



Unraveling mechanisms
and searching for cures for
learning disabilities:
Parallels with Epilepsy

Temporal Profile of Learning and Memory Consolidation



Emergence of a consolidated memory

Training

Minutes

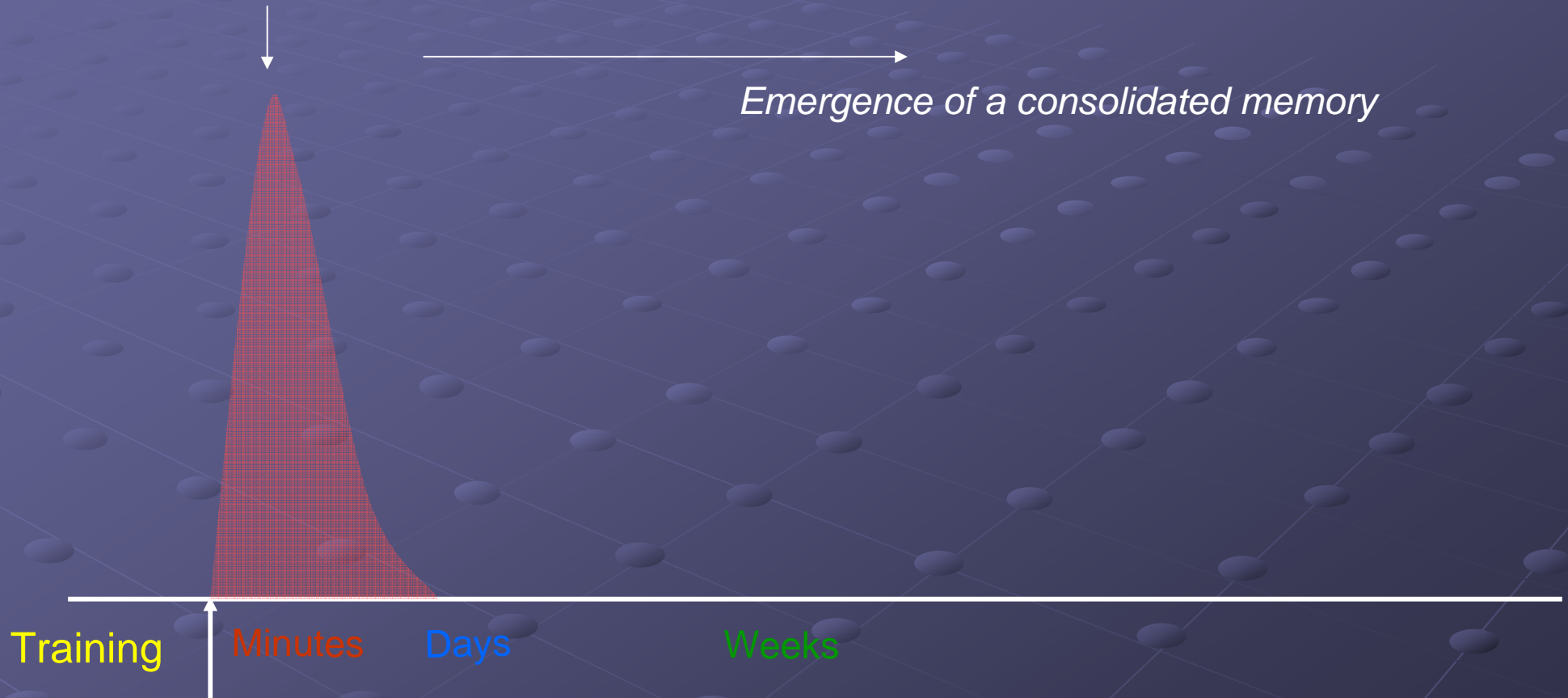
Days

Weeks

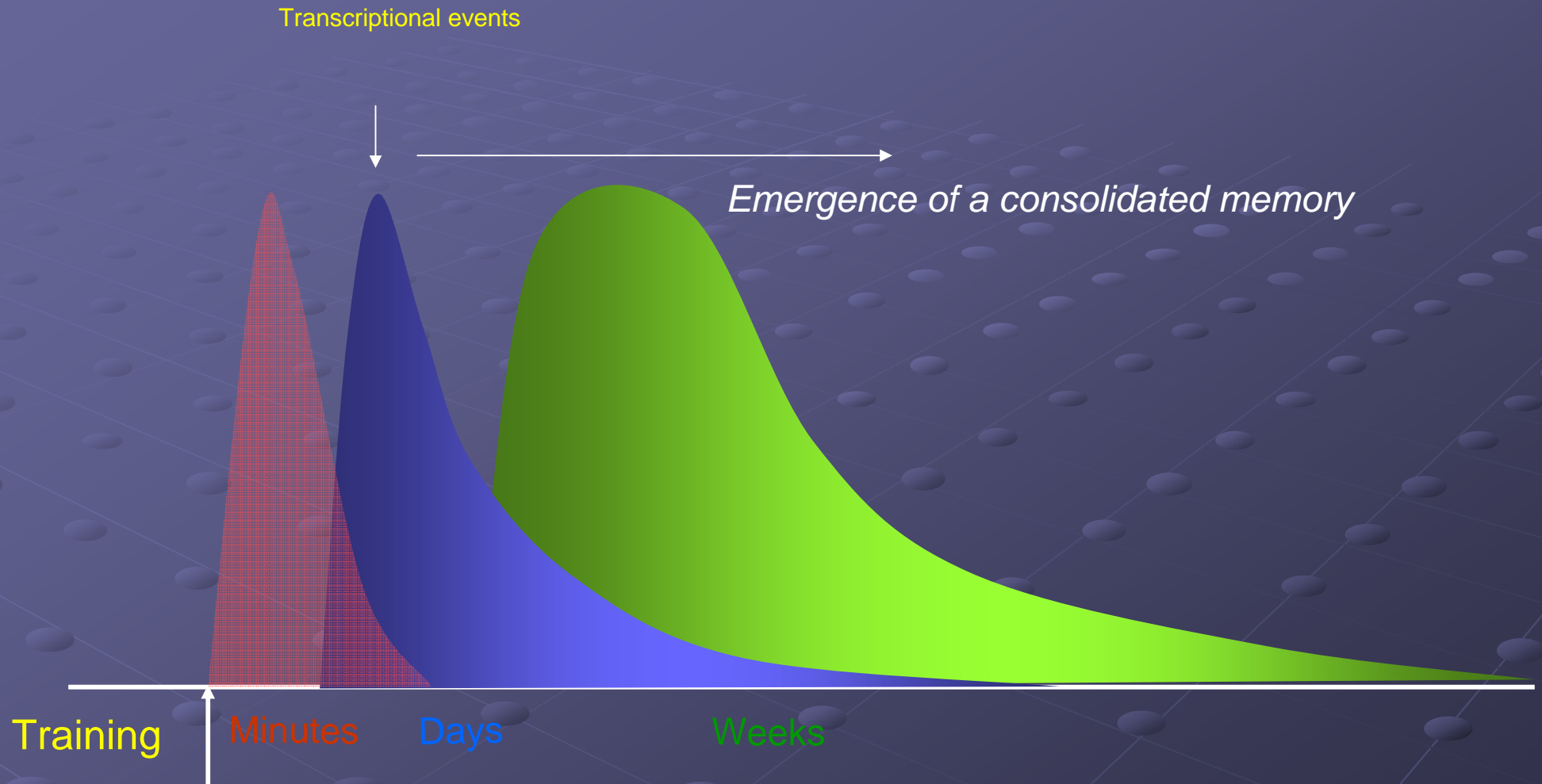


Temporal Profile of Learning and Memory Consolidation

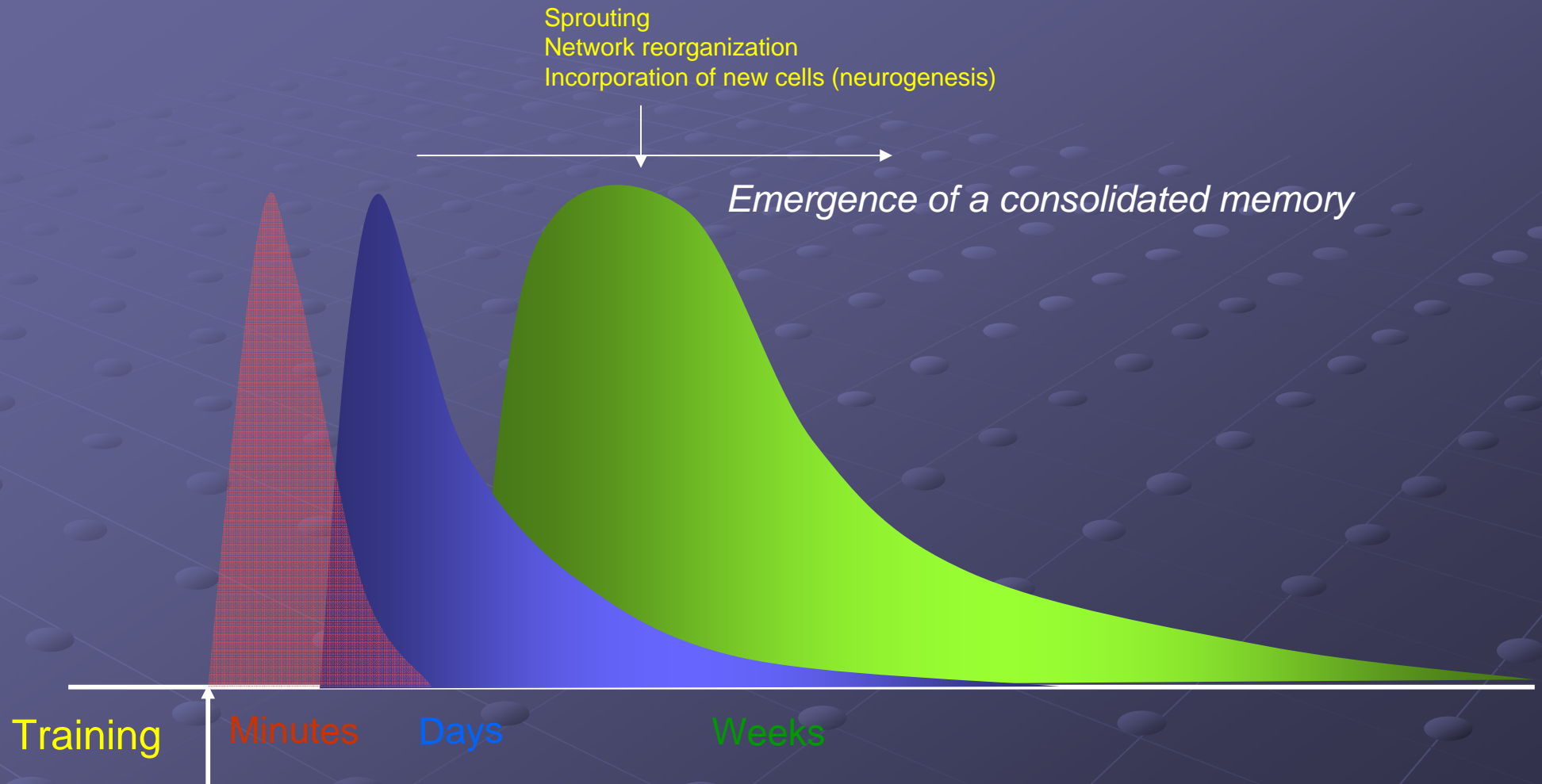
Ion channel activation
Post-translational changes
Immediate early genes



Temporal Profile of Learning and Memory Consolidation



Temporal Profile of Learning and Memory Consolidation



Cognitive deficits associated with learning disabilities, mild mental retardation

- Affect $> 5\%$ of the population
- Enormous economic and personal impact
- Very few treatments
- Increases in Epilepsy are not rare in this patient population (I.e. NF1, TBS1, TBS2)

Neurofibromatosis type I and Learning Disabilities

- NF1 is a dominant inherited disorder (1/3500 people affected).
- *NF1* encodes a multi-functional Ras-GAP
- NF1 causes benign tumors
- **NF1 is associated with cognitive and neurological deficits, including an increased rate for epilepsy.**

What is the mechanism for the learning disabilities in Neurofibromatosis type I ?

- Increased Ras signaling

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- Increased Ras signaling
- Enhanced GABA release

What is the mechanism for the learning disabilities in Neurofibromatosis type I ?

- Increased Ras signaling
- Enhanced GABA release
- Deficits in synaptic plasticity

NF1 and learning



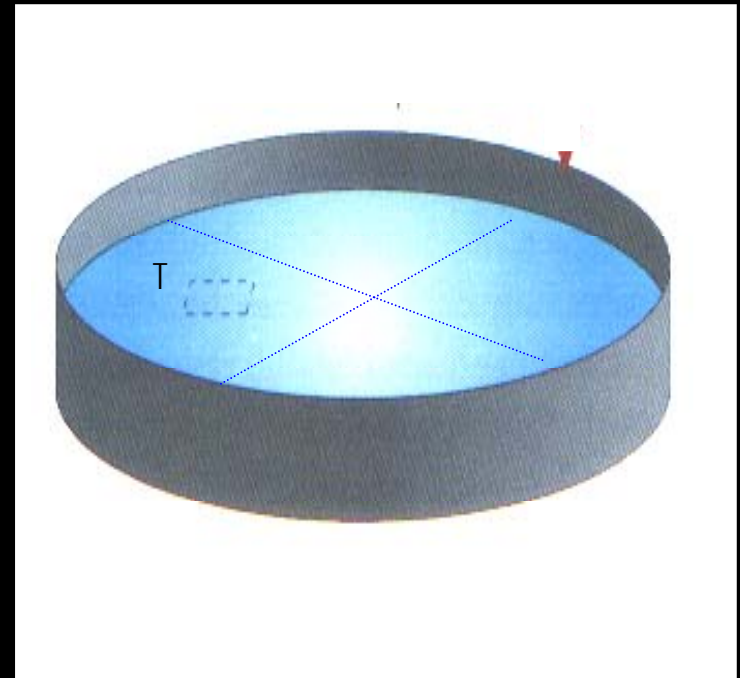
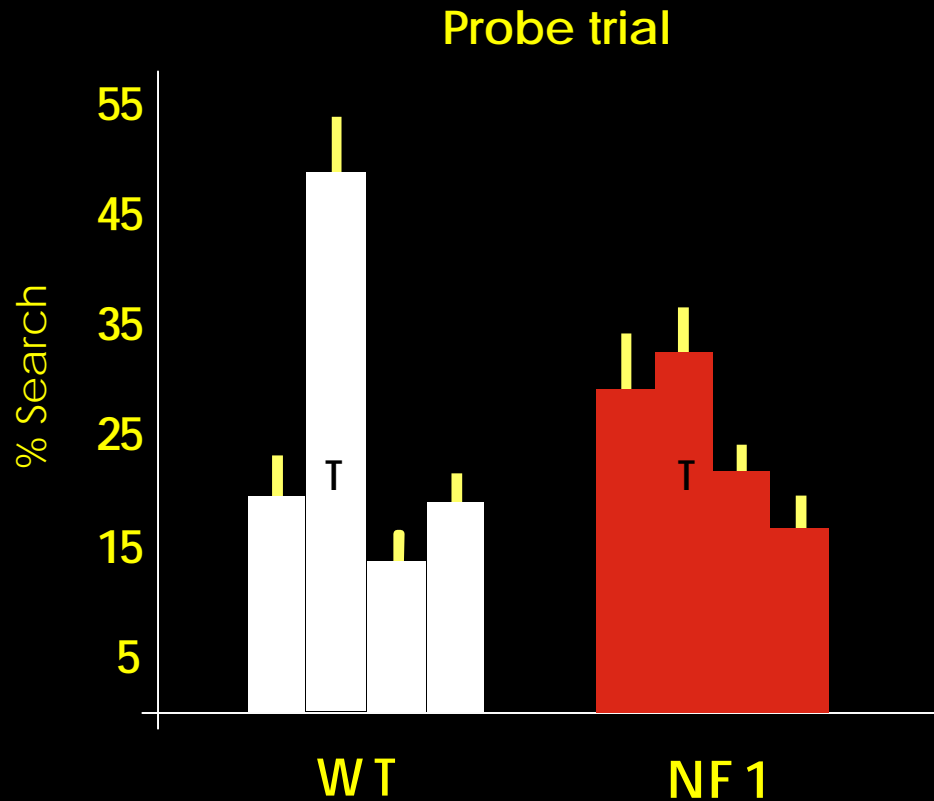
Rui Costa



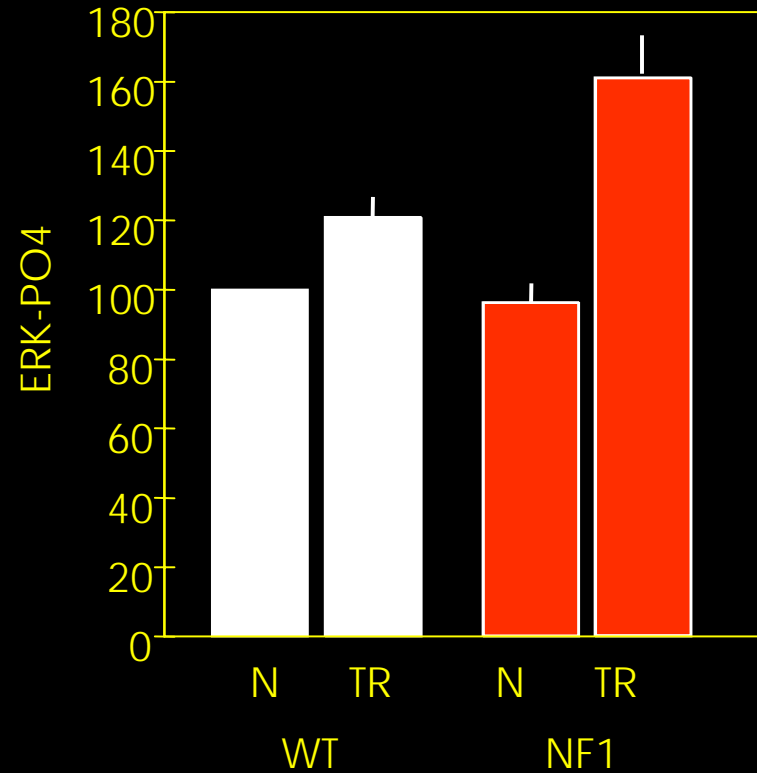
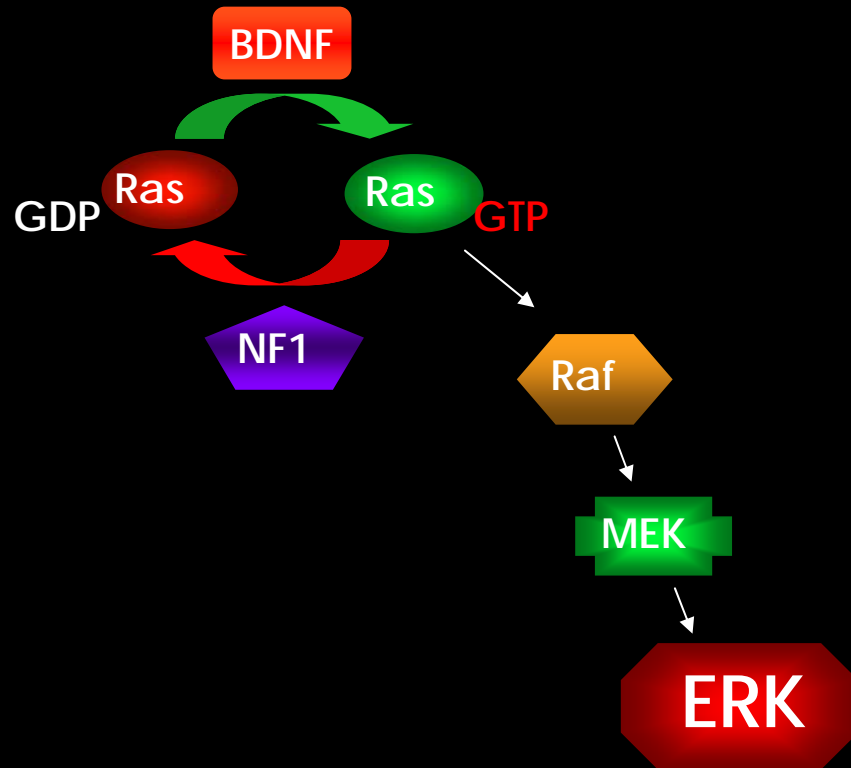
Nikolai Fedorov

The Morris Water Maze

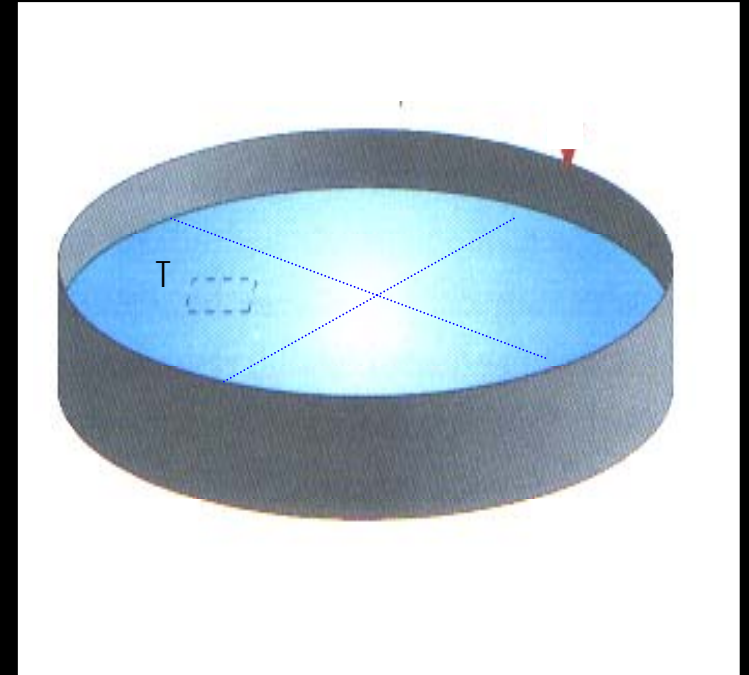
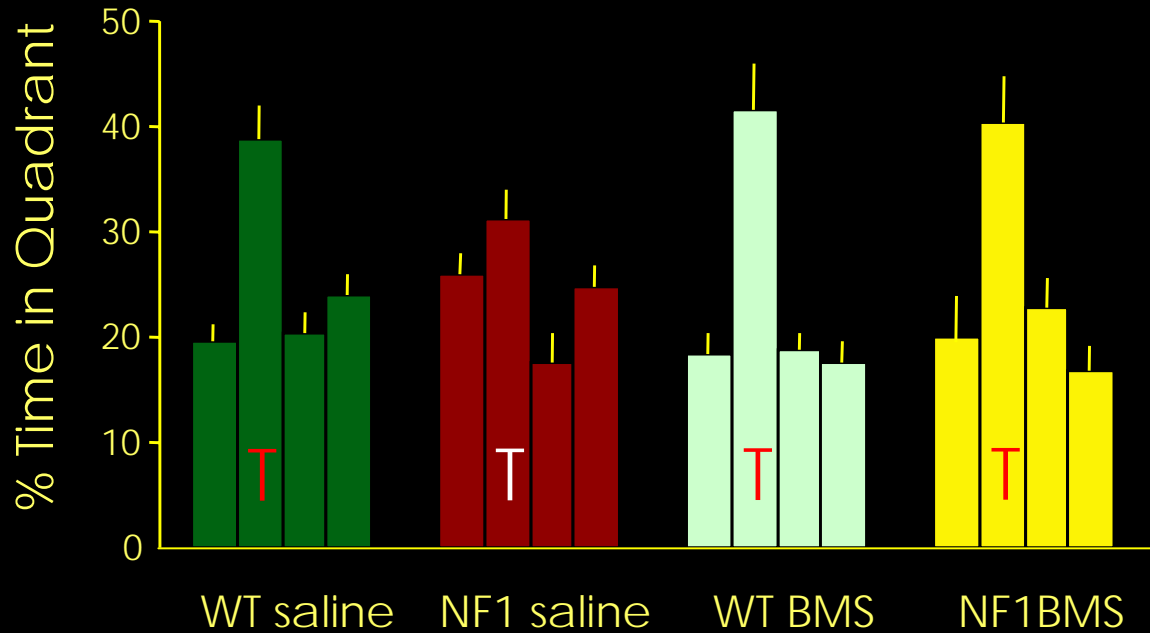
The NF1 Mutation Causes Spatial Learning Deficits in Mice



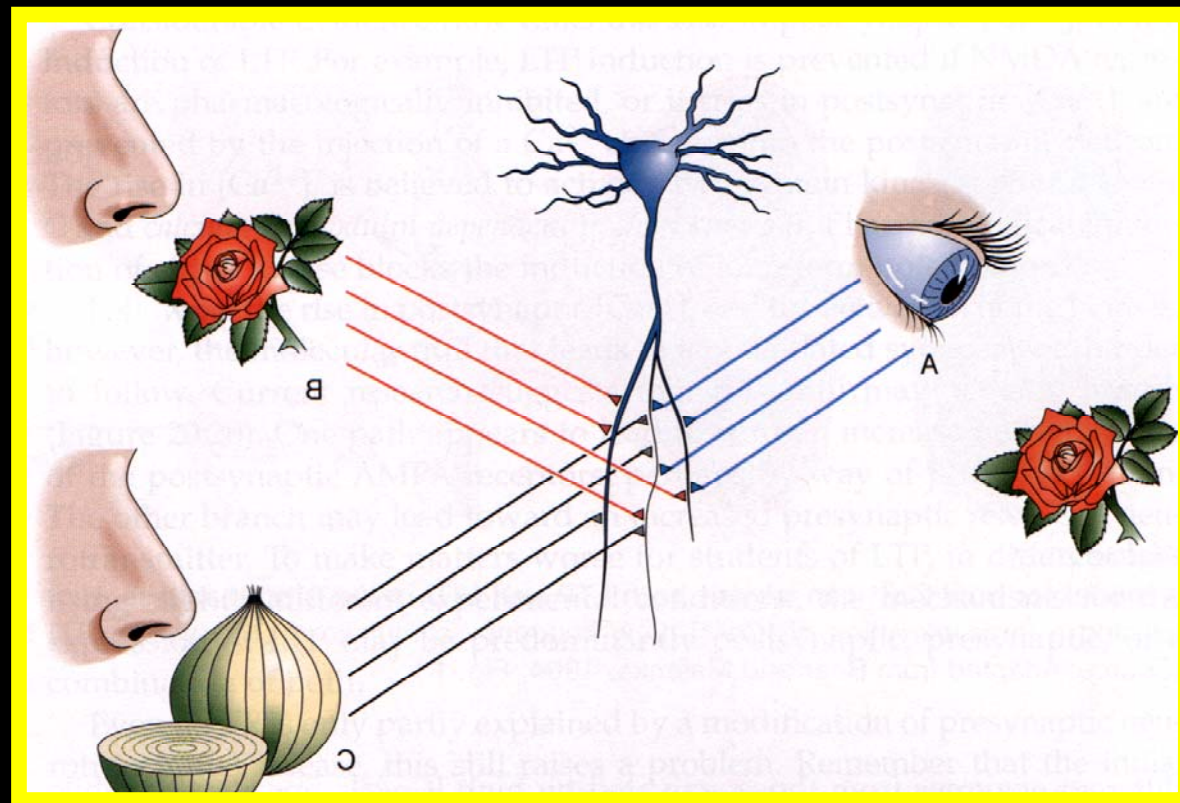
Enhanced ERK activation after contextual training in NF1^{+/-} mice



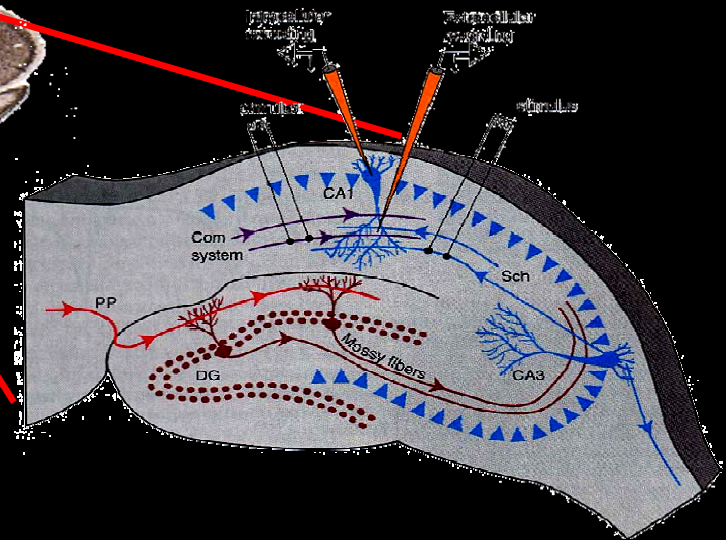
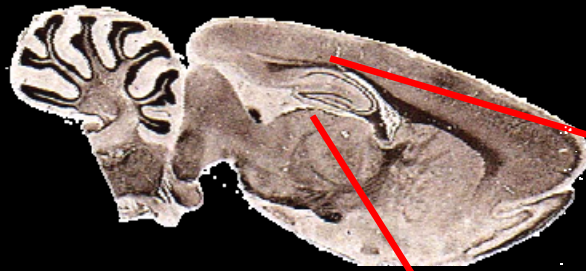
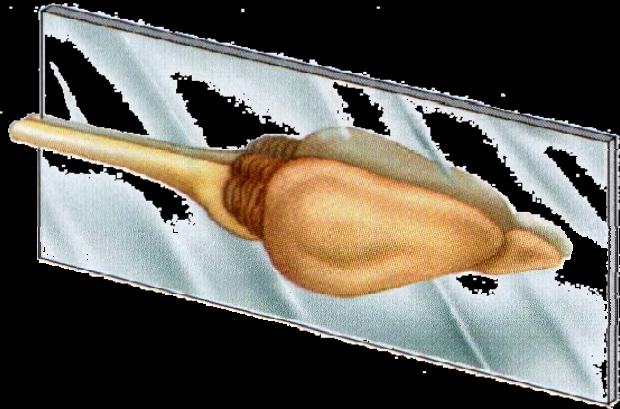
A Farnesyl Transferase Inhibitor (BMS 191563) rescues the spatial learning deficits caused by the NF1 mutation



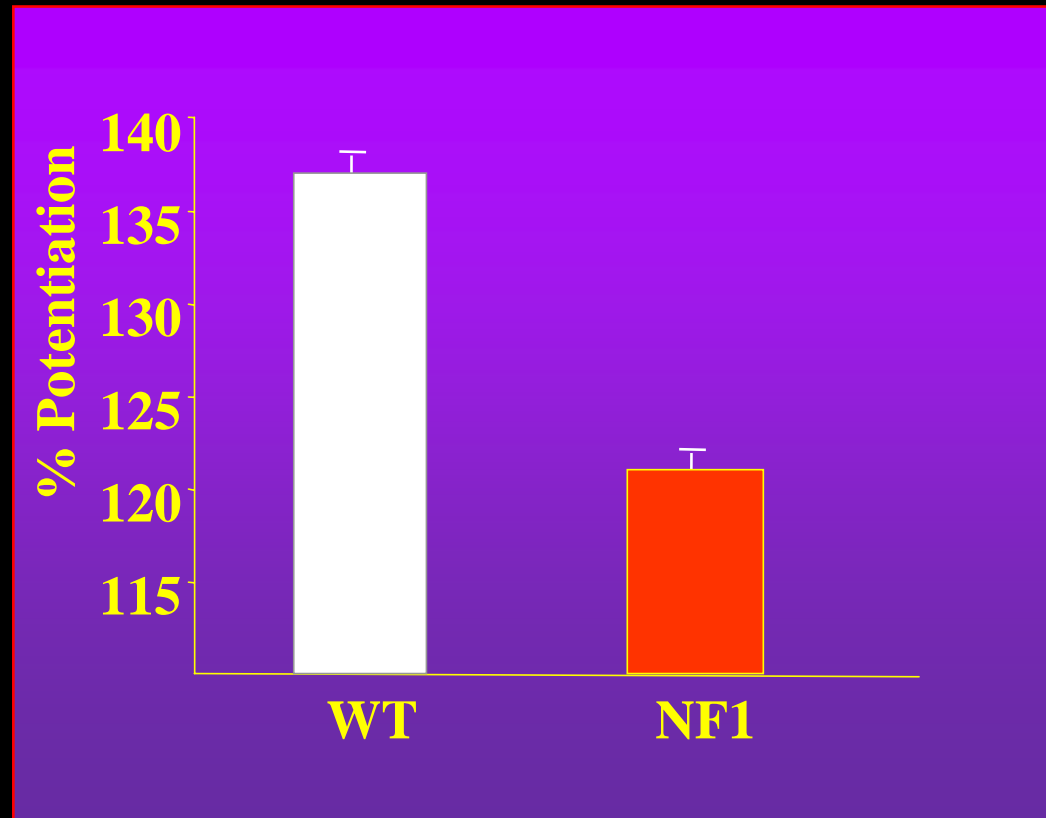
The brain makes associations and stores them as memories



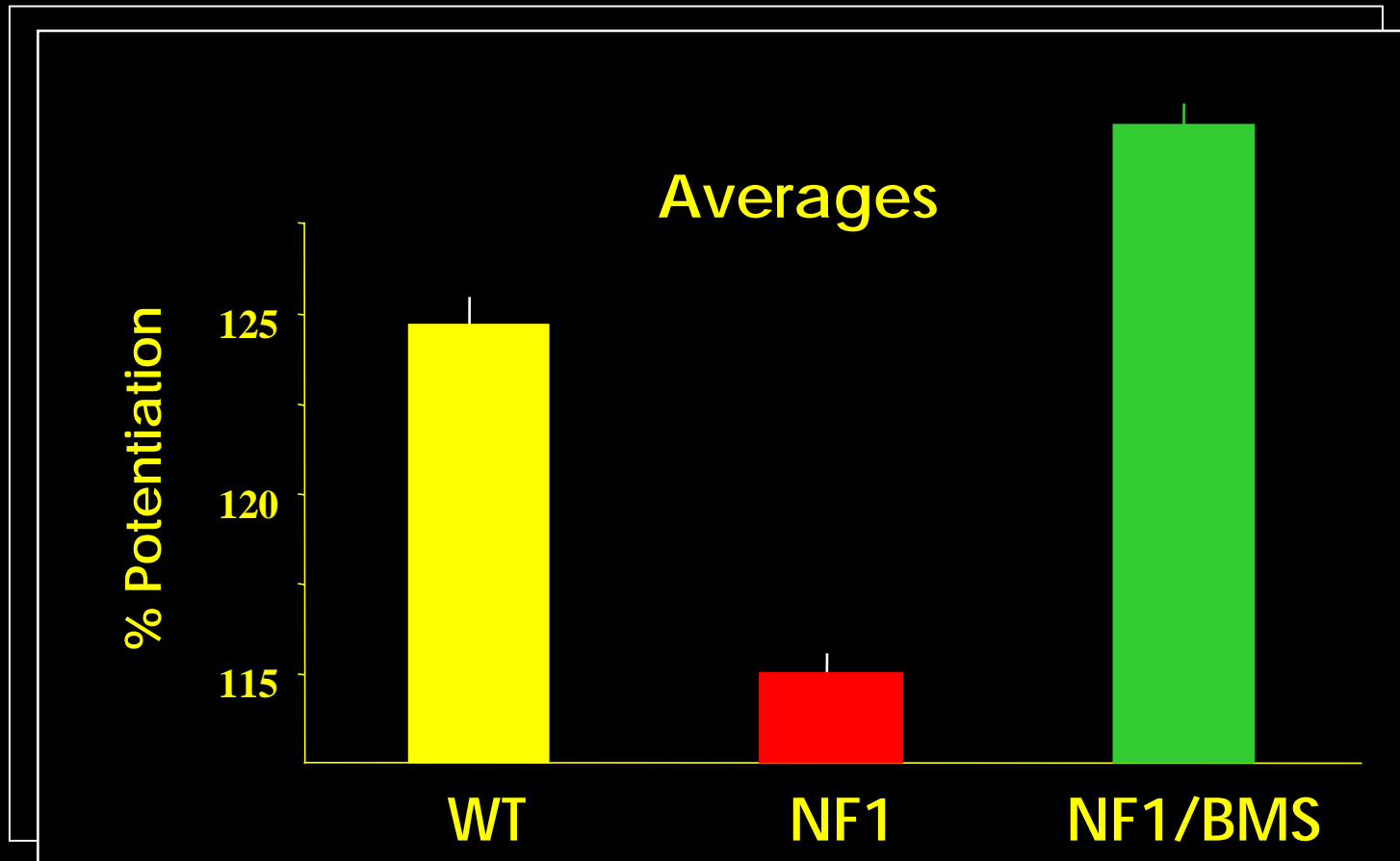
Plasticity studies



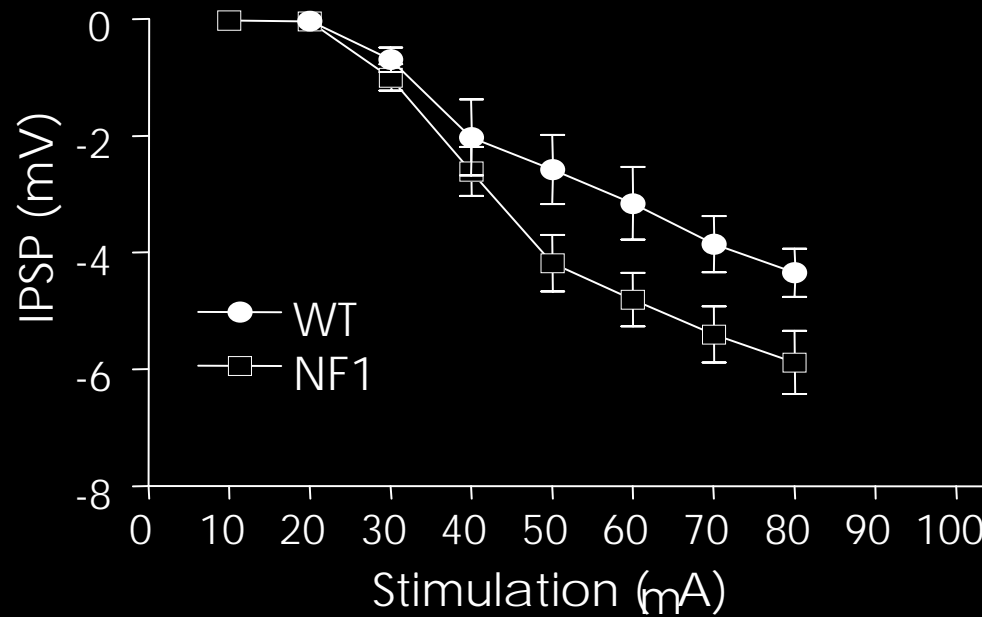
Synaptic plasticity deficits in the NF1^{+/-} mutants



The NF1 mutation affects plasticity: rescue by the BMS drug



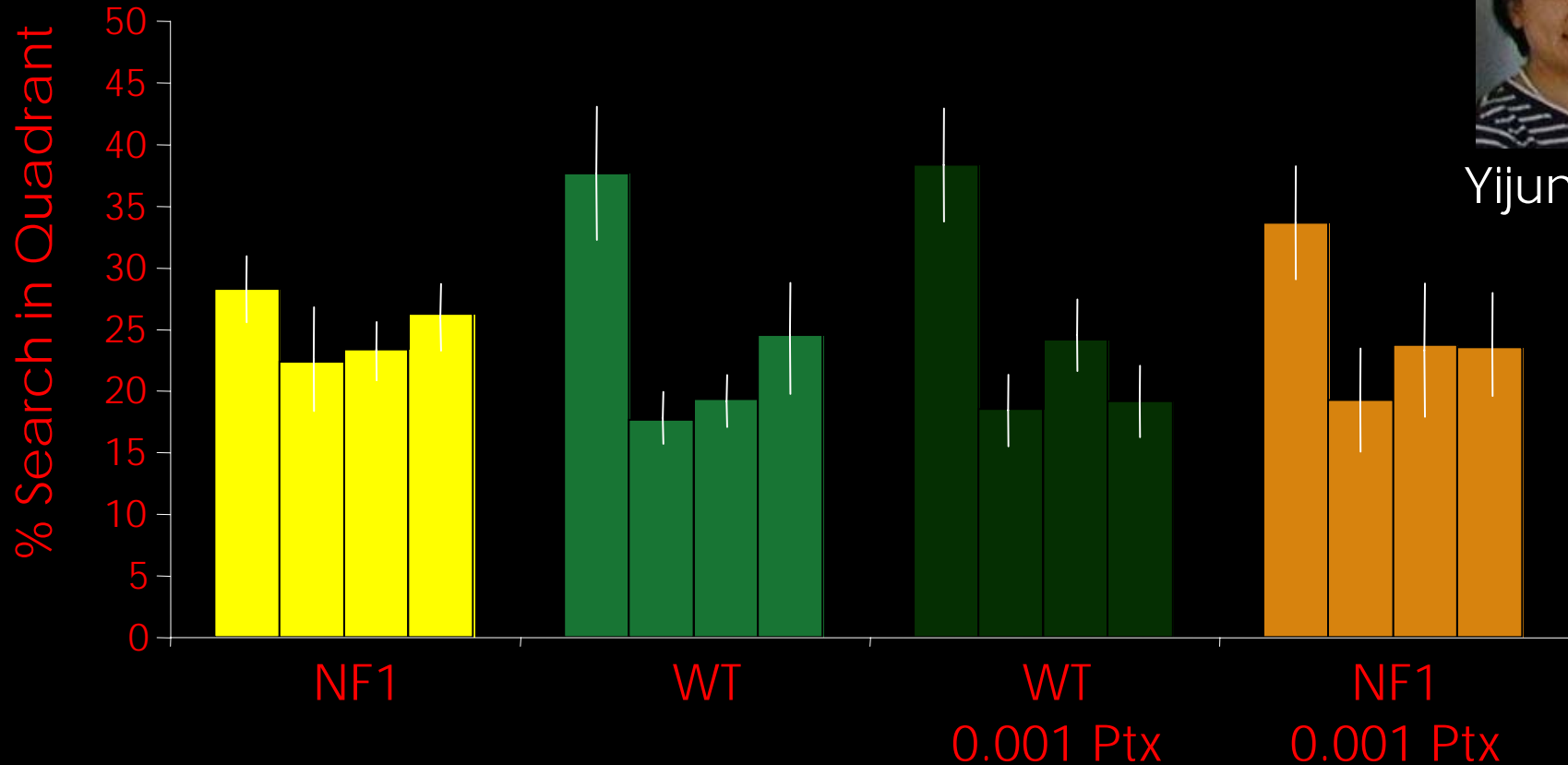
Enhanced Inhibition in NF1 +/- mice



Decreasing GABA_A inhibition rescues the learning-deficits of NF1 mice



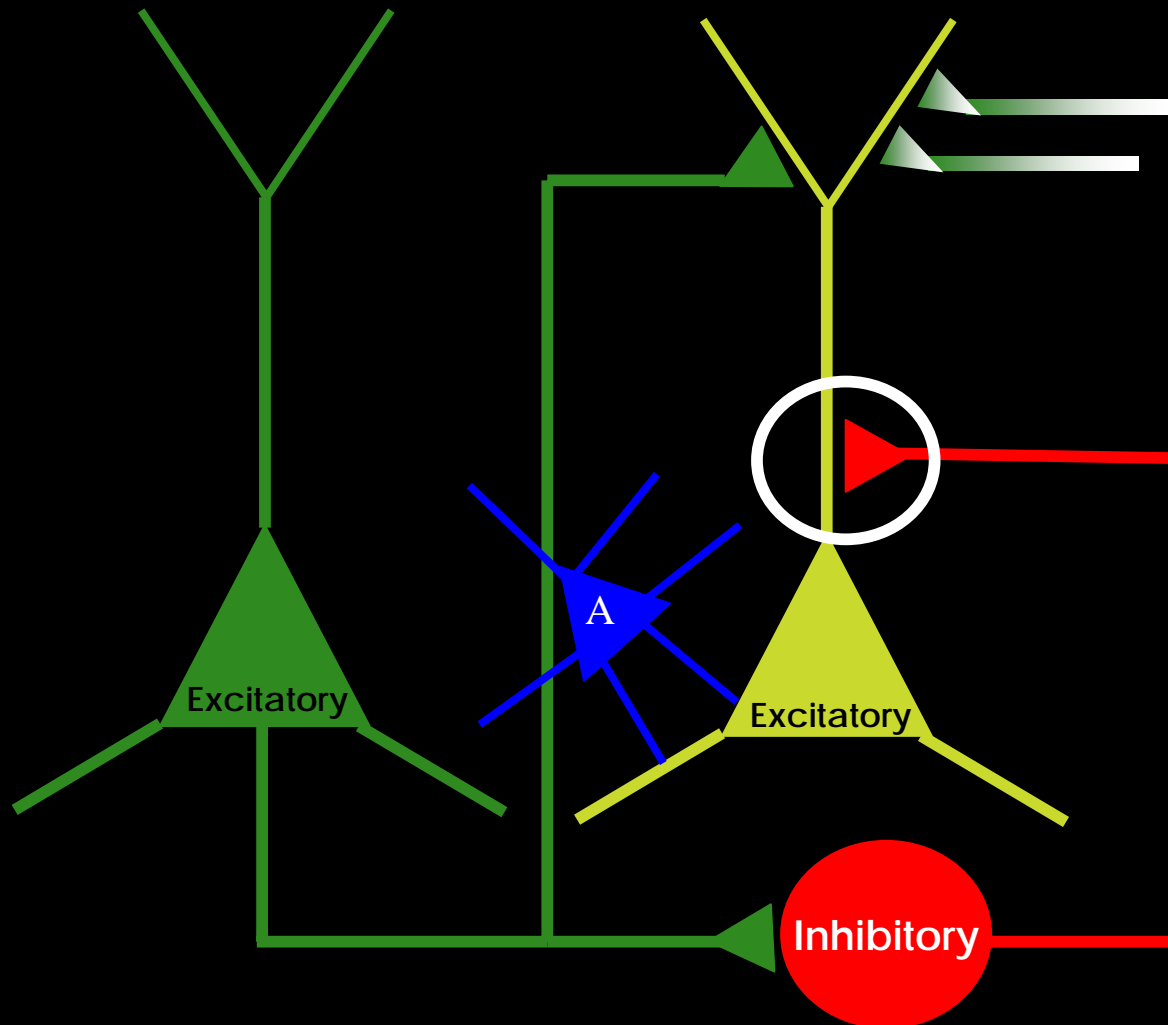
Yijun Cui



What is the mechanism for the learning disabilities in Neurofibromatosis type I ?

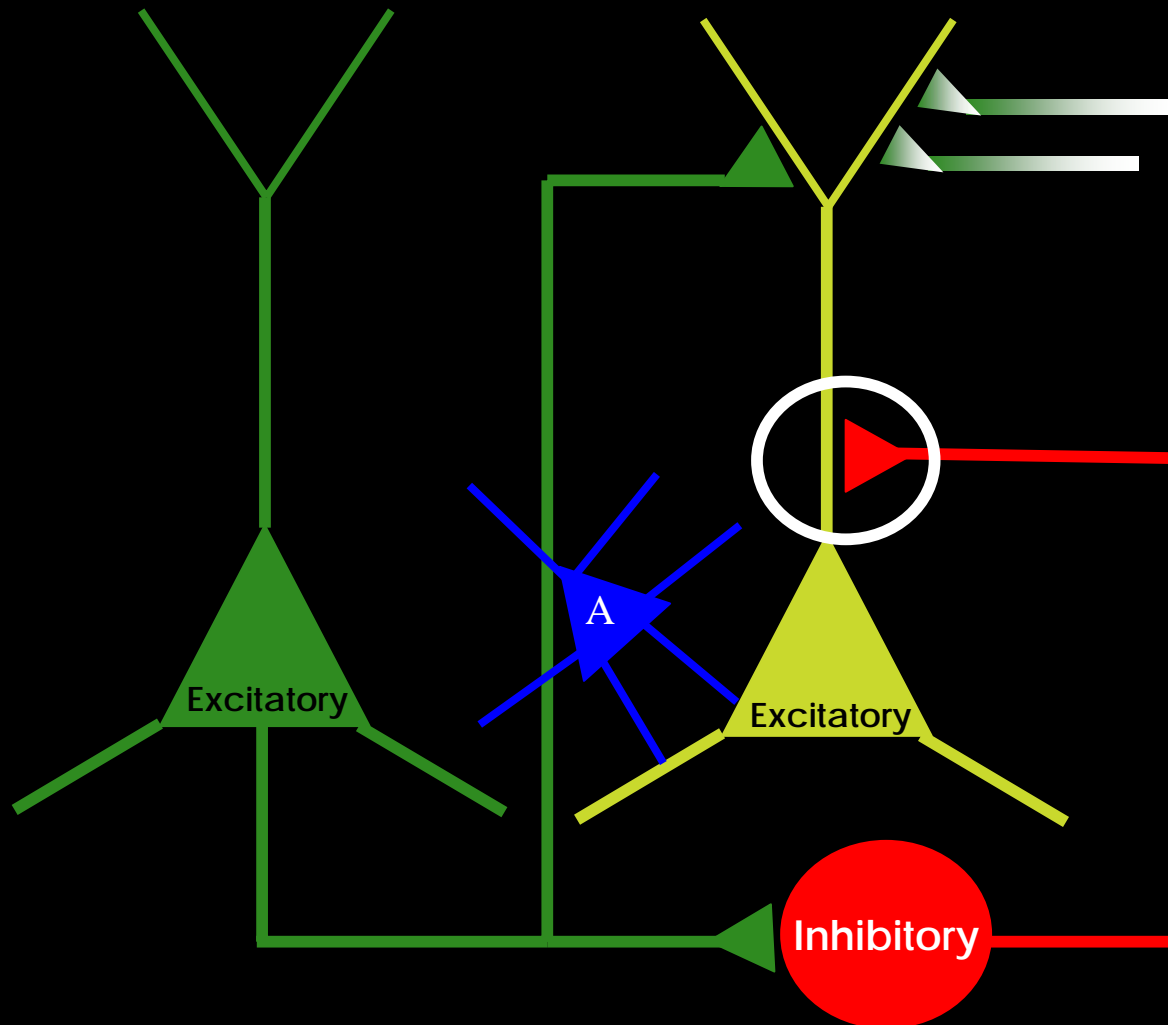
- Increased Ras signaling (reversible)
- Enhanced GABA release (reversible)
- Deficits in synaptic plasticity (reversible)

The cellular locus of the NF1 deficit: Electrophysiological studies



Yijun Cui

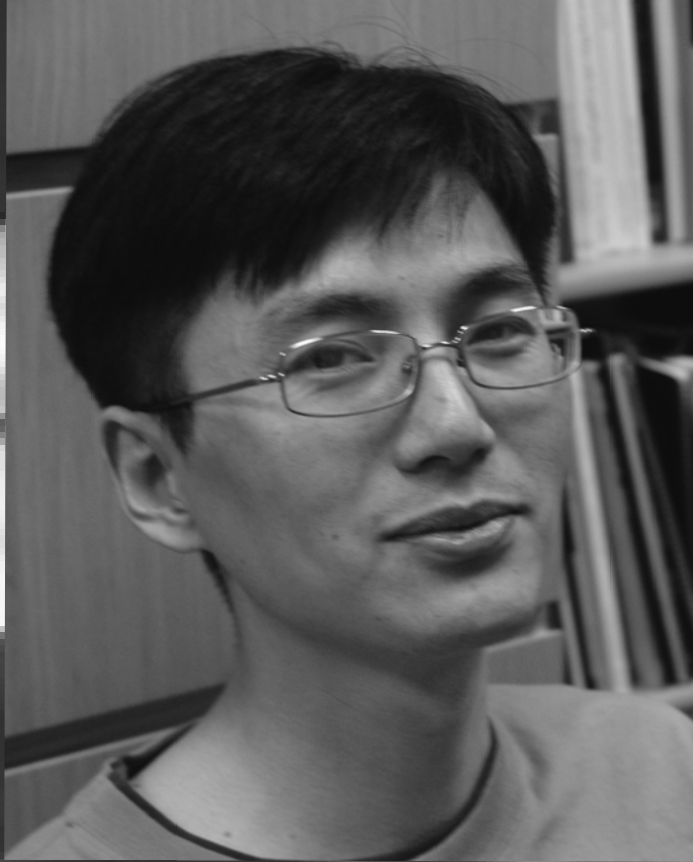
The cellular locus of the NF1 deficit: Genetic studies



Yijun Cui

Statins treat the underlying causes for the learning disabilities in Neurofibromatosis type I

- Increased Ras signaling
- Enhanced GABA release
- Deficits in synaptic plasticity
- Deficits in learning



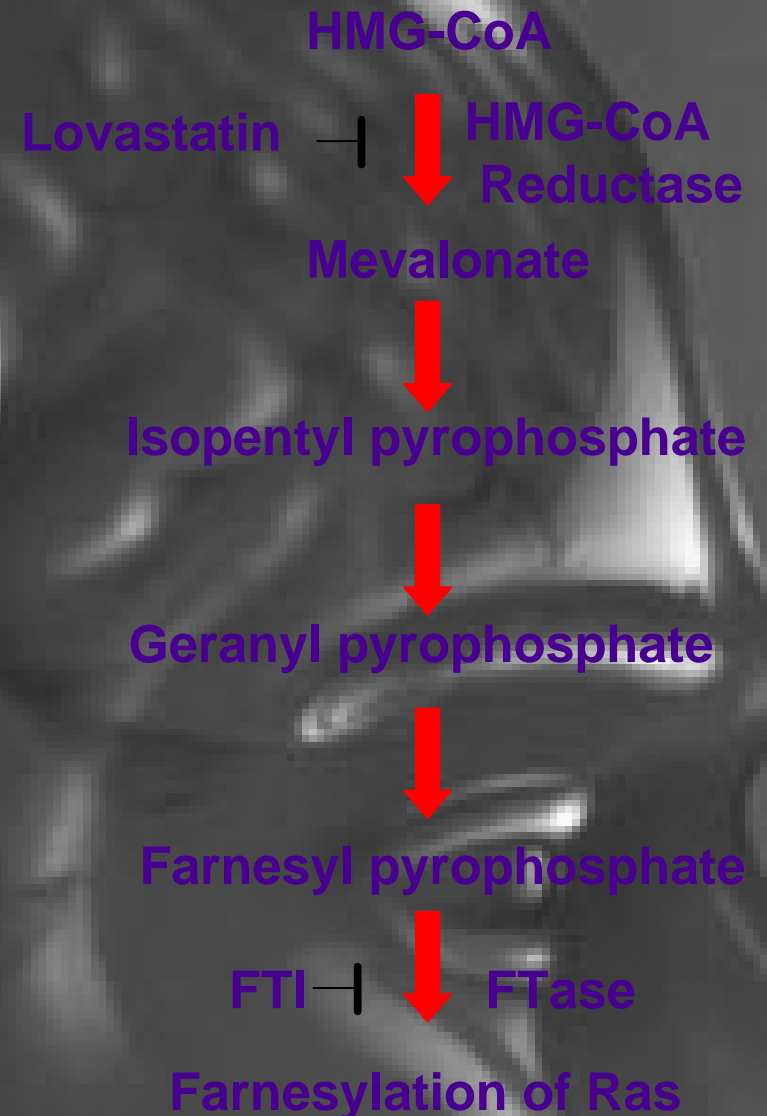
Weidong Li



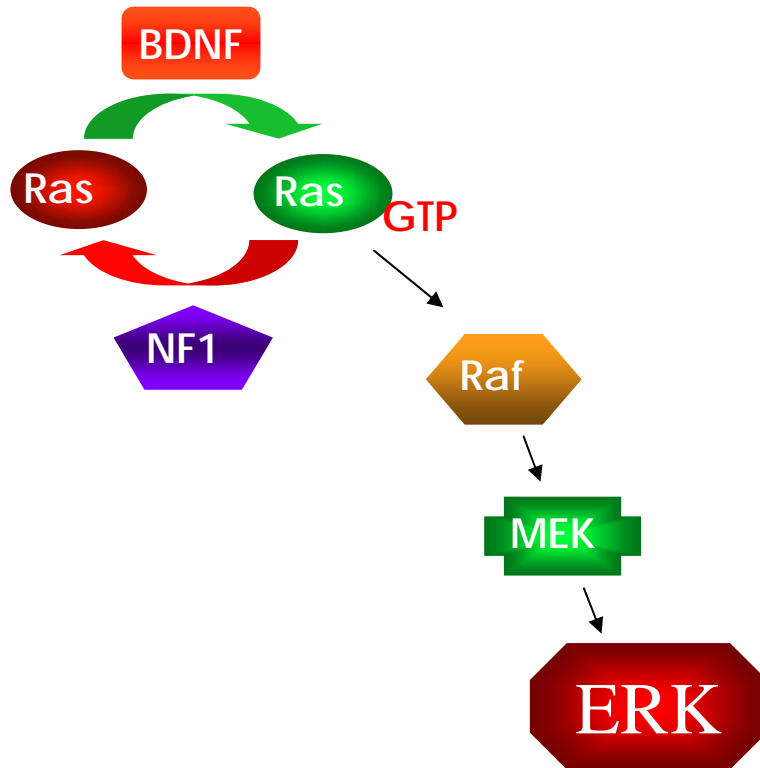
Steven Kushner

Statins

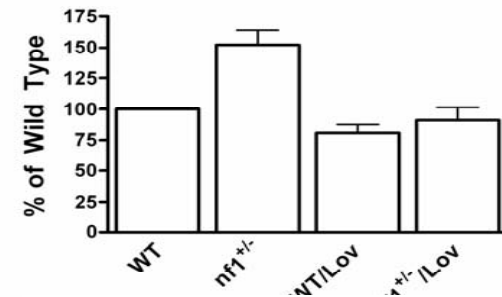
- Used for 20 years to control lipid levels in blood
- Highly prescribed, safe, very low side-effects
- Can be taken for *very* extended periods of time
- Some Statins cross the blood-brain barrier
- HMG-CoA reductase inhibitors
- Inhibit geranyl and farnesyl biosynthesis
- **Inhibit isoprenylation of Ras!**



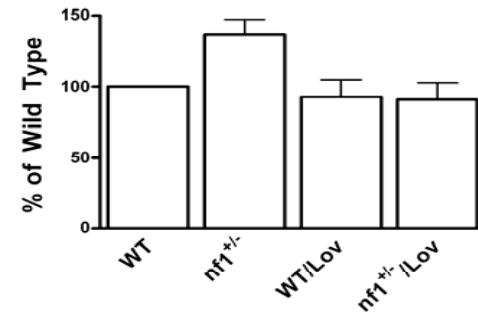
Lovastatin rescues the increase in the levels of active Ras and MAPK-PO4 in the brain of Nf1 mice



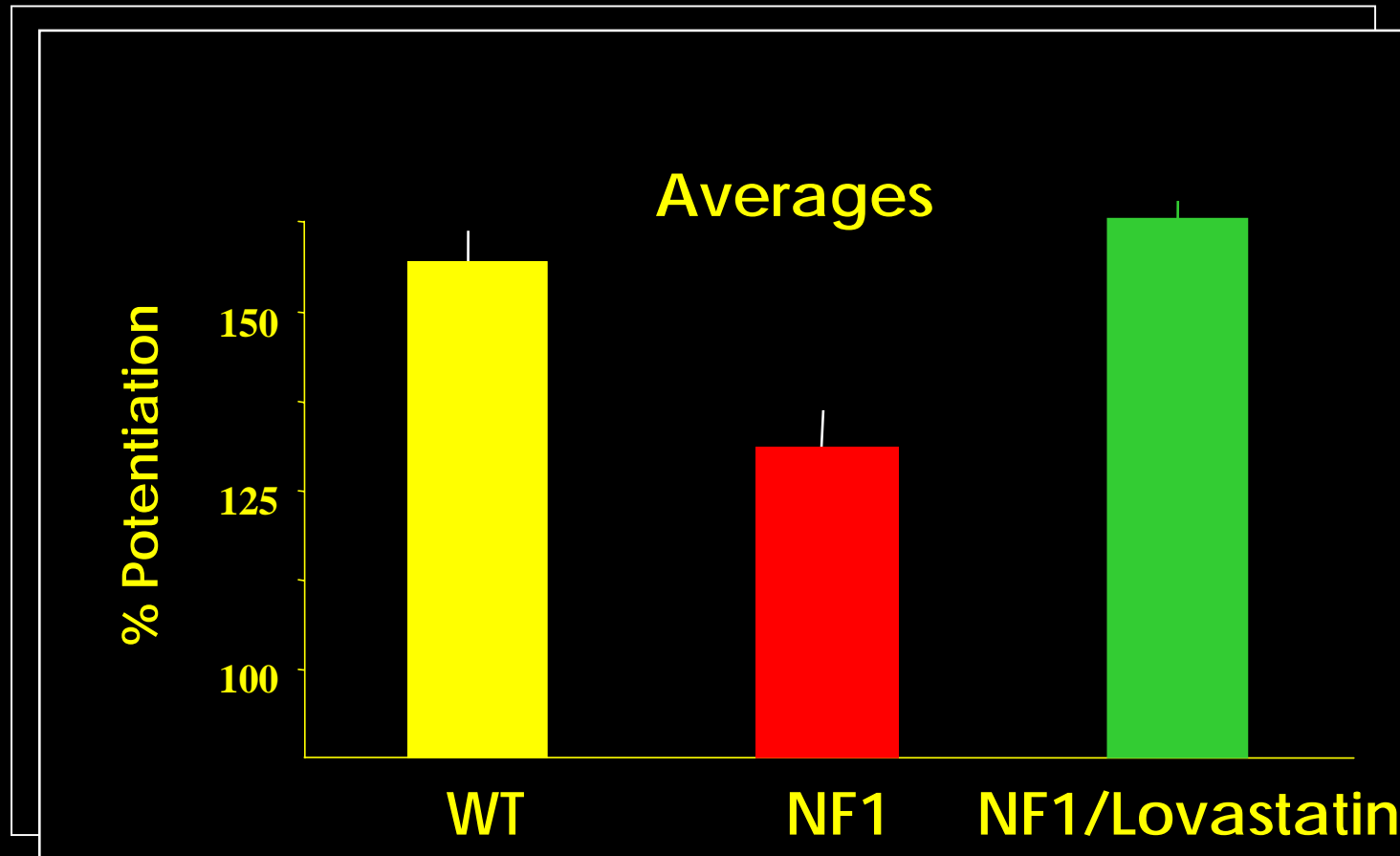
Ras Levels



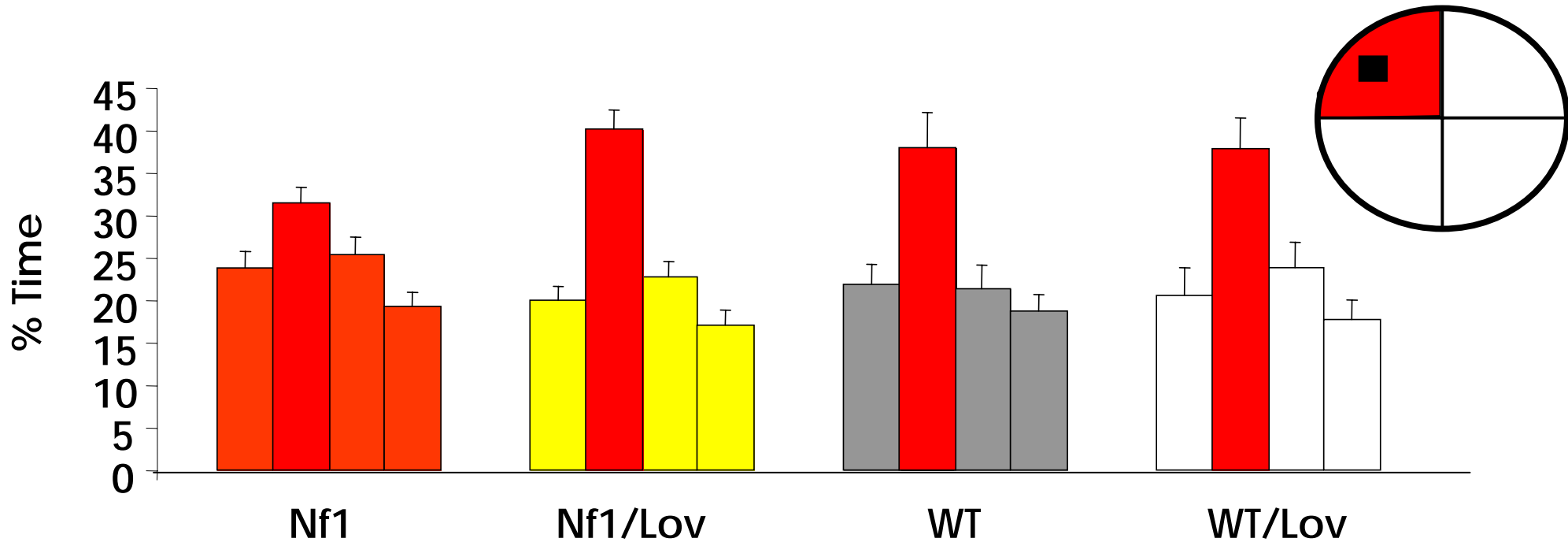
MAPK-PO4 Levels



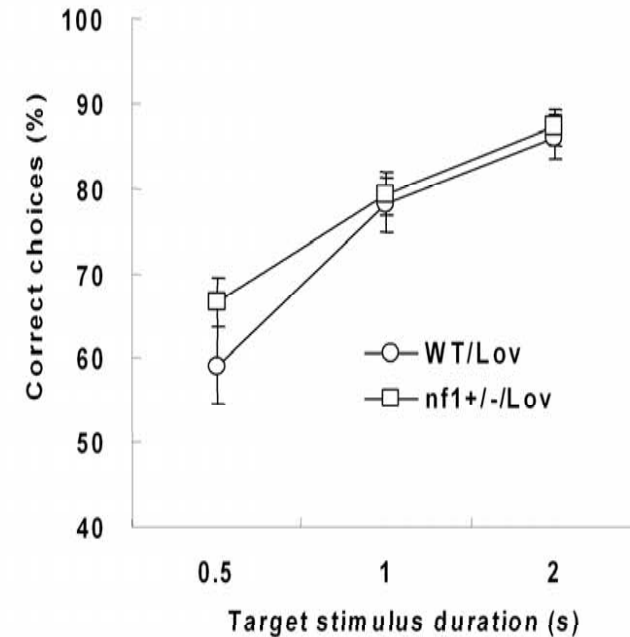
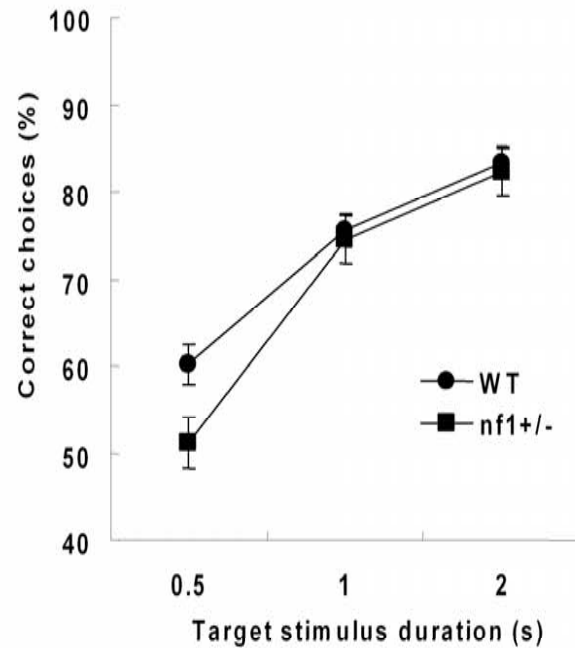
The LTP Impairment of the NF1 mutants is rescued by Lovastatin



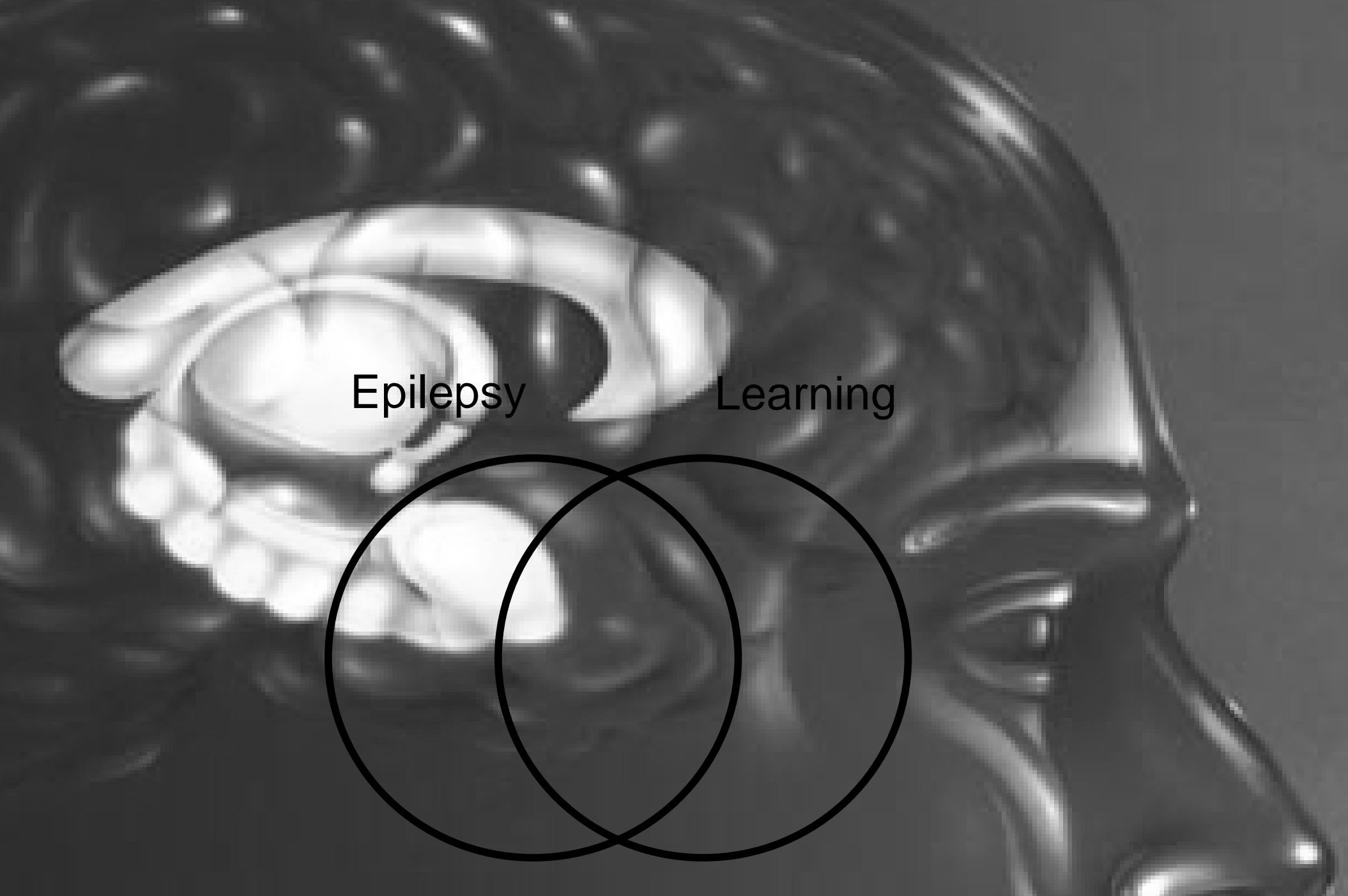
Lovastatin reverses the spatial learning deficits of Nf1 mutant mice!



Impaired attention in NF1 Mutants is rescued by Lovastatin (lateralized reaction-time task)







Epilepsy

Learning

NF1 and Learning

- Weidong Li
- Steve Kushner
- Yijun Cui
- Rui Costa
- Ype Elgersma
- Geoffrey Murphy
- Jennifer Johnson
- Katie Karlsgodt
- Tyrone Cannon
- William Yang (Dlx Cre)
- Istvan Mody
- David Jentsch
- Yuan Zhu, Luis Parada (FloxNF1; Syn Cre)
- David Guttmann (GFAP Cre)
- Tyler Jacks (NF1; K-ras)