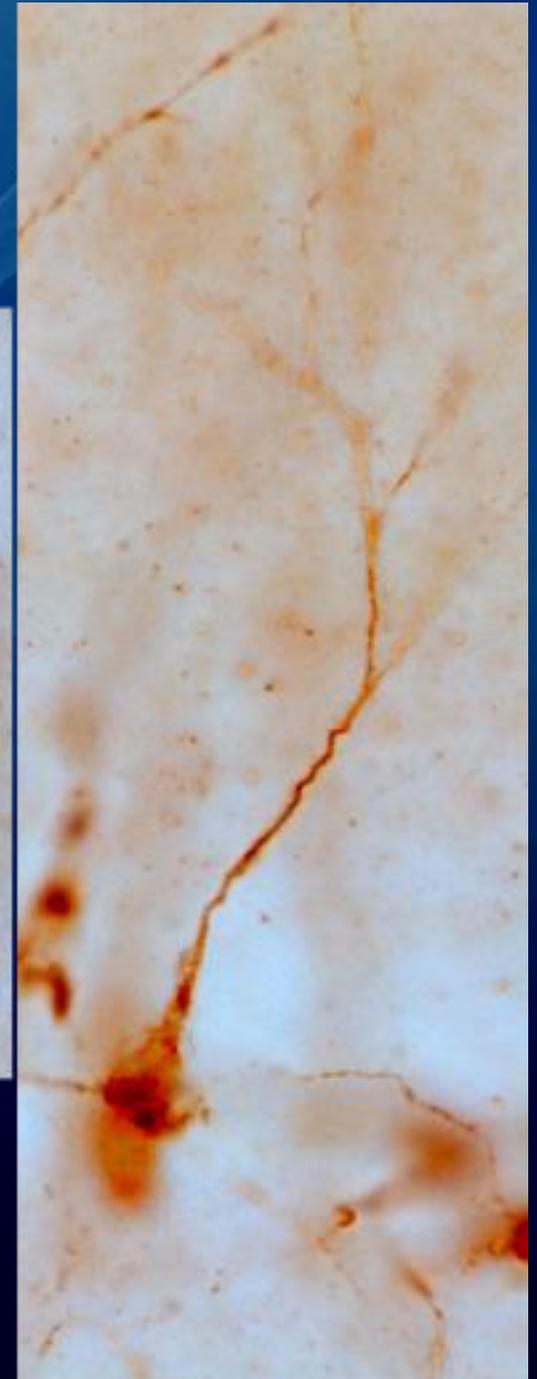
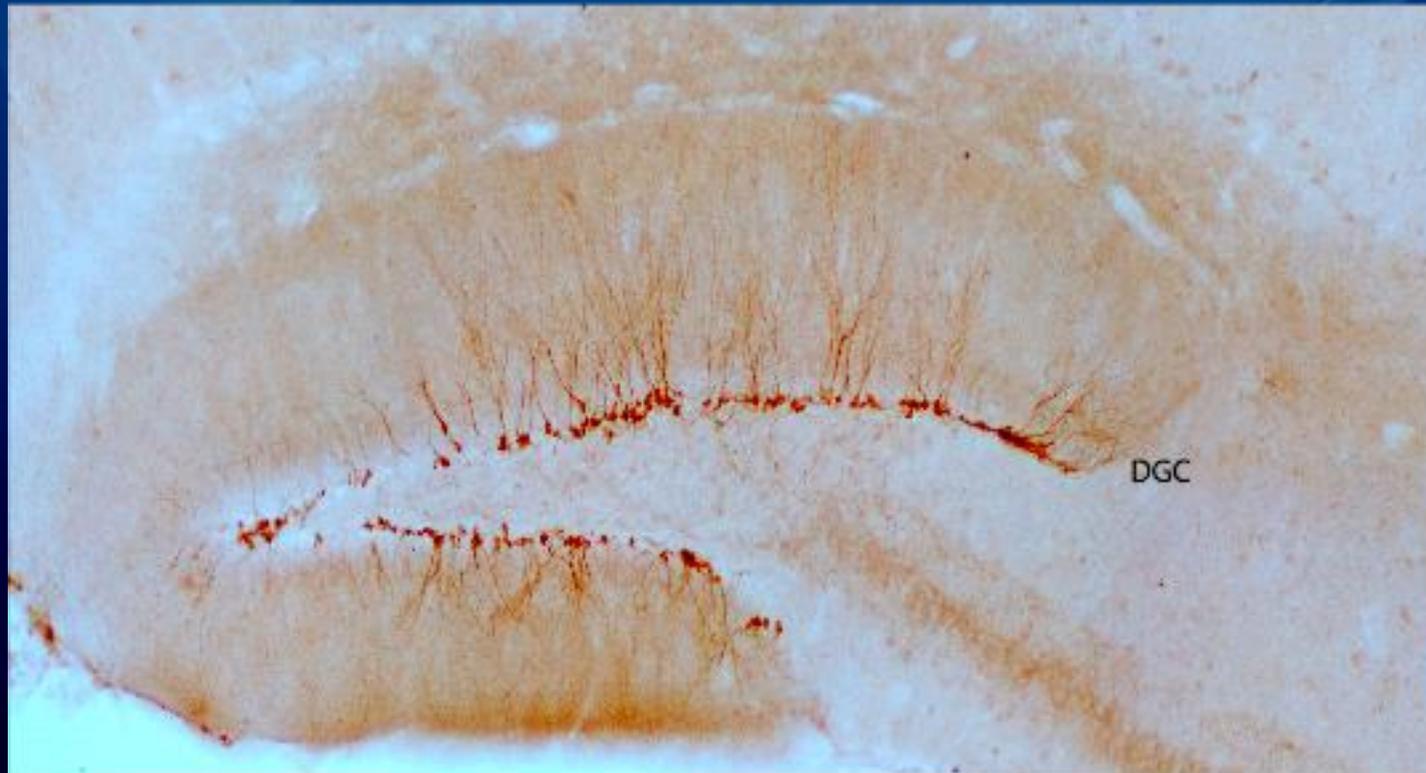
Short Term Use of formoterol Leads to a Significant Increase in the Synaptic Density in the Dentate Gyrus in Ts65Dn Mice



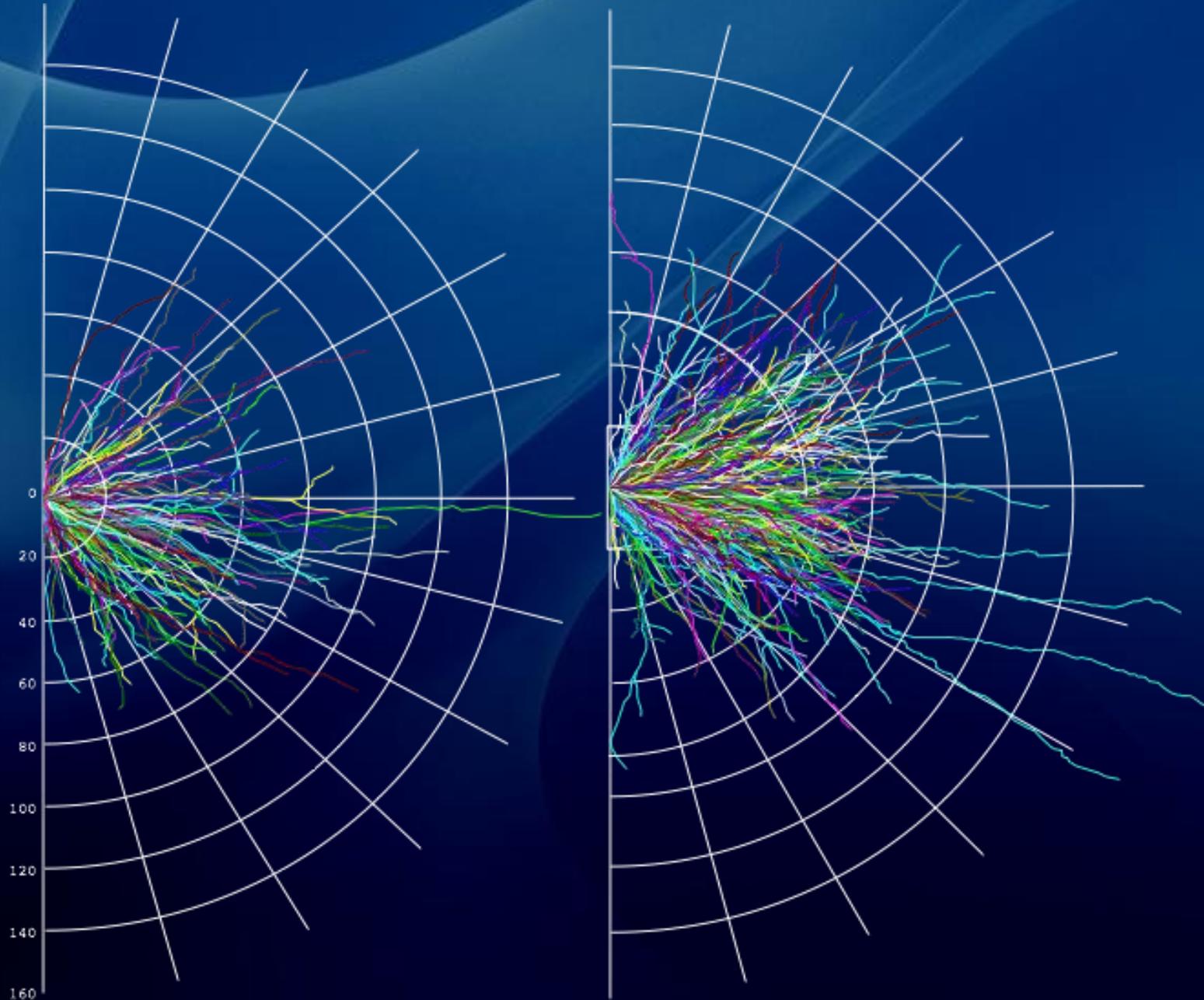
Increased Density of C-Fos-positive Neurons in the Dentate Gyrus of Ts65Dn mice



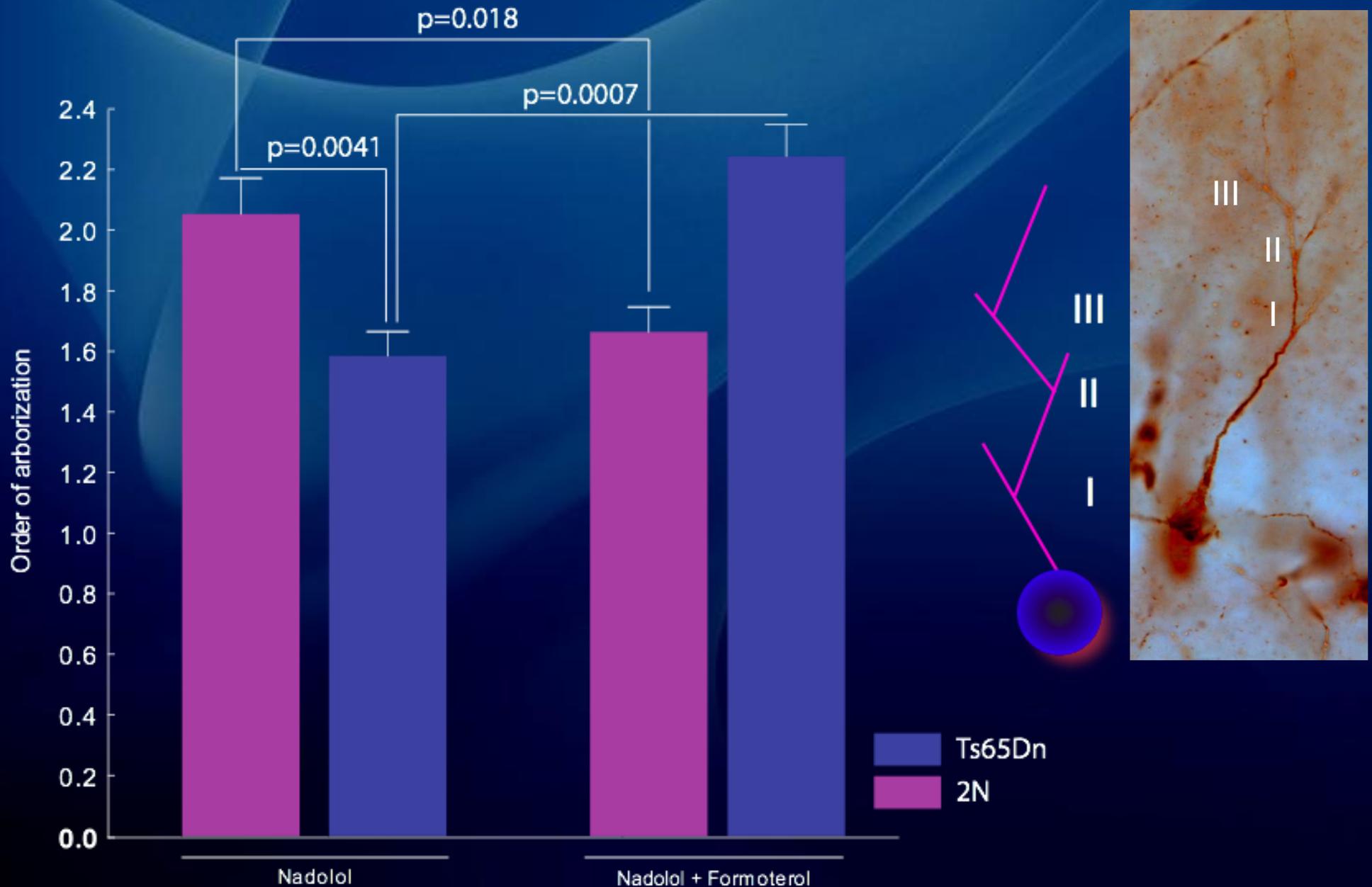
Doublecortin Labels Newly-born Cells Destined to Become Neurons



Formoterol Significantly Increases the Dendritic Complexity of New-born Neurons



Formoterol Significantly Increases the Dendritic Complexity of New-born Neurons



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