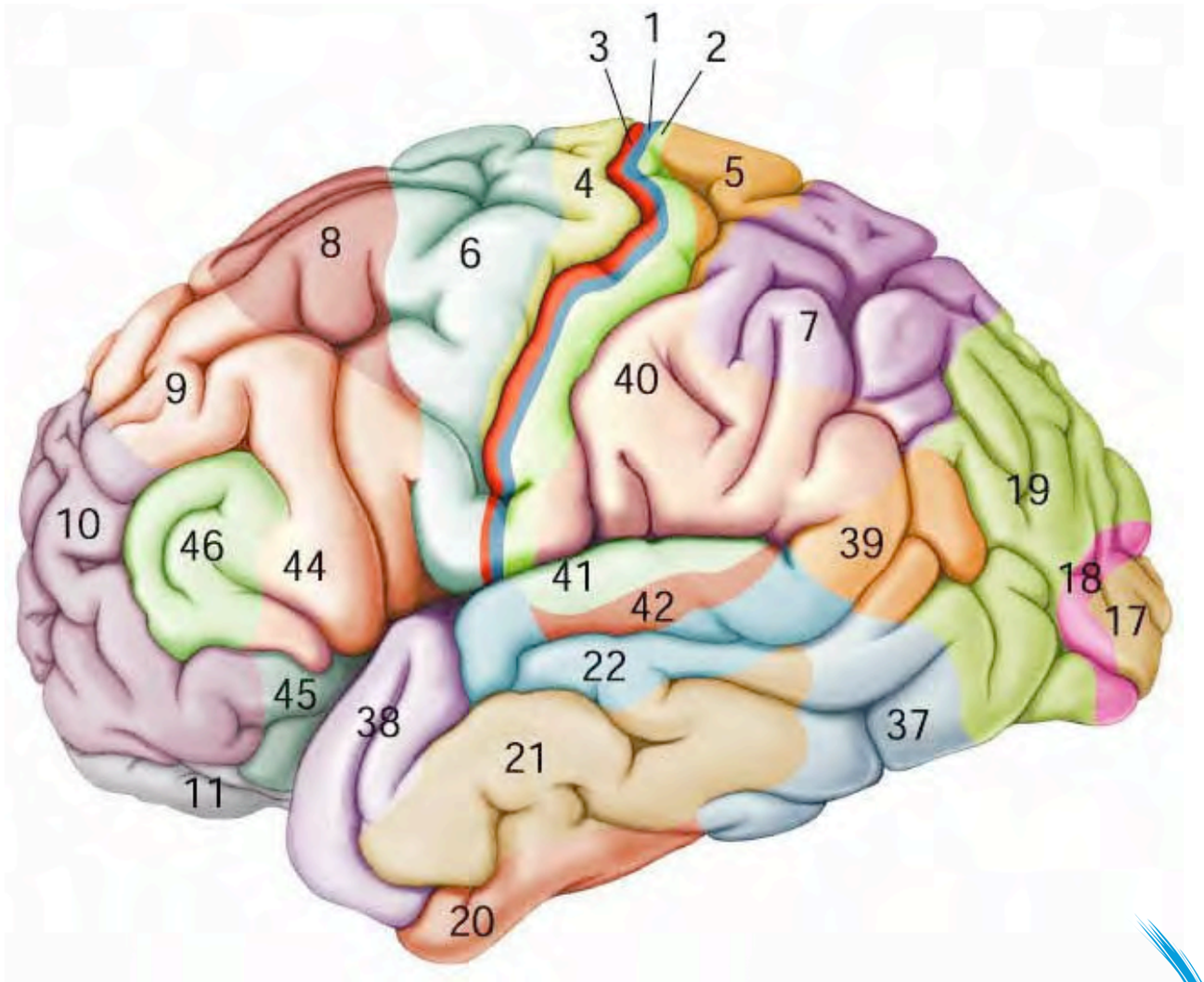
From gene to pathophysiology to treatment in a developmental brain disorder

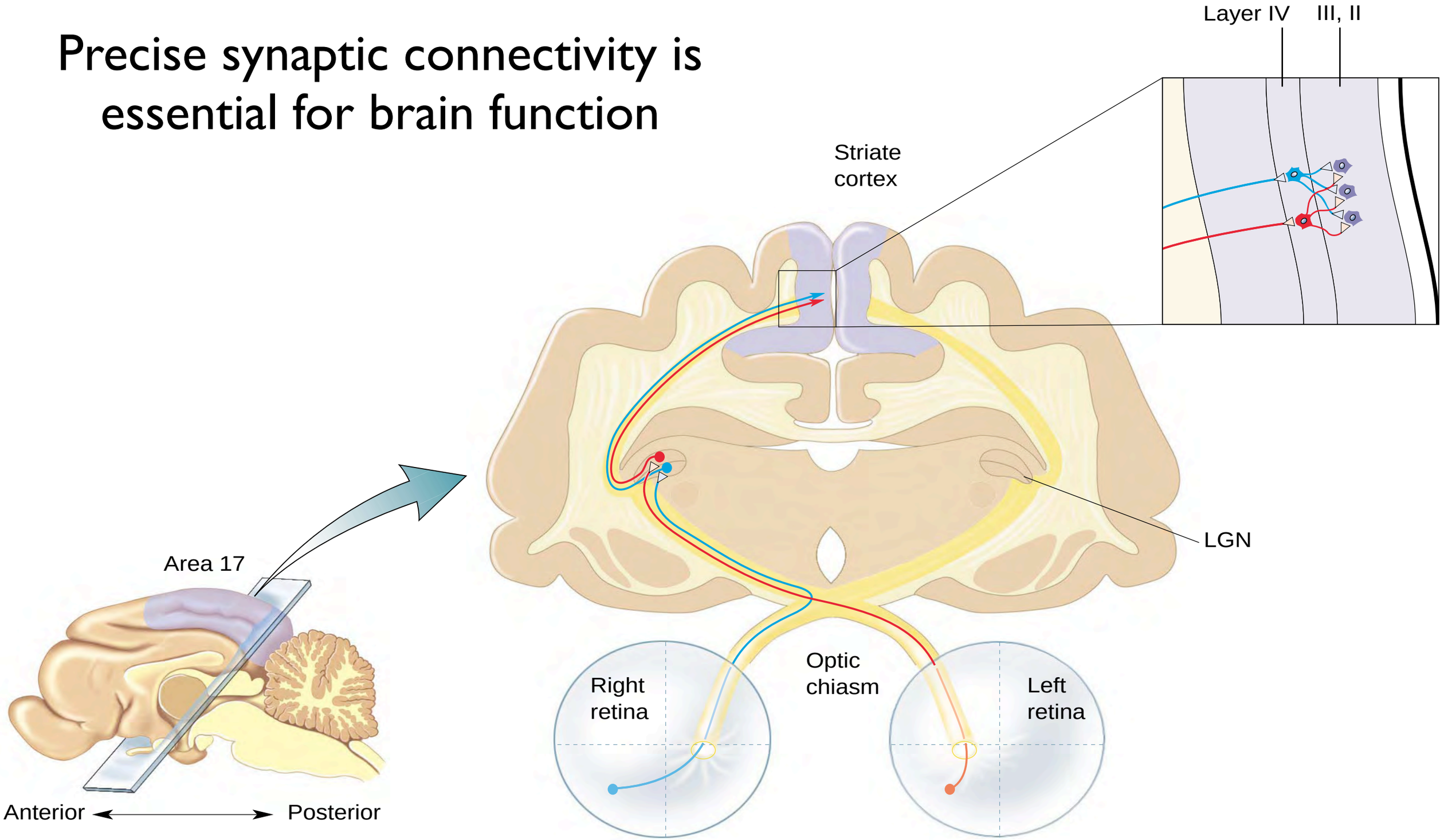


Mark F. Bear, Ph.D.

HHMI
HOWARD HUGHES MEDICAL INSTITUTE

The Picower Institute
for learning and memory

Precise synaptic connectivity is essential for brain function



The Changing Brain

Synaptic loss

Synaptic gain

Age period:

Perinatal

Postnatal

Mature

Senescent

Synapsopathies

Synaptic loss

Synaptic gain

Age period:

Perinatal

Developmental disorders

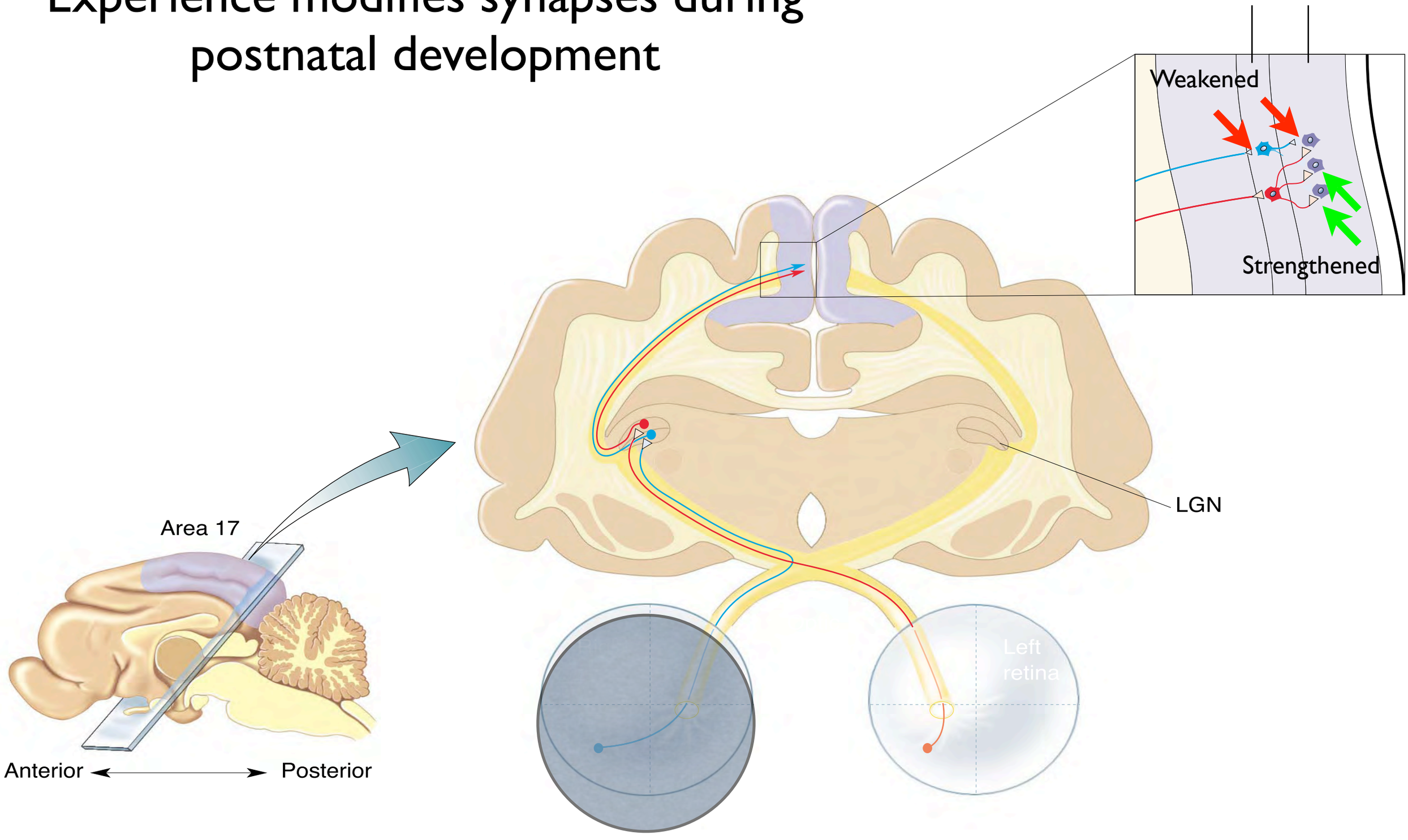
Postnatal

Mature

Cognitive, degenerative disorders

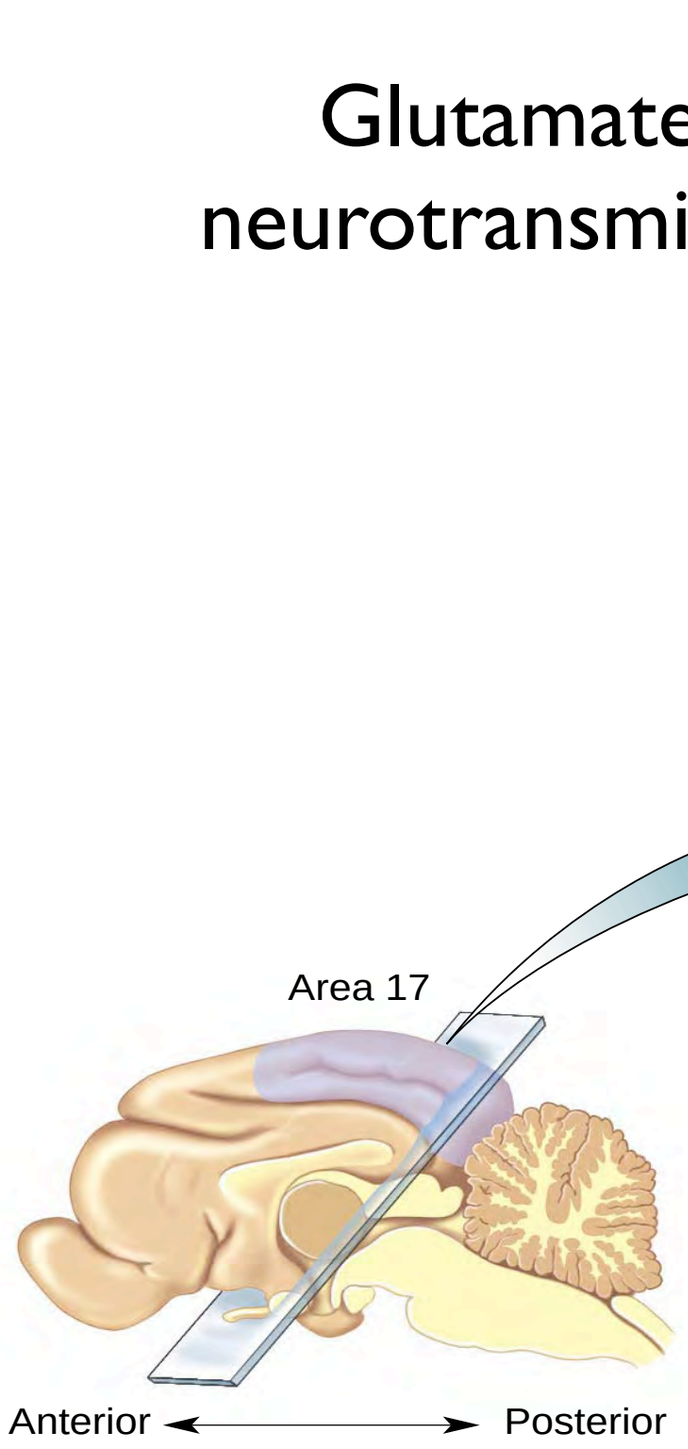
Senescent

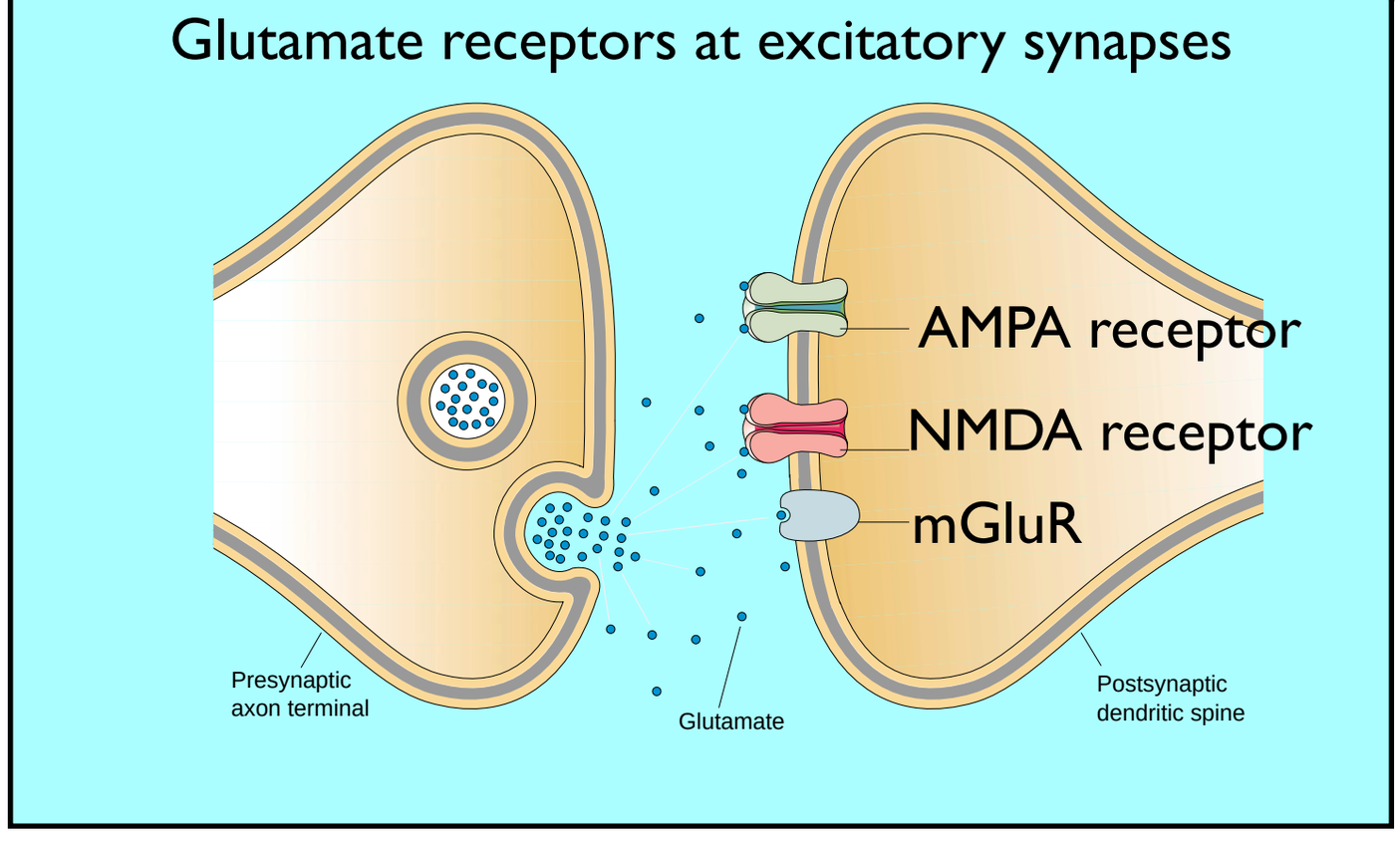
Experience modifies synapses during postnatal development

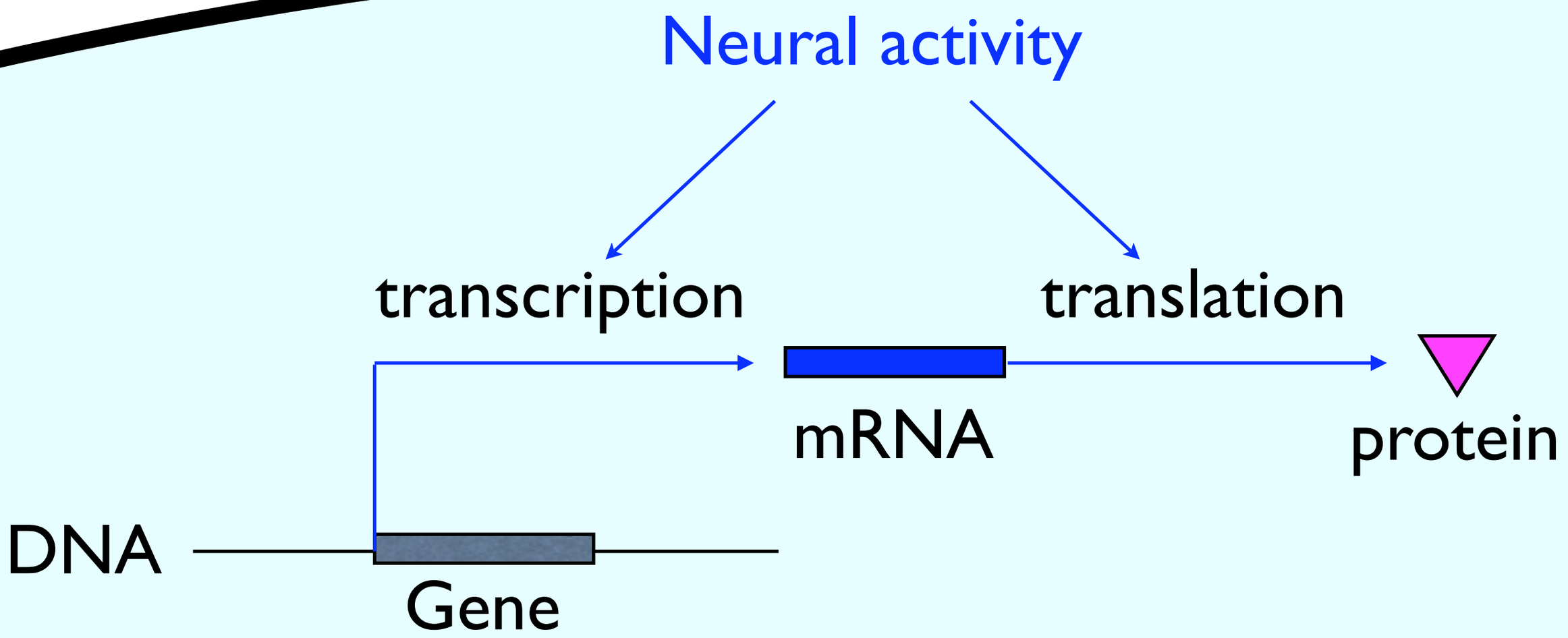


Monocular deprivation

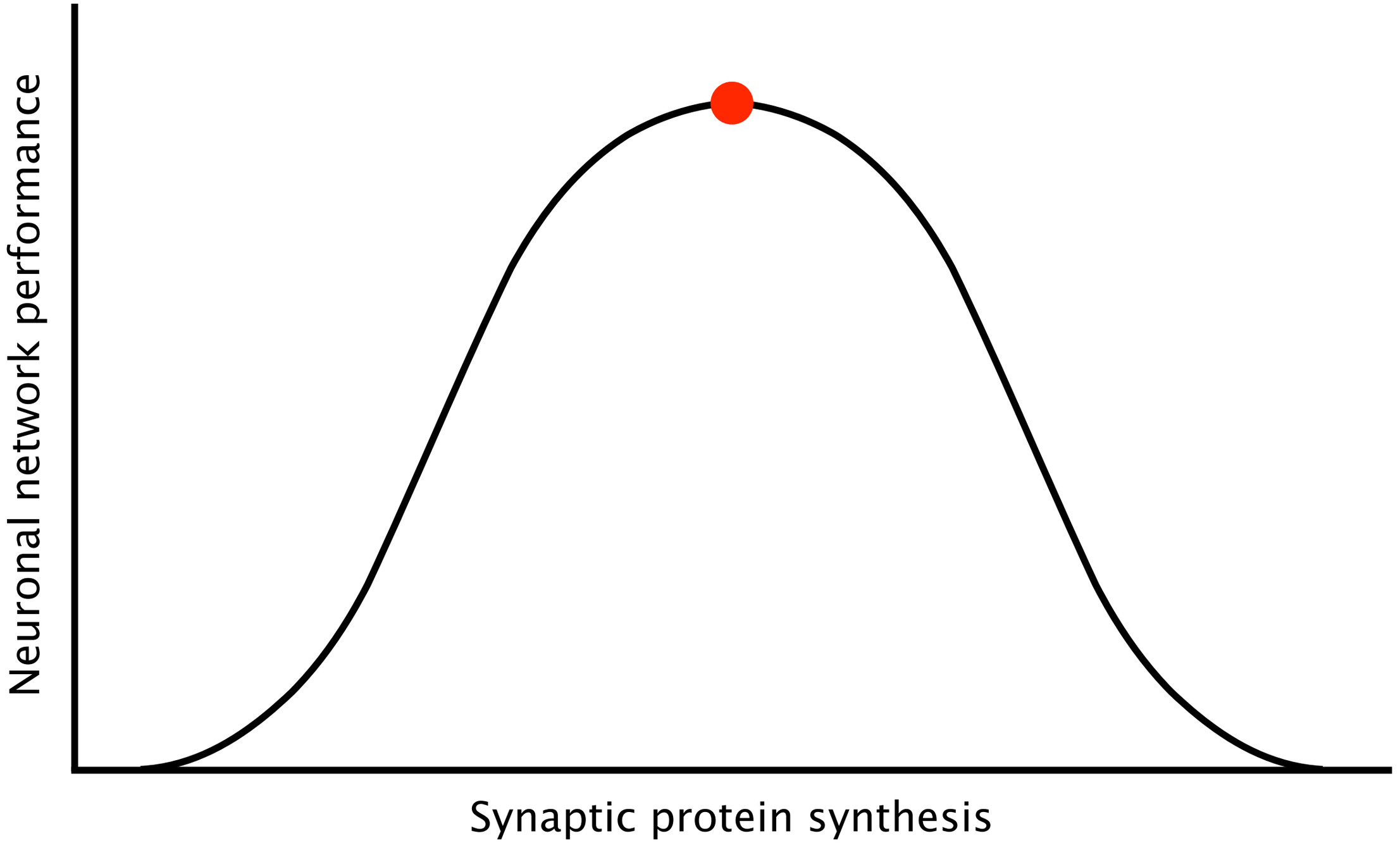
Glutamate is the major neurotransmitter of the brain

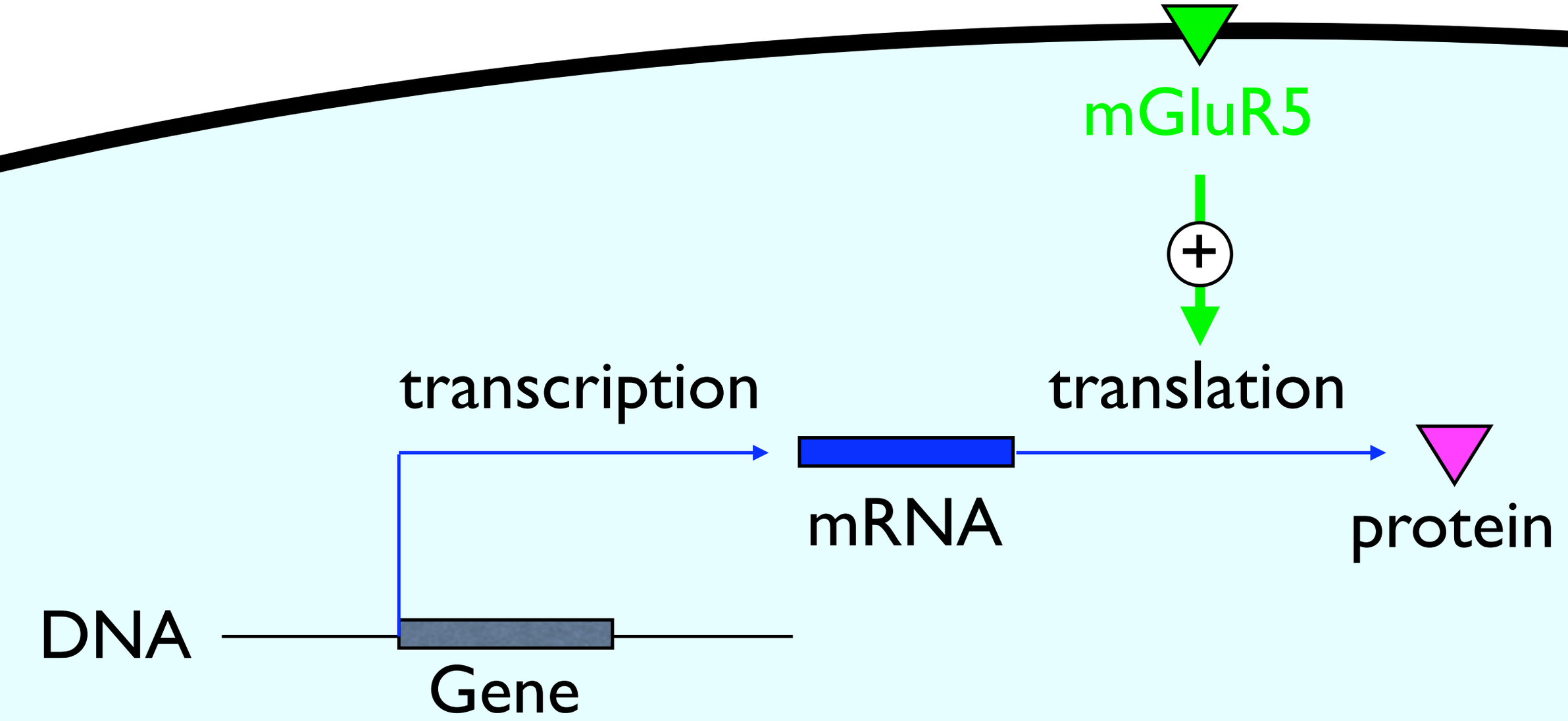






Appropriate modification of glutamatergic synapses requires the timely synthesis of new proteins


Neuronal network performance
Synaptic protein synthesis

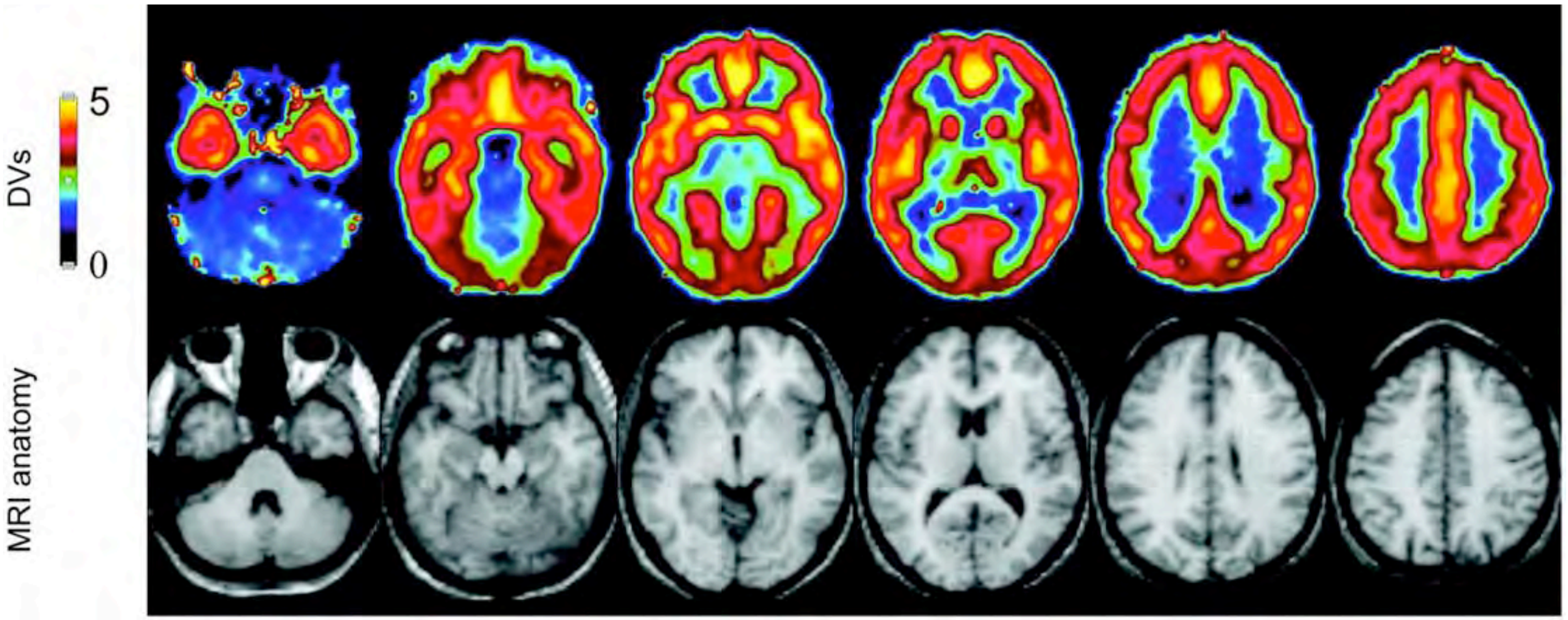


Metabotropic glutamate receptors couple synaptic activity to protein synthesis

Human PET Studies of Metabotropic Glutamate Receptor Subtype 5 with ^{11}C-ABP688

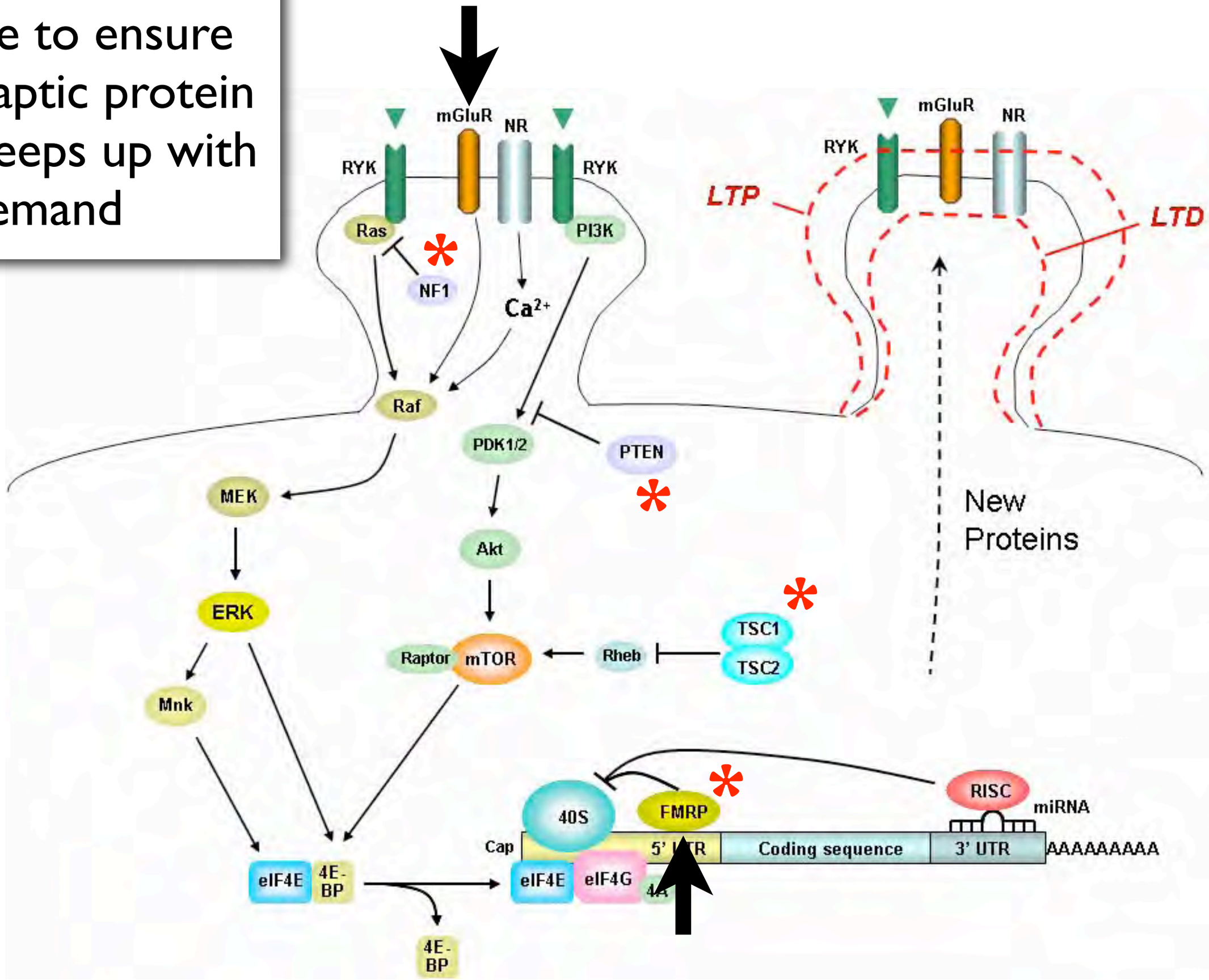
Simon M. Ametamey[1], Valerie Treyer[2], Johannes Streffer[3], Matthias T. Wyss[2], Mark Schmidt[4], Milen Blagoev[1], Samuel Hintermann[4], Yves Auberson[4], Fabrizio Gasparini[4], Uta C. Fischer[3], and Alfred Buck[2]

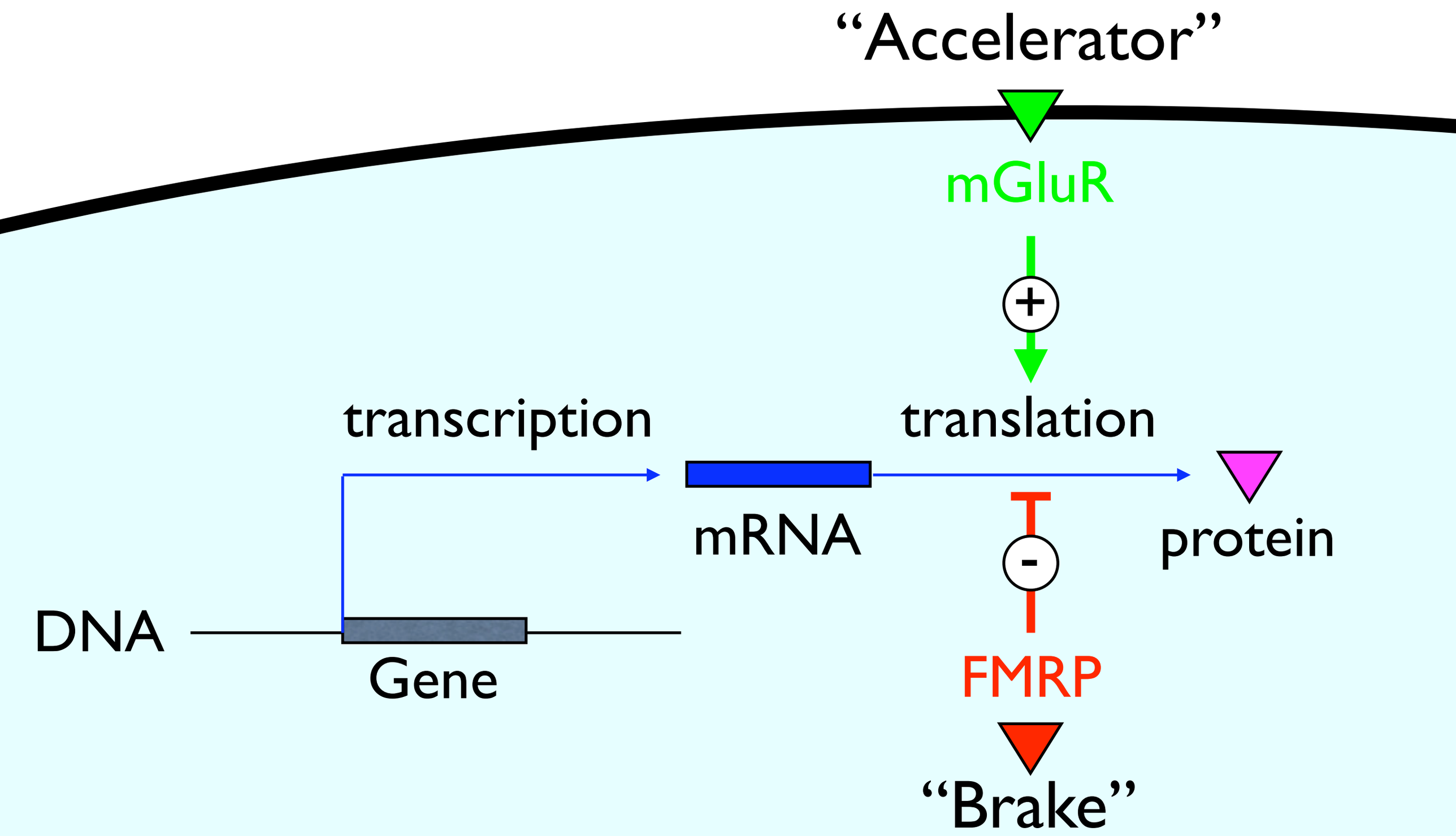
[1]Center for Radiopharmaceutical Science of ETH, PSI, and USZ, Department of Chemistry and Applied Biosciences of ETH, Zurich, Switzerland; [2]PET Center, Division of Nuclear Medicine, University of Zurich, Zurich, Switzerland; [3]Division of Psychiatric Research, University of Zurich, Zurich, Switzerland; and [4]Novartis Institutes for Biomedical Research Basel, Novartis Pharma AG, Basel, Switzerland

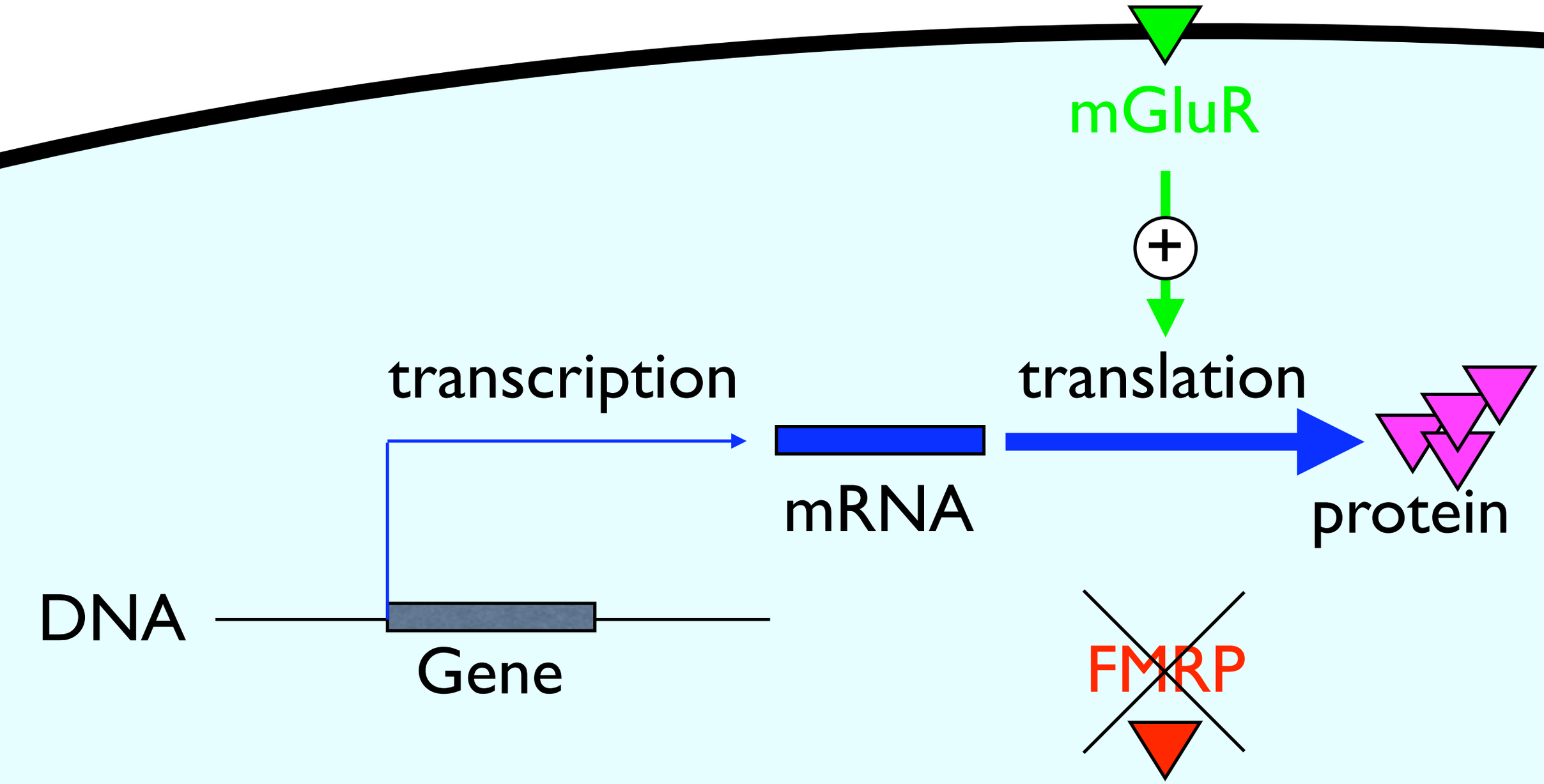


Kelleher and Bear, *The Autistic Neuron*

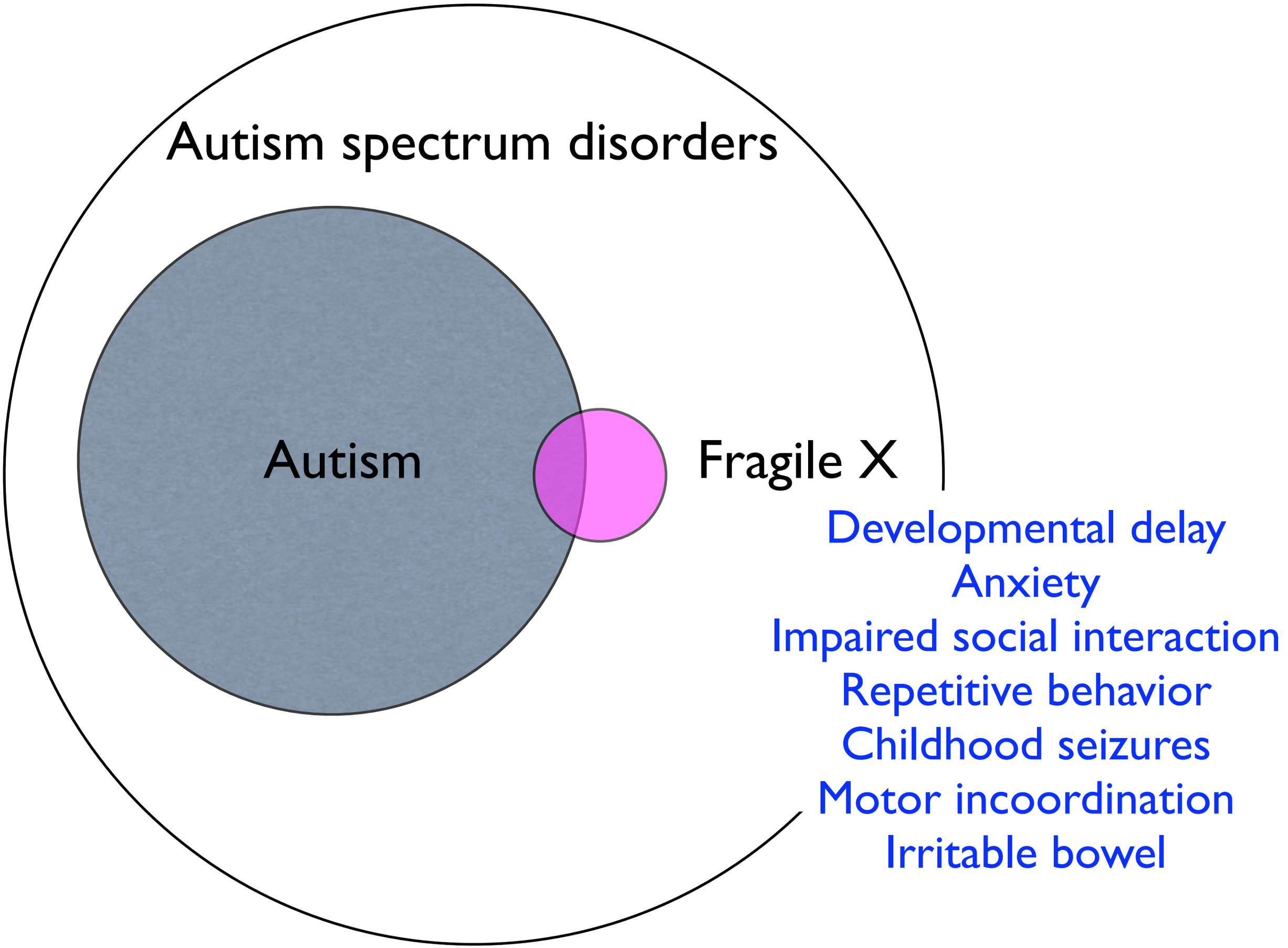
A molecular machine to ensure that synaptic protein supply keeps up with demand




"Accelerator"
mGluR
+
transcription
translation
mRNA
protein
-
DNA
Gene
FMRP
"Brake"

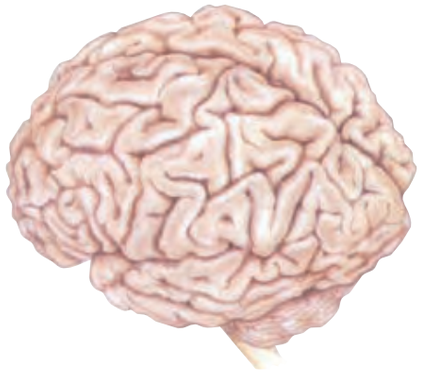


Fragile X syndrome is caused
by loss of FMRP...
Too many proteins produced


Autism spectrum disorders
Autism
Fragile X
Developmental delay
Anxiety
Impaired social interaction
Repetitive behavior
Childhood seizures
Motor incoordination
Irritable bowel

Towards fulfilling the promise of molecular medicine

Fragile X



Human psychiatric disease

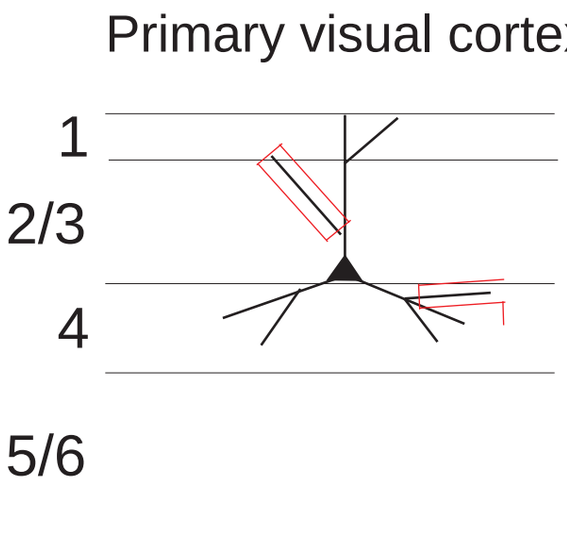
FMR1

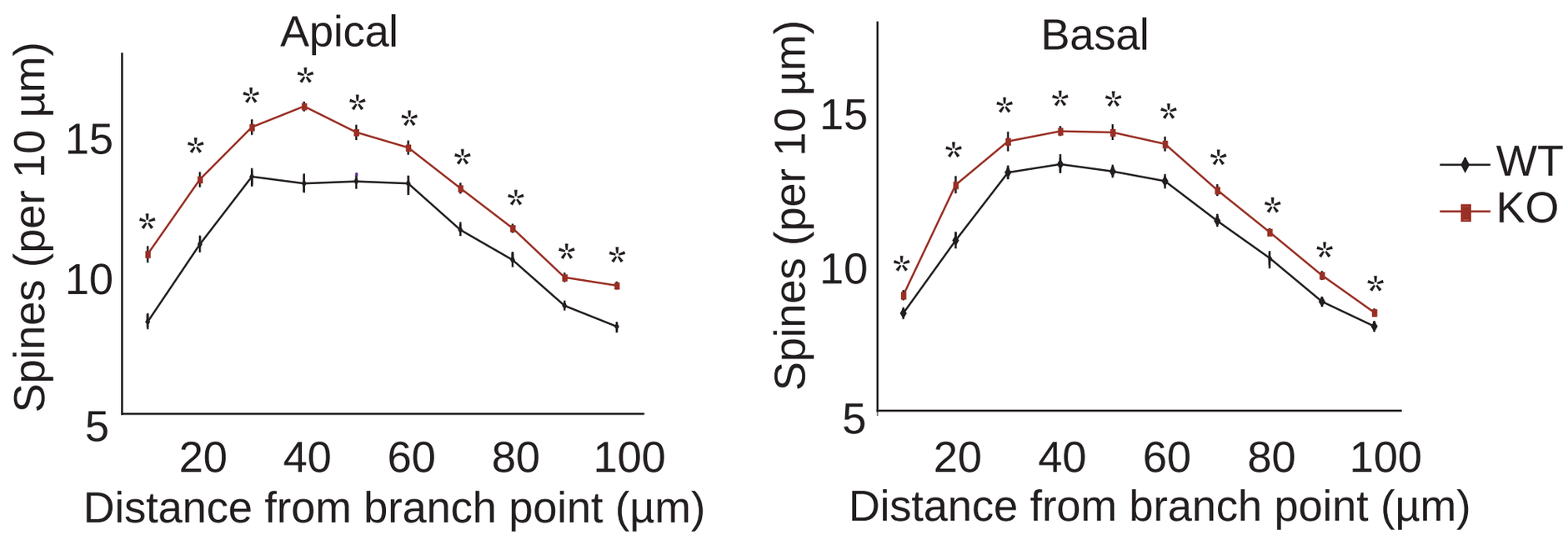
Gene discovery

Fmr1 KO

Mouse disease model

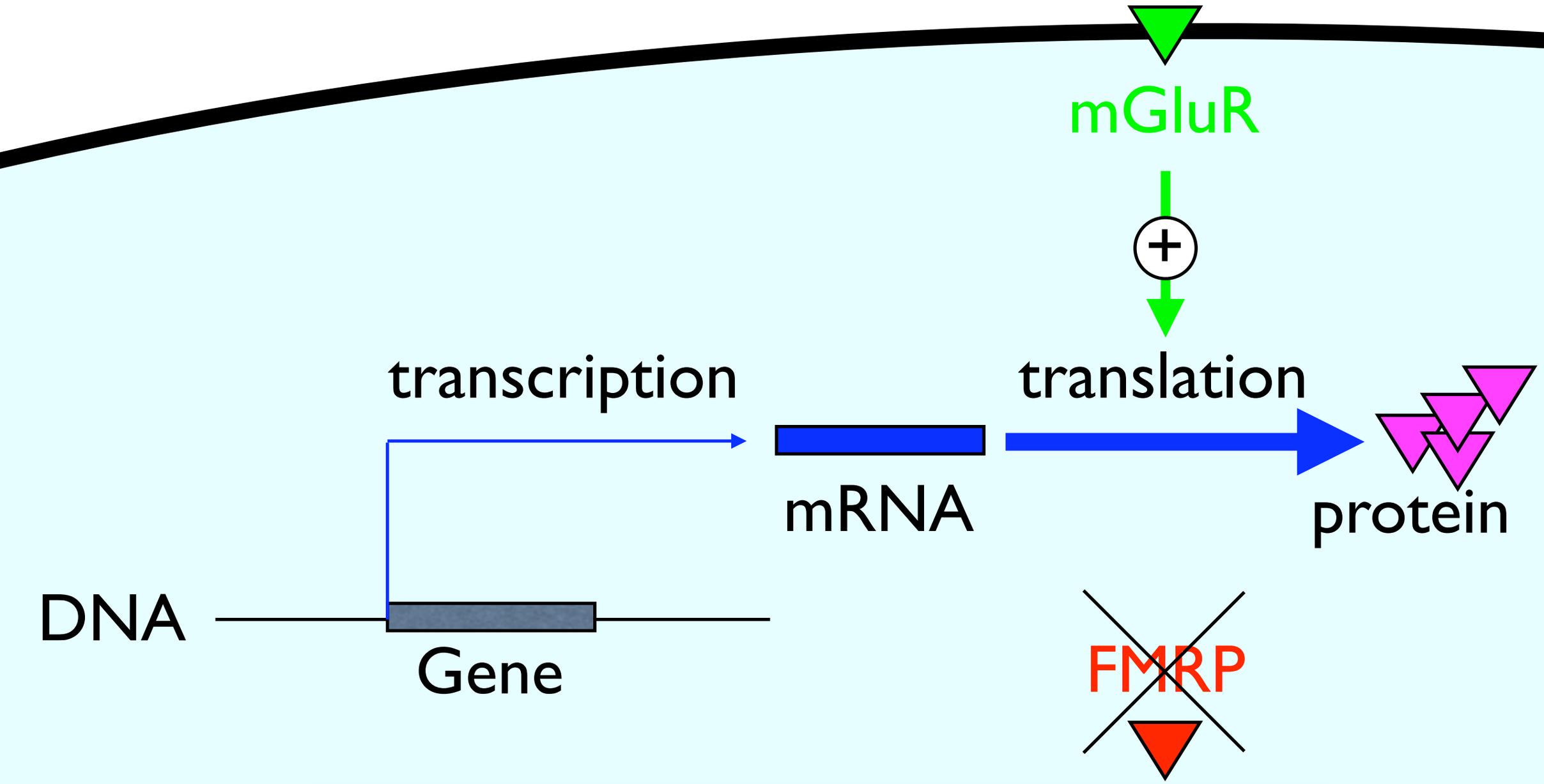
Too much protein synthesis, too many synapses





BS Shankaranarayana Rao

Gül Dölen, *et al.*, *Neuron*, 2007



Fragile X syndrome is caused
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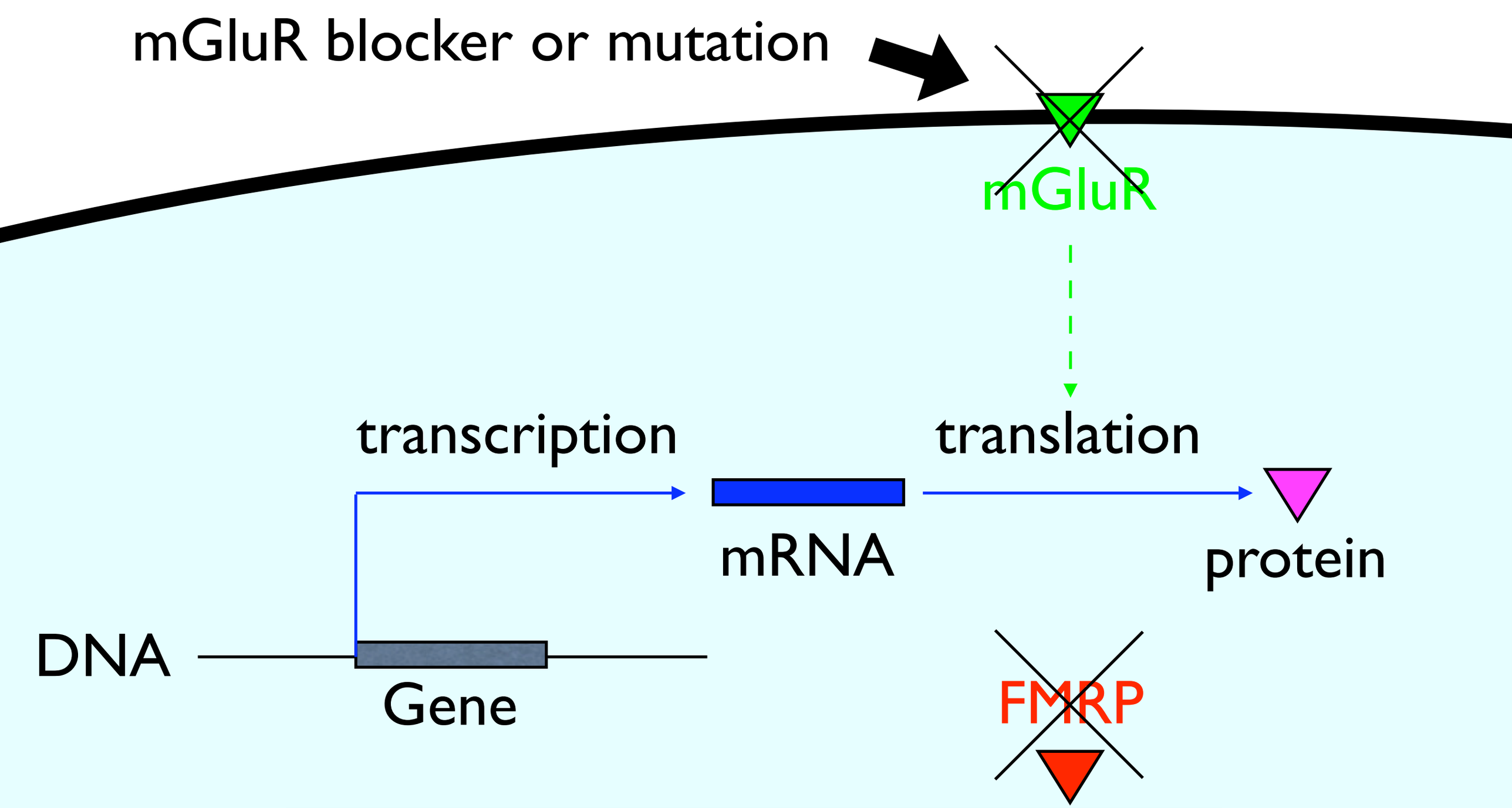
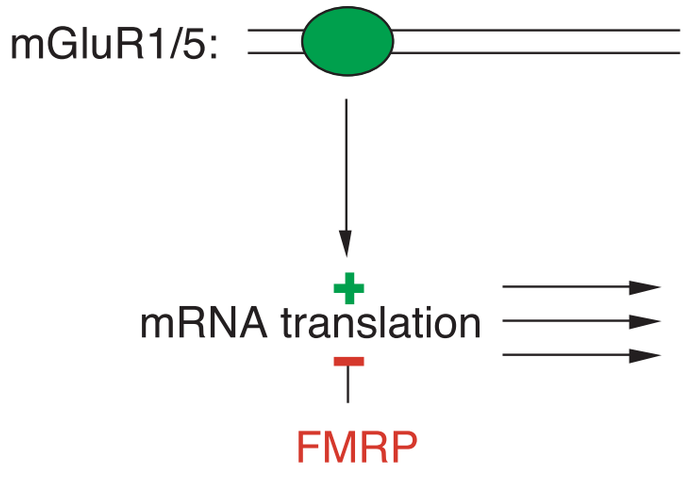
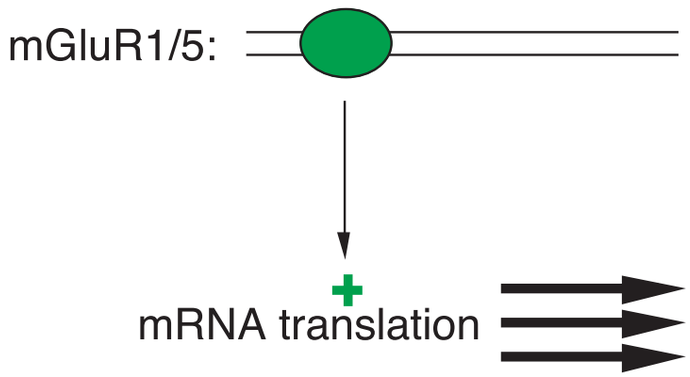
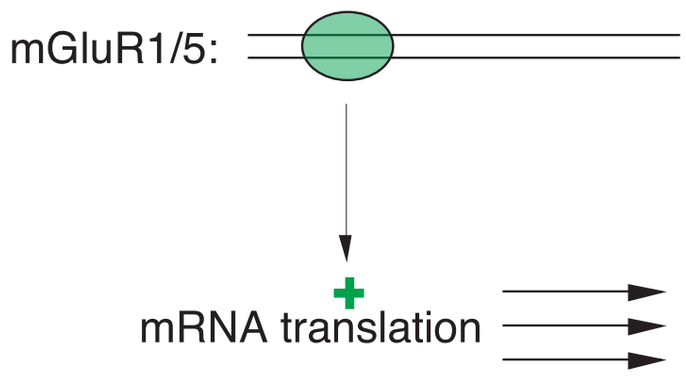
Too many proteins produced

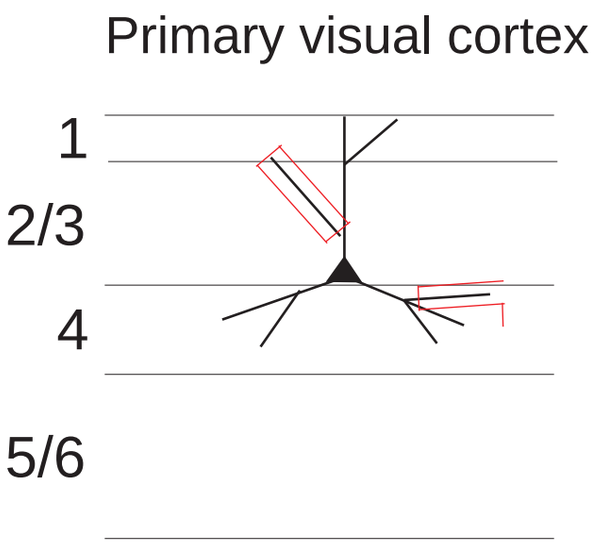


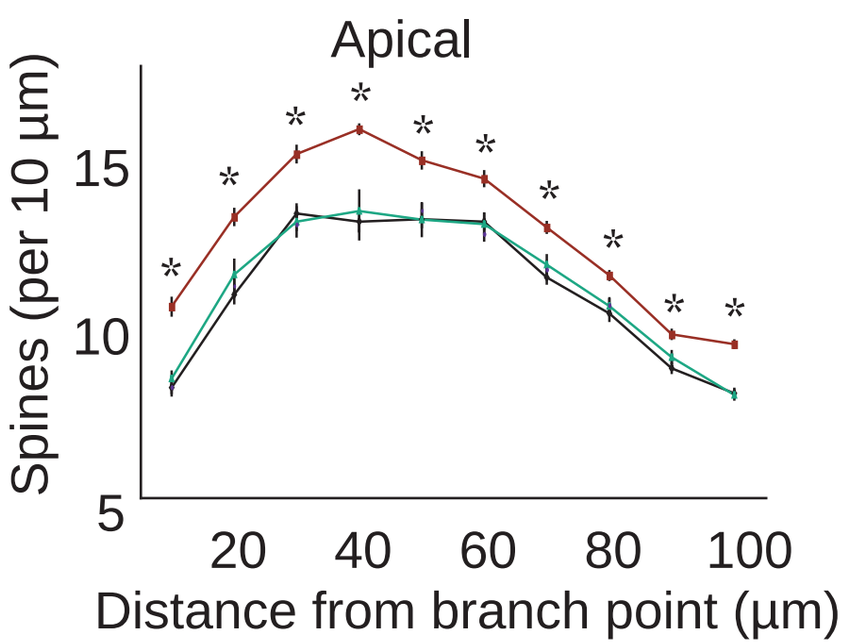
Correction of fragile X syndrome by down-regulation of mGluR5 signaling?

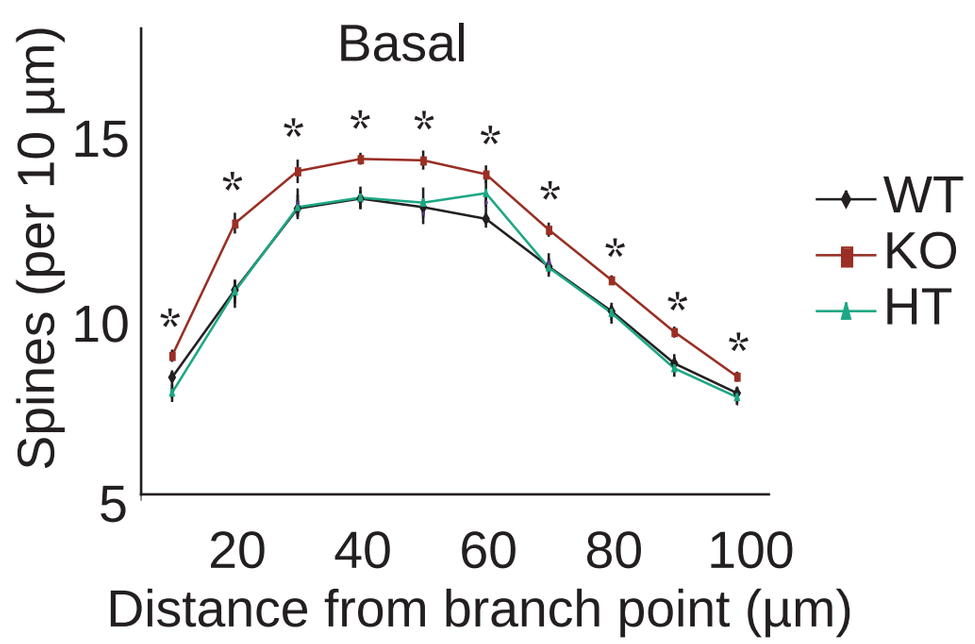
A genetic rescue strategy

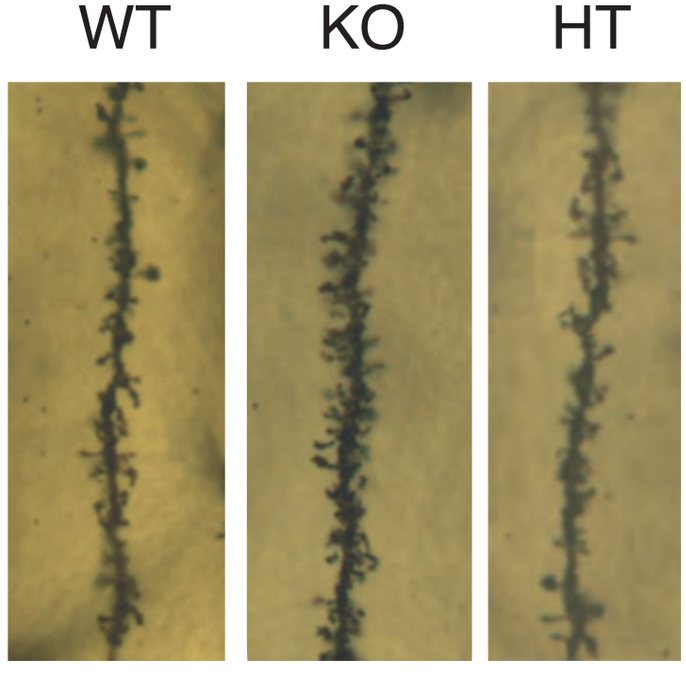
Genotype:		Phenotype:
Wild type (WT)		Normal
Fmr1 knockout (KO)		Exaggerated
KO/*Grm5* HT cross (CR)		Corrected

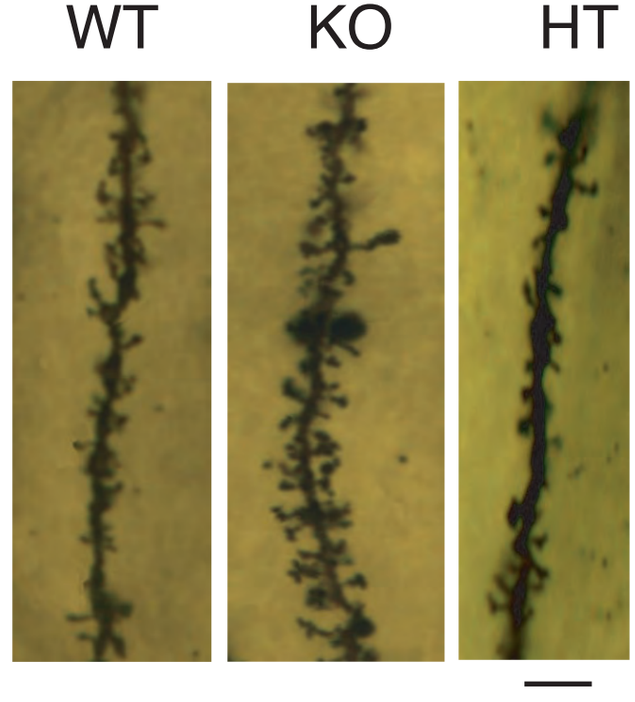
No effect of 50% mGluR5 reduction alone...











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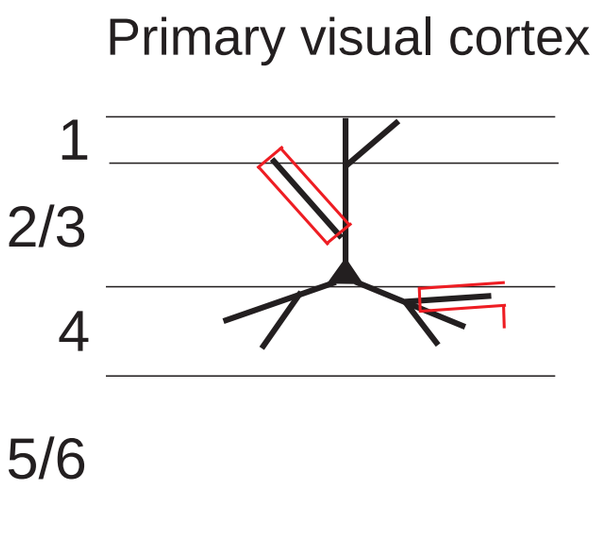
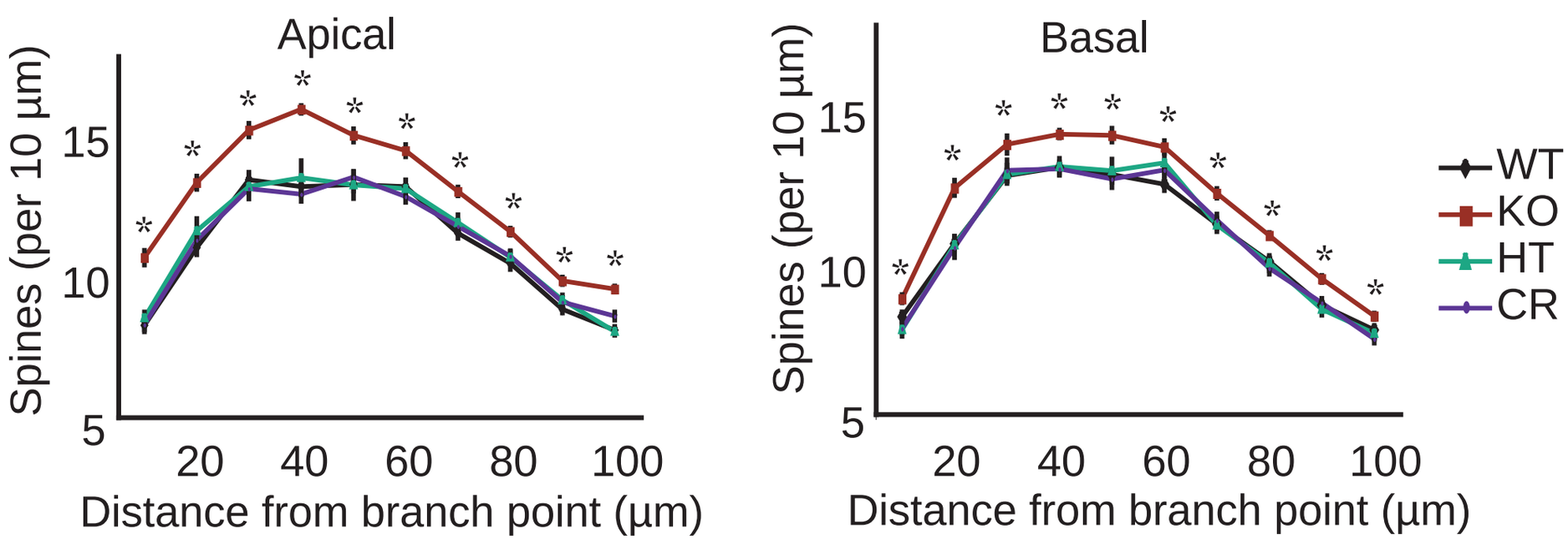
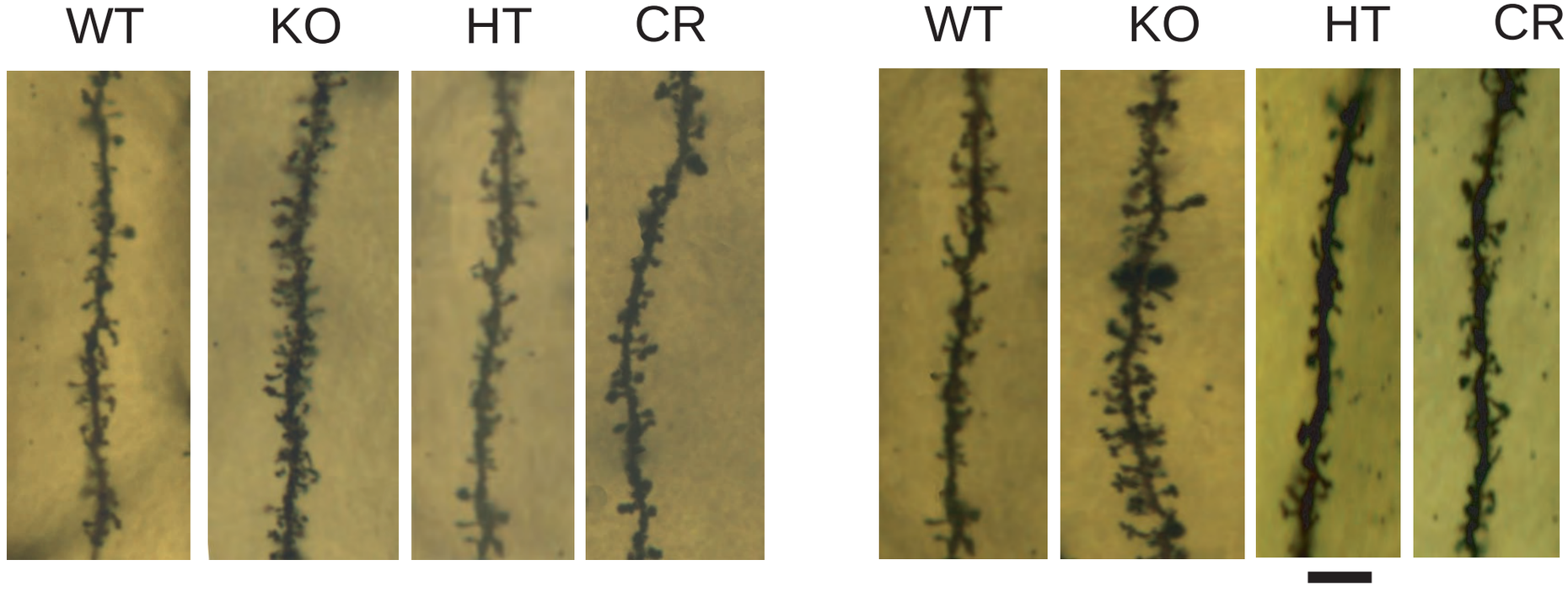
Gül Dölen, *et al.*, *Neuron*, 2007

...but complete rescue of fragile X mutant phenotype







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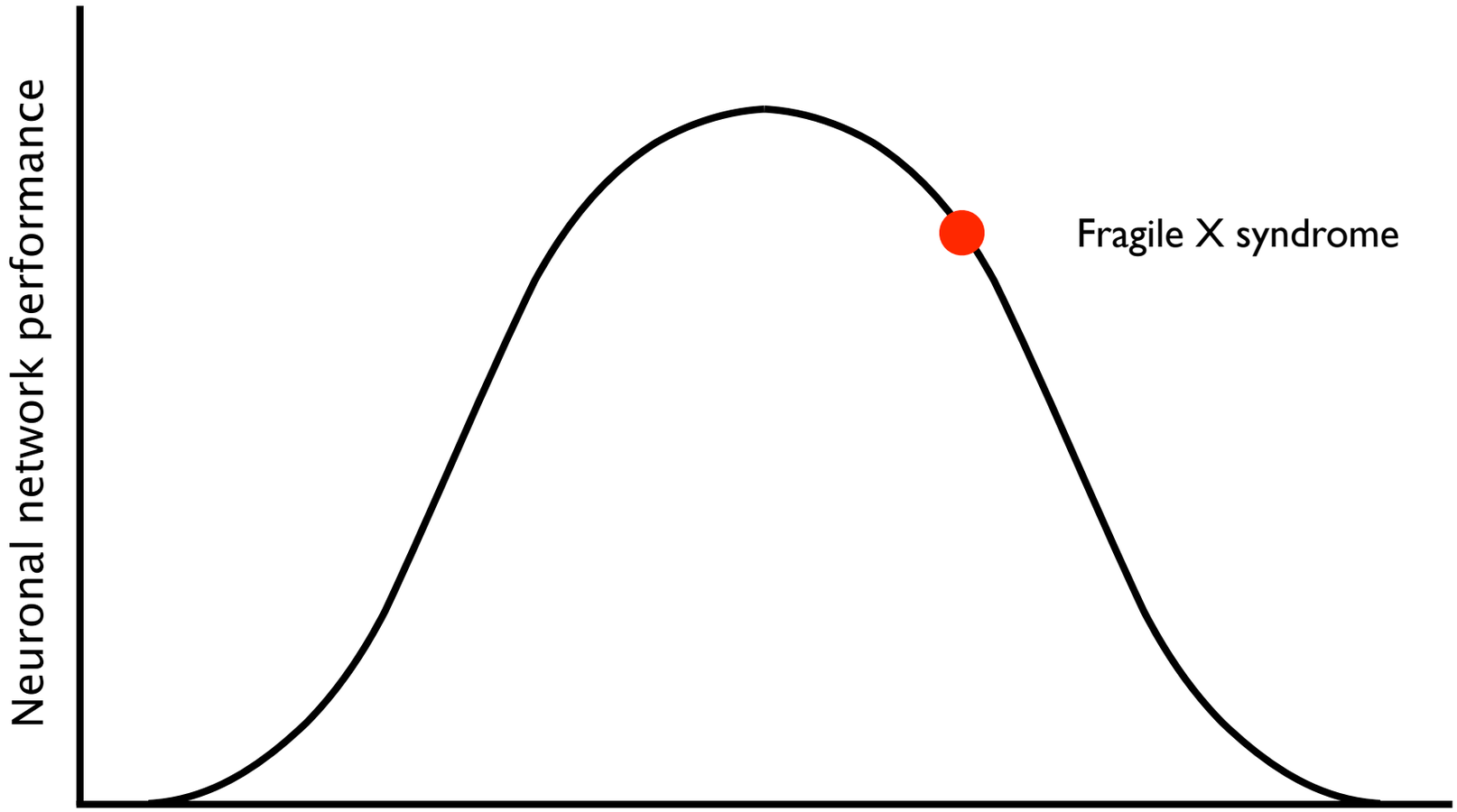
Gül Dölen, *et al.*, *Neuron*, 2007

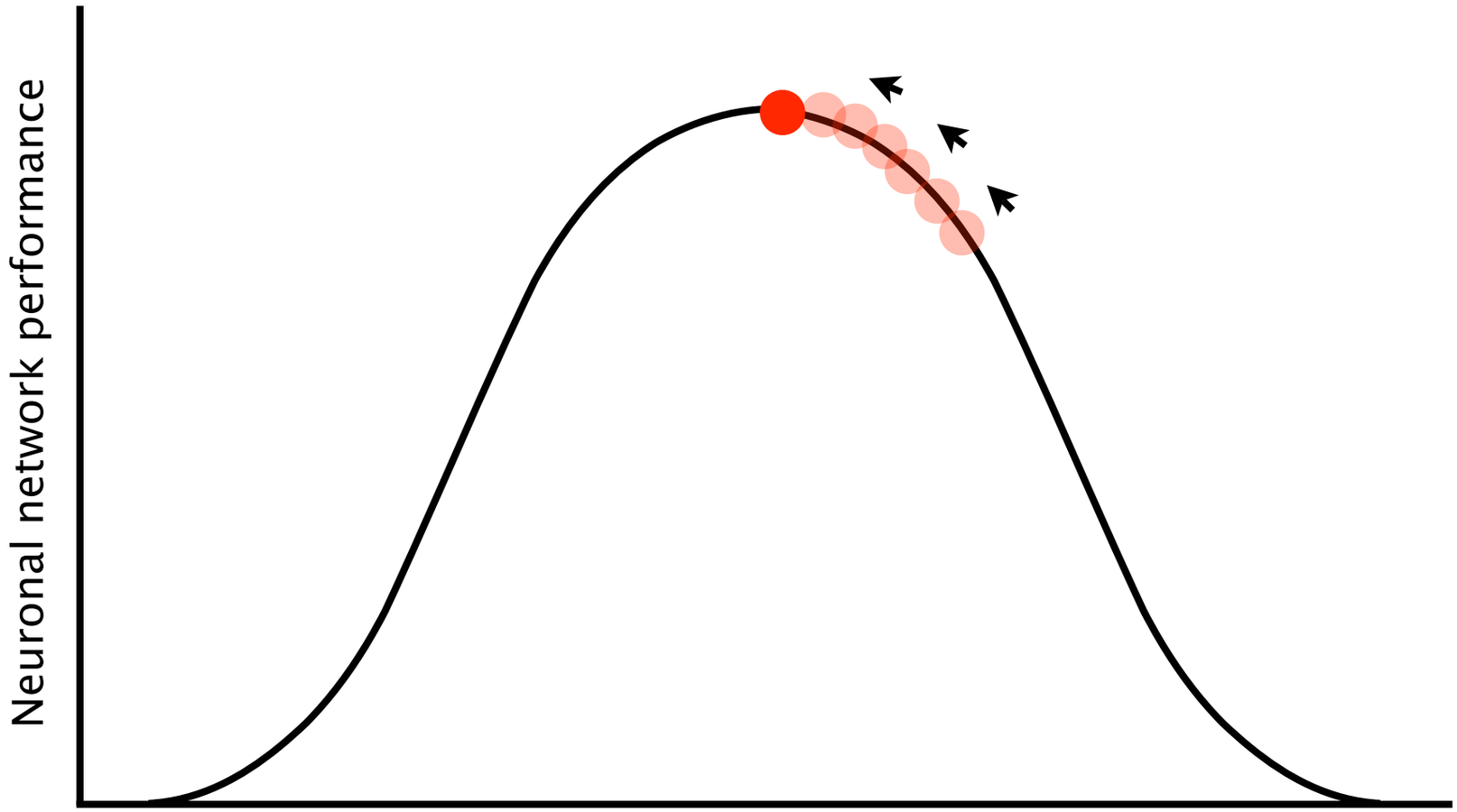
Genetic rescue strategy

Phenotypes rescued:	KO	HT	CR
√ • Long-term depression	↑	↔	↔
√ • Ocular dominance plasticity	↑	↓	↔
⇨ √ • Increased spine density	↑	↔	↔
√ • Fear memory extinction	↑	↔	↔
√ • Basal rate of protein synthesis	↑	↔	↔
√ • Weight gain	↑	↔	↔
√ • Audiogenic seizure	↑	↔	↔
• Macroorchidism	↑	↔	↑



Synaptic protein synthesis

Glutamate → mGluR5 → Protein synthesis → Spine proliferation, etc

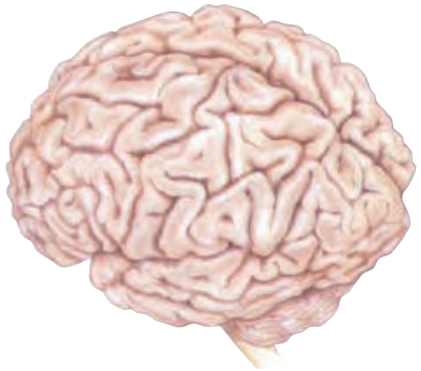


Synaptic protein synthesis

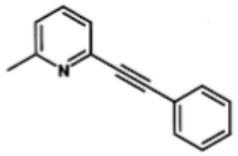
Glutamate → mGluR5 → Protein synthesis → Spine proliferation, etc

Therapeutic targets

Towards fulfilling the promise of molecular medicine

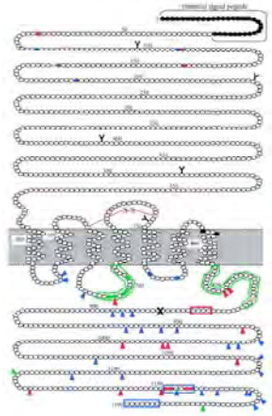


Human psychiatric disease



Novel therapeutics

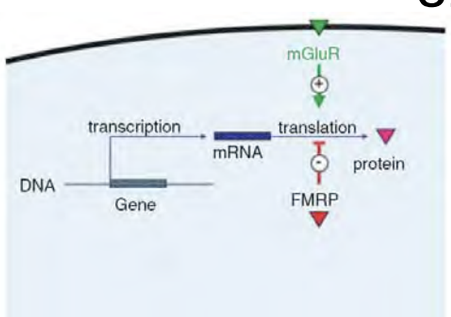
Gene discovery



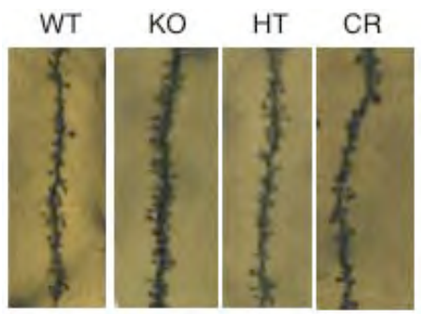
Target ID and drug development

Mouse disease model

Basic neurobiology



Disease pathophysiology



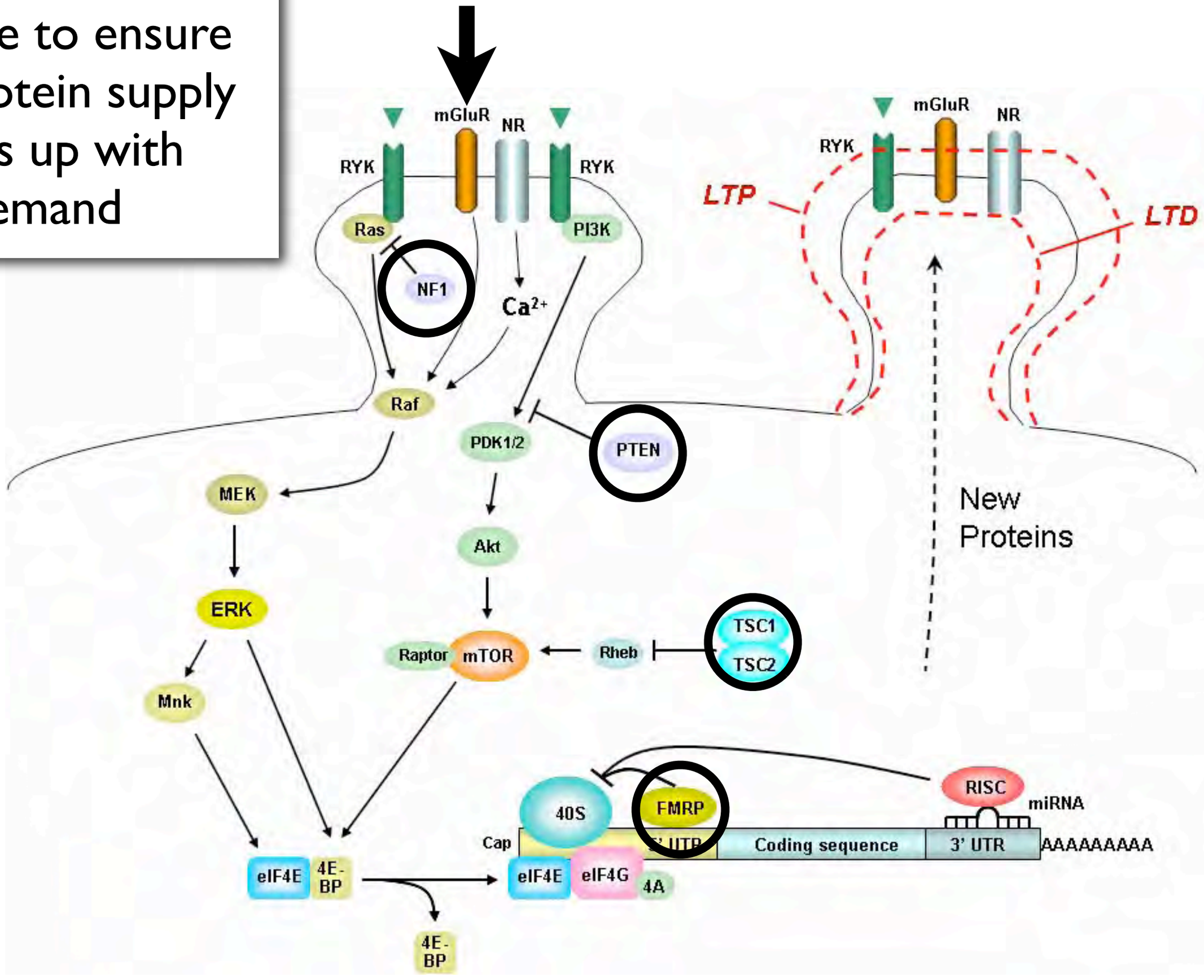
Pharmacological rescue with mGluR5 antagonists

- *Audiogenic seizure in mice (Bauchwitz)*
- *Hippocampal epileptogenesis (Wong)*
- *Increased protein synthesis in mice (Vanderklish)*
- *Altered brain structure and memory in flies (Jongens)*
- *Altered viability in flies (Warren)*
- *Altered synaptic growth on hippocampal neurons (Nagarajan)*

This year, three pharmaceutical companies have initiated human clinical trials of drugs targeting mGluR5 for the treatment of fragile X syndrome

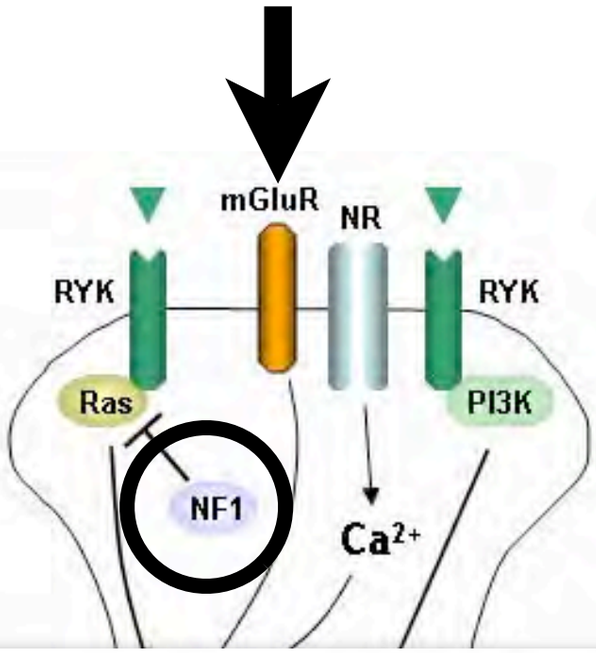
A molecular machine to ensure that protein supply keeps up with demand

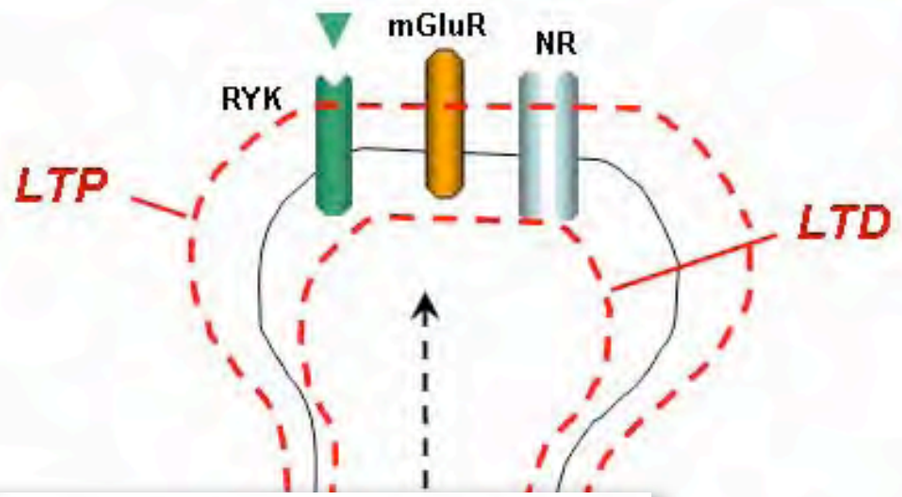
Kelleher and Bear, *The Autistic Neuron*



Kelleher and Bear, *The Autistic Neuron*

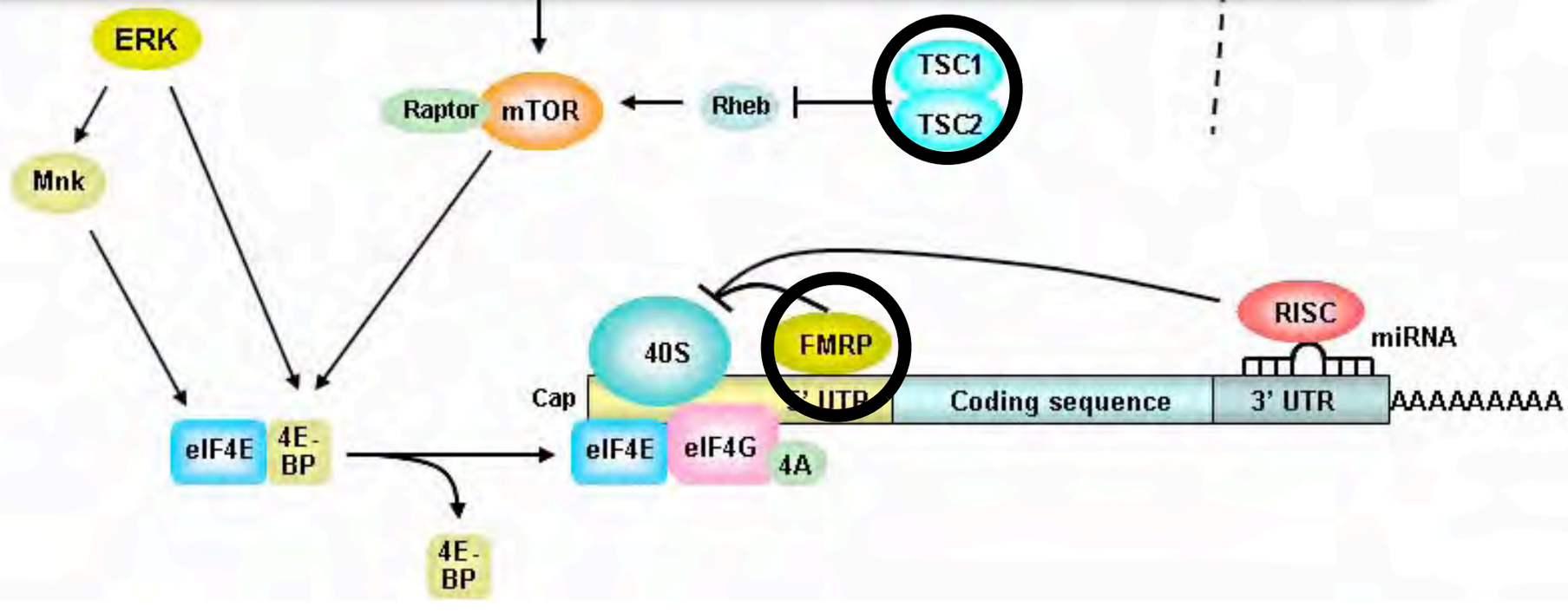
A molecular machine to ensure that protein supply keeps up with demand





Reversal of learning deficits in a *Tsc2*$^{+/-}$ mouse model of tuberous sclerosis

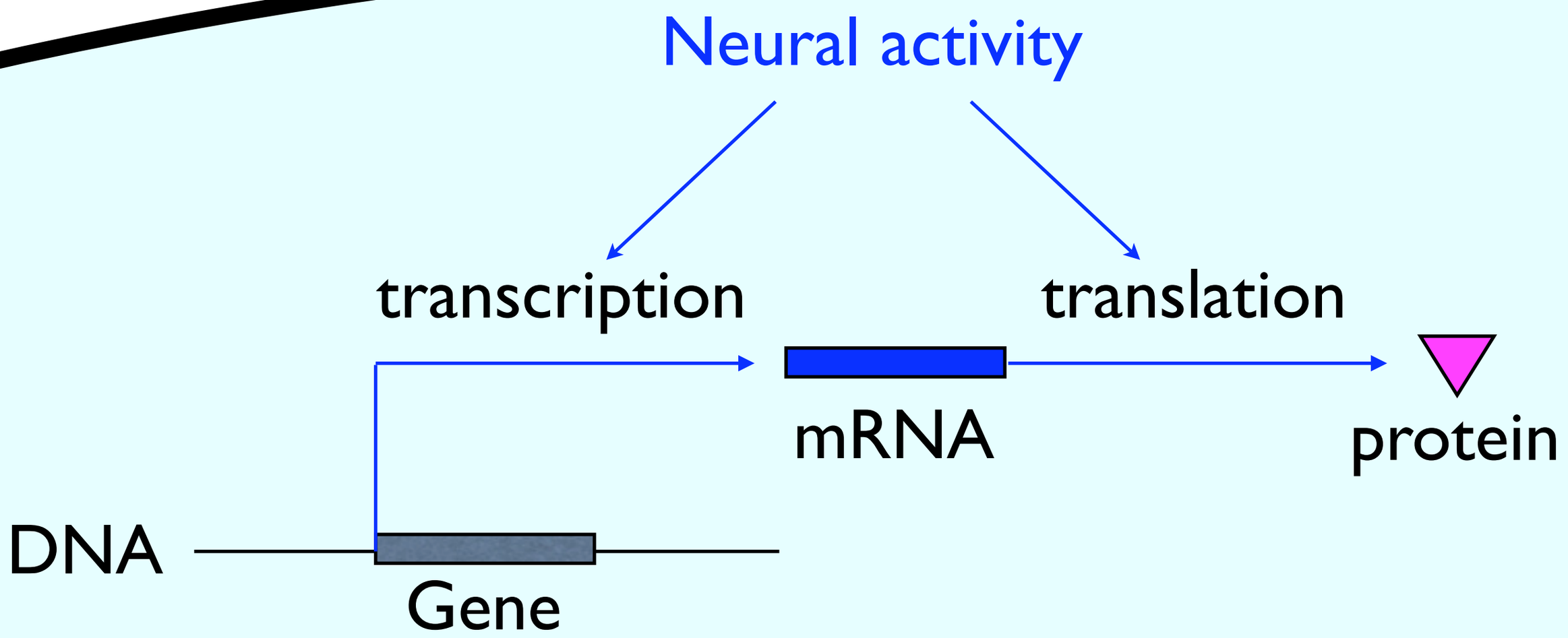
Dan Ehninger[1], Sangyeul Han[2], Carrie Shilyansky[1], Yu Zhou[1], Weidong Li[1], David J Kwiatkowski[3], Vijaya Ramesh[2] & Alcino J Silva[1]



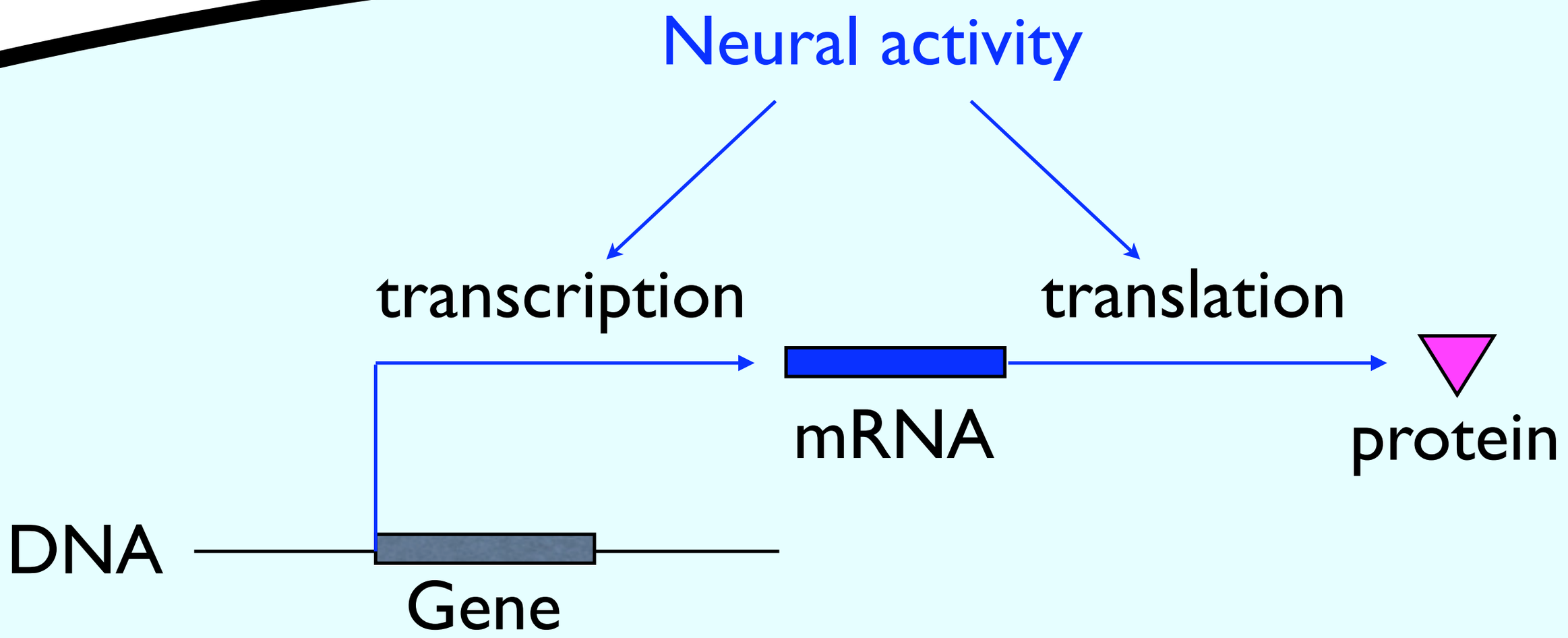
Hot off the press....

Identifying Autism Loci and Genes by Tracing Recent Shared Ancestry

Eric M. Morrow,[1,2,3,4,5*] Seung-Yun Yoo,[1,2,4,5*] Steven W. Flavell,[5,6] Tae-Kyung Kim,[5,6] Yingxi Lin,[5,6] Robert Sean Hill,[1,2,4,5] Nahit M. Mukaddes,[7] Soher Balkhy,[8] Generoso Gascon,[8,9] Asif Hashmi,[10] Samira Al-Saad,[11] Janice Ware,[5,12] Robert M. Joseph,[5,13] Rachel Greenblatt,[1,2] Danielle Gleason,[1,2] Julia A. Ertelt,[1,2] Kira A. Apse,[1,2,5] Adria Bodell,[1,2] Jennifer N. Partlow,[1,2] Brenda Barry,[1,2] Hui Yao,[1] Kyriacos Markianos,[1] Russell J. Ferland,[14] Michael E. Greenberg,[5,6] Christopher A. Walsh[1,



Many genes implicated in autism appear to fall within a pathway that couples brain activity with synaptic protein synthesis



Knowledge of this pathway has suggested novel therapeutics for autism spectrum disorders that are now in clinical trials

Thanks to

NIMH

NICHD

NINDS

NEI

HHMI

FRAXA

NFXF

The Simons Foundation

The Boston Autism Consortium