An Architectonic Perspective on Autism

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Outline of Talk

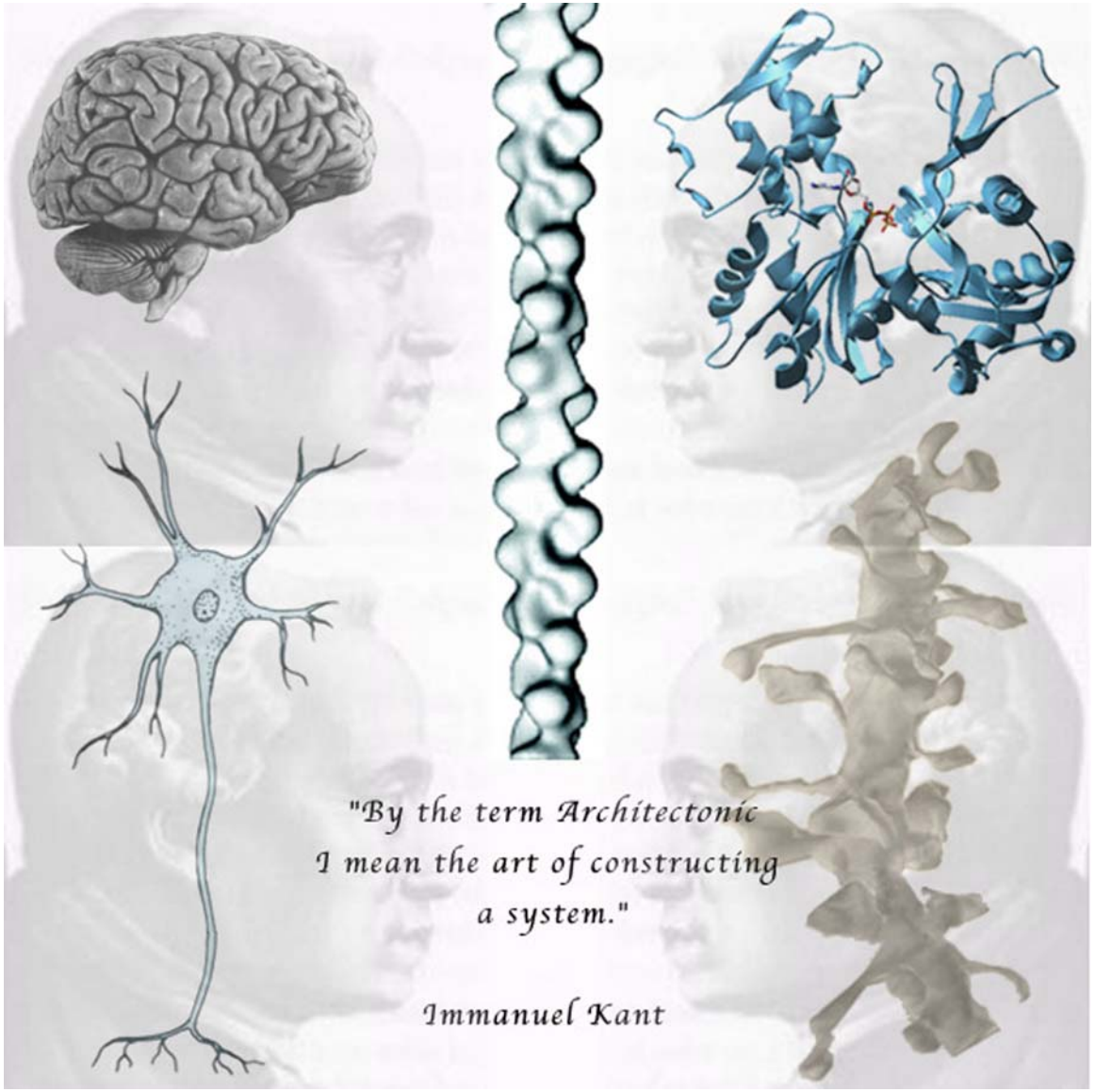
I What is architectonics?

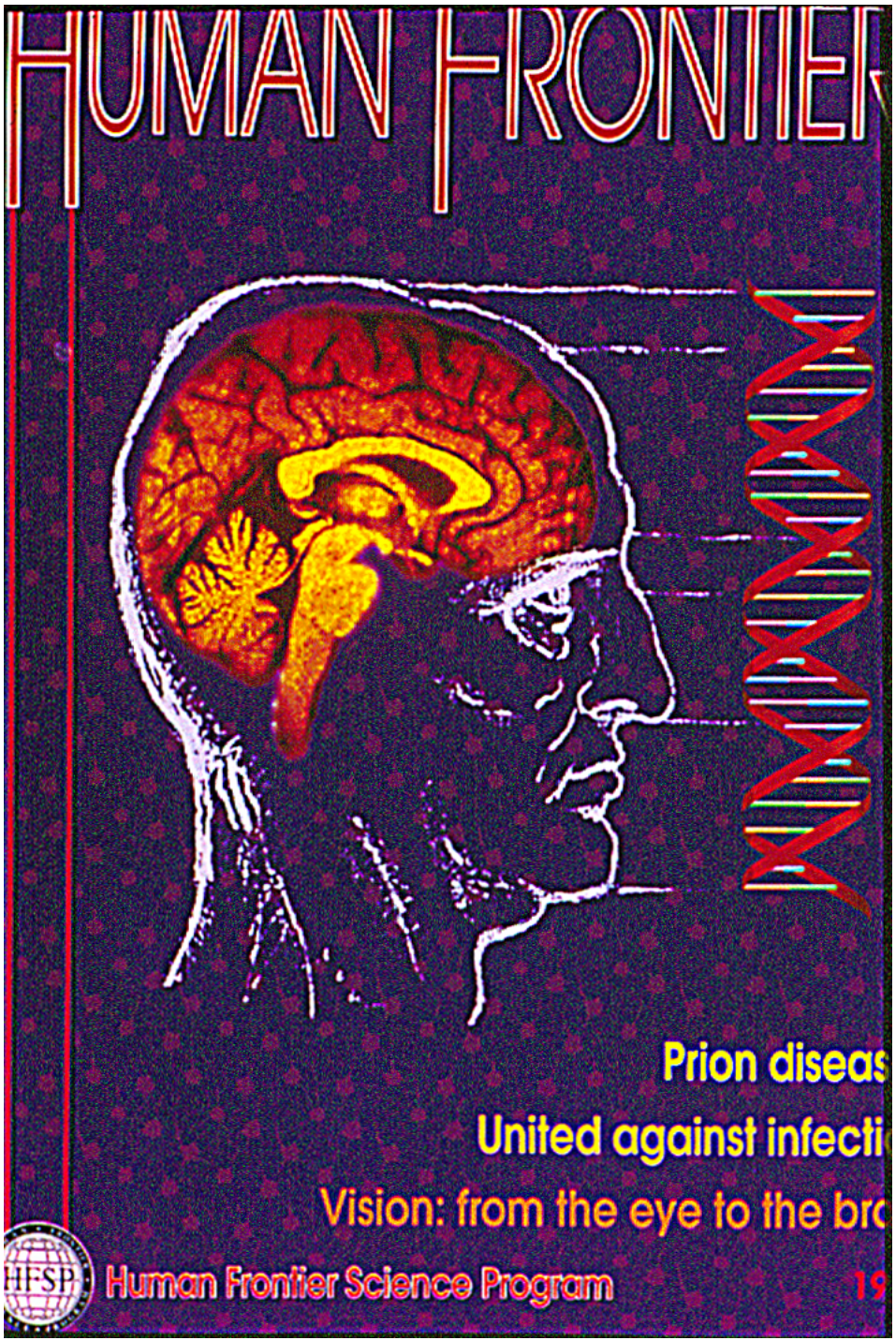
II The Structural Biology of Autism

III Cancer Biology & Autism

IV Can the Effects of Autism be Reversed?

What is Architectonics?


"By the term Architectonic
I mean the art of constructing
a system."
Immanuel Kant

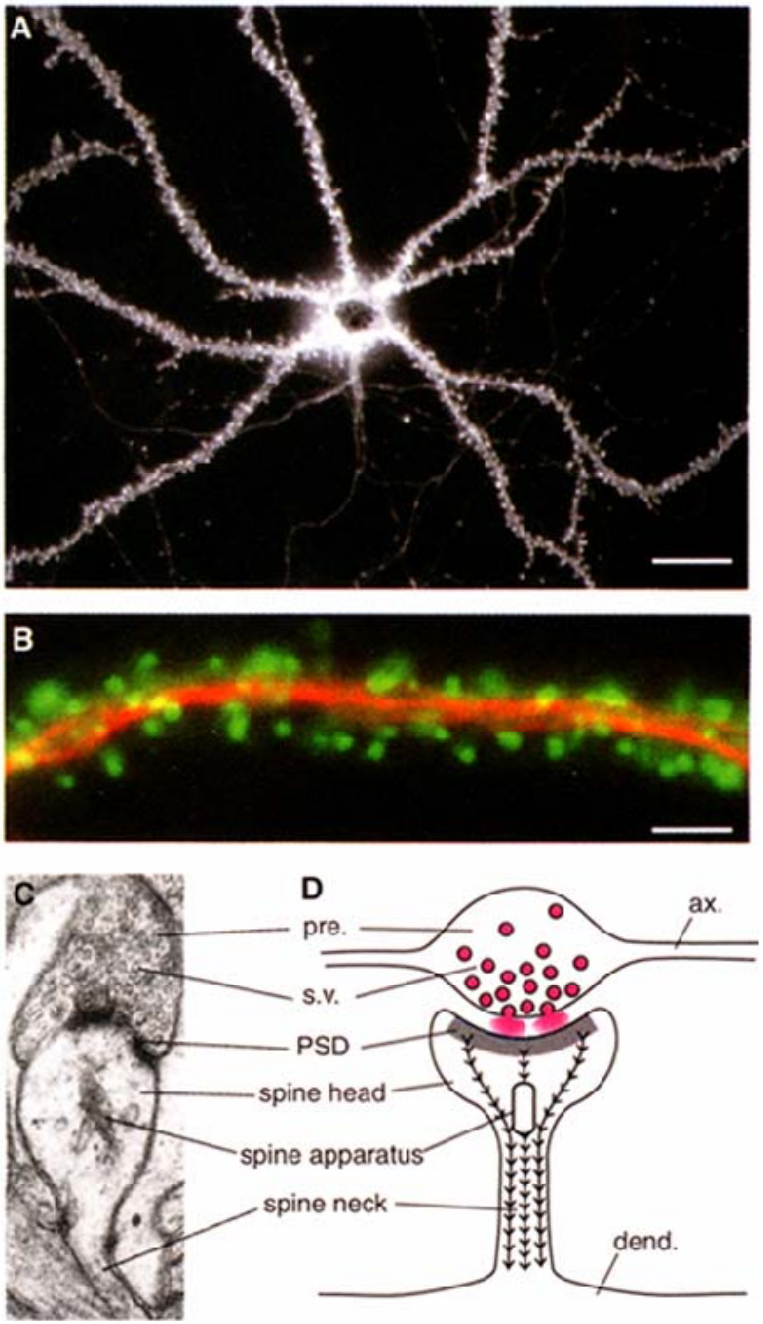


Decade of the Brain
(1990-2000)

Human Genome Project
(1988-2007)

NICHD Workshop
(1993)

NAAR (ATP), CAN (AGRE)
(1994)



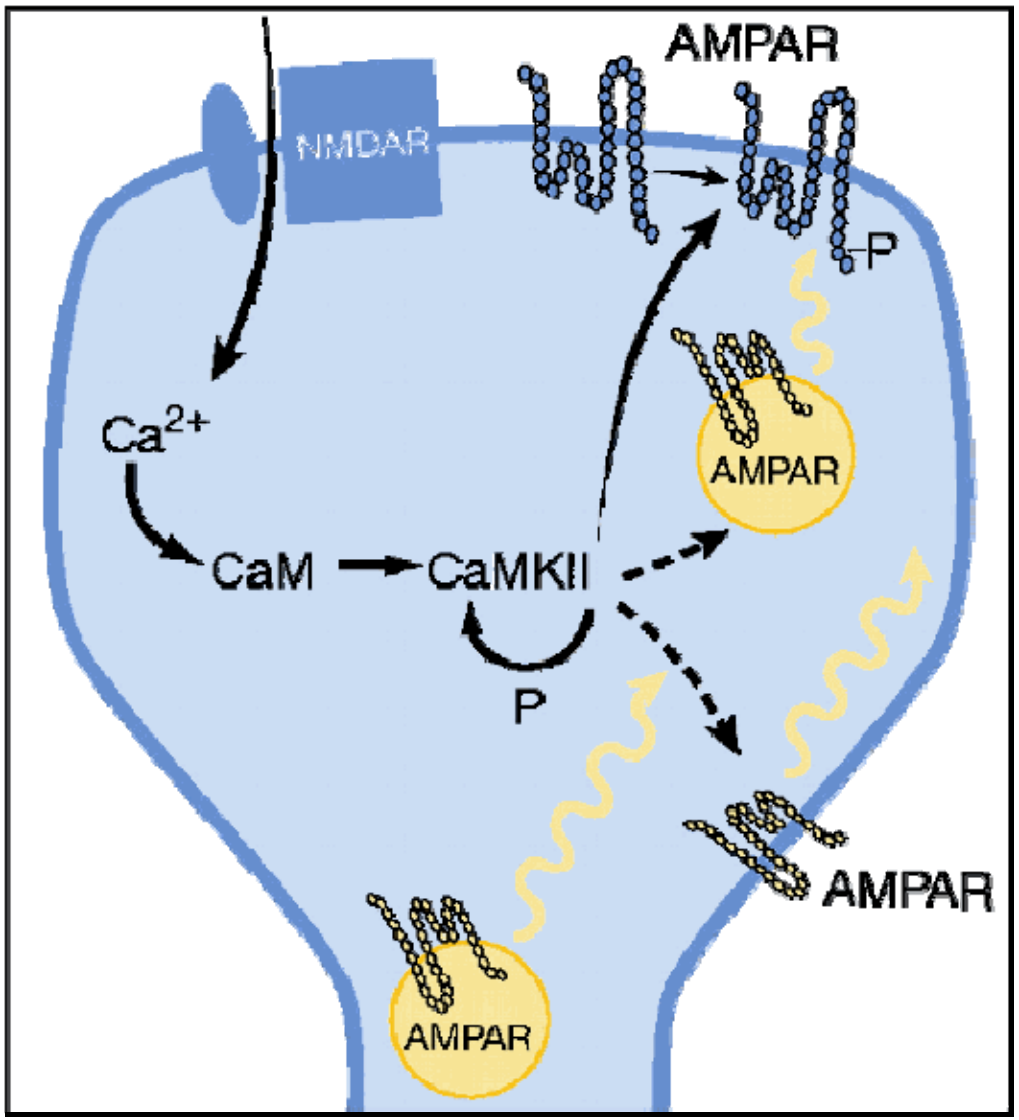
Andrew Matus, Science 2000

Molecular Basis of Learning & Memory

Synaptic plasticity: frequently-used connections ('synapses') between nerve cells are physically changed. This requires gene transcription and protein synthesis.

Mutated genes in (syndromic) autism code for proteins that play crucial roles in synaptic plasticity.

The Biology of Synaptic Strength (LTP)



Learning & Memory: Long Term Potentiation (LTP)

New results show that LTP produces an increase in actin-rich spines. Furthermore these spines have large synapses, strongly suggesting that LTP involves synaptic growth. The process appears to require LIMK-1 phosphorylation of the actin depolymerizing factor cofilin.

Lisman, Neuron 38: 361-365 (2003)

Actin Depolymerization Inhibits Spine Motility

QuickTime™ and a
decompressor
are needed to see this picture.

Andrew Matus

II

The Structural Biology of Autism

Synaptic Plasticity & Autism

I Fragile-X (FMR1, mGluR)

II Tuberous Sclerosis (TSC1/TSC2)

III Rett Syndrome (MecP2)

IV Prader-Willi, Angelman (UBE3a, GABAR3)

V Rare Genetic Forms (neuroligin 3/4, neurexin-β, SHANK3 -- copy number variations -CNV)

Synaptic Plasticity & Autism

"Quantitative analysis of mRNA levels in FMRP-specific immunoprecipitates from synaptoneurosomes demonstrated the association of FMRP with CAMKIIa, PSD-95, and GluR1/2 ... causing the impairments of synaptic plasticity observed in Fmr1 knockout mice...".

R.S. Muddashetty et al., J. Neuroscience 27, 5338-5348 (2007)

Synaptic Plasticity & Autism

QuickTime™ and a
TIFF (Uncompressed) decompressor
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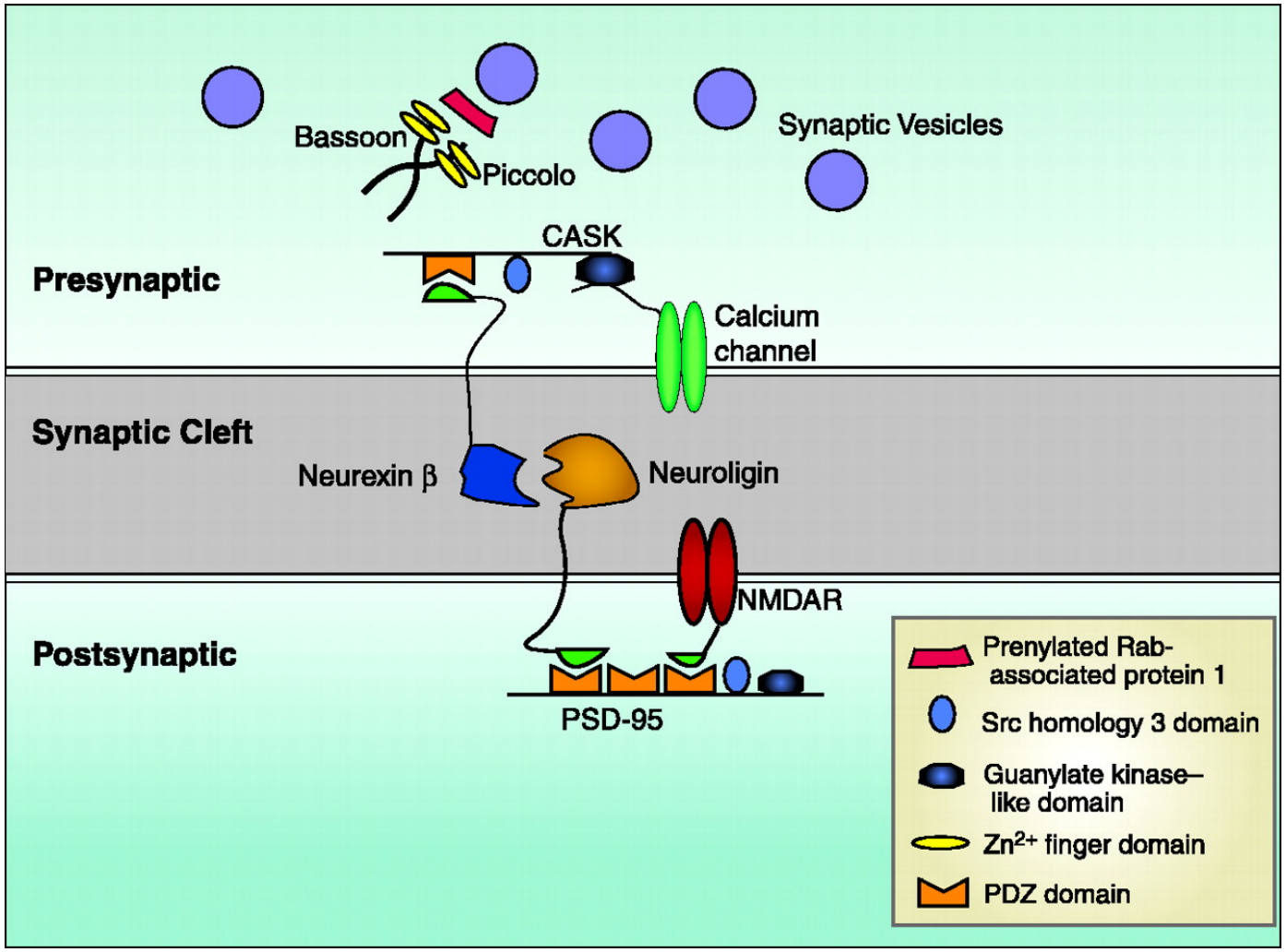
Bagni & Greenough, 2006

A model depicting the role of neuroligins for clustering β-neurexin and inducing presynaptic differentiation



H. Y. Zoghbi Science 302, 826 -830 (2003)

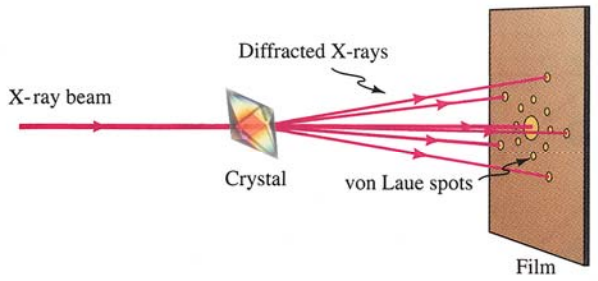
Synaptic Plasticity & Autism

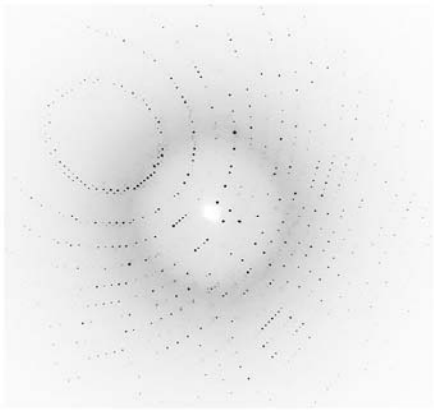
"The mutations identified in these affected individuals are thought to affect the function and localization of SHANK3 at PSD's and dendritic spines".

"Therefore, we hypothesize that the protein complex including neuroligins and SHANK participate in the assembly of specialized post-synaptic structures required for the development of language and social communication".

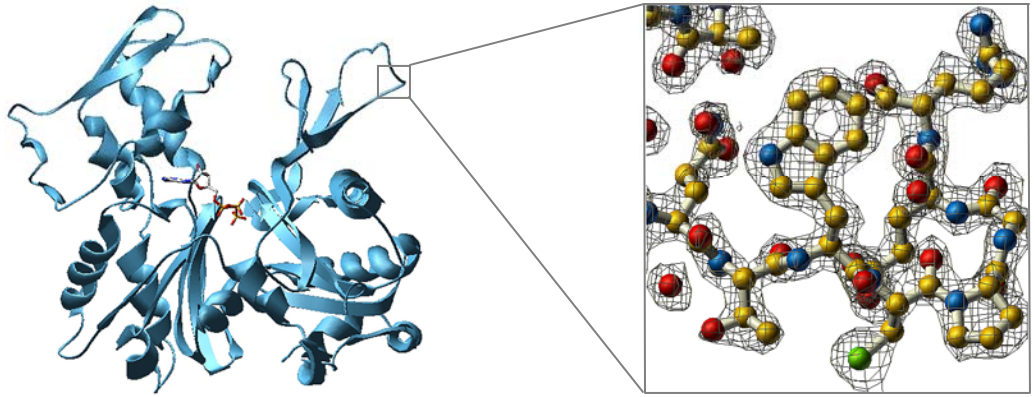
Durand et al., Nat. Genetics **39**, 25-27 (2007)

“Seeing” Molecules with X-rays





Fourier synthesis
& Model building



Synaptic Plasticity & Autism

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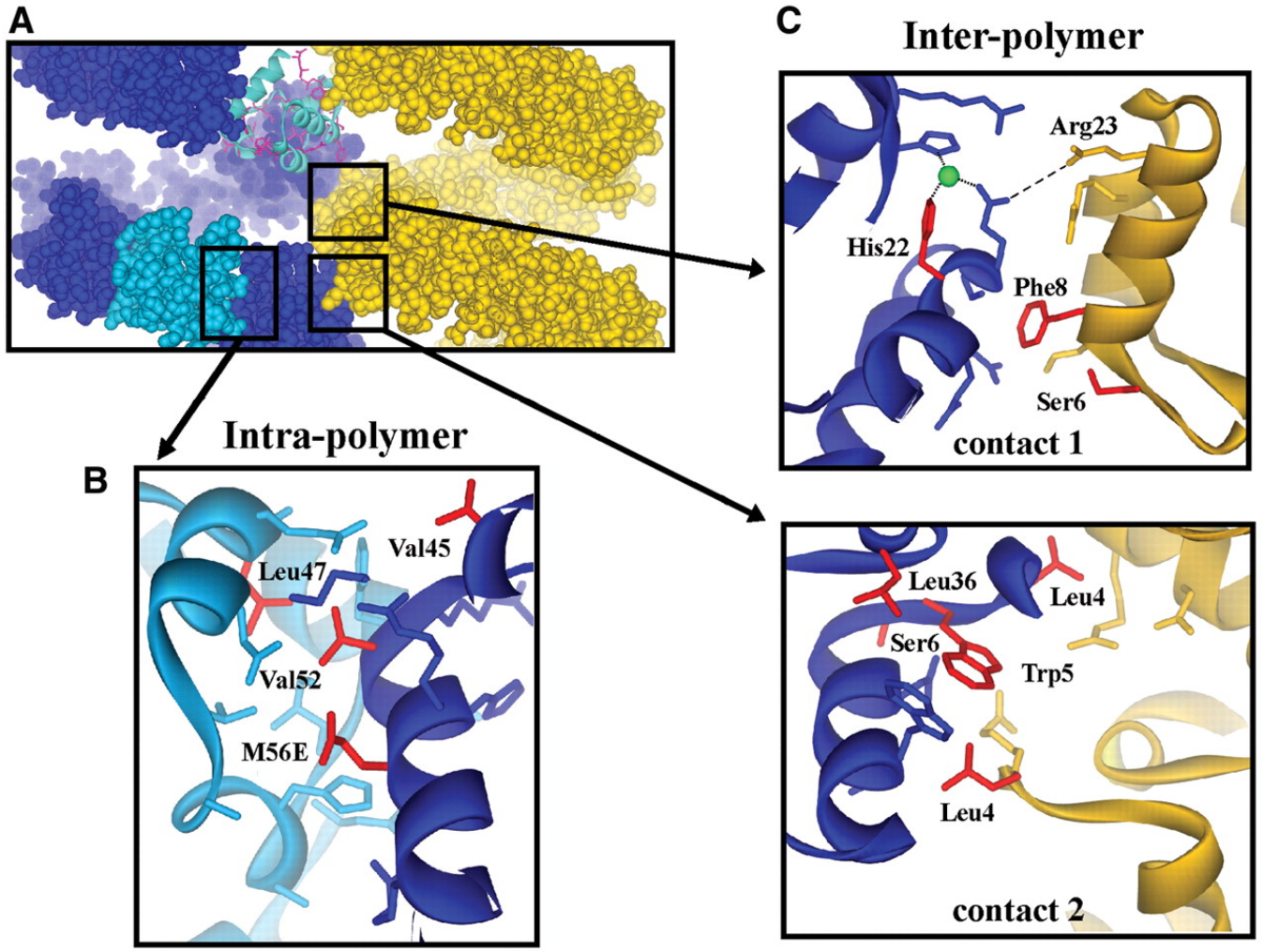
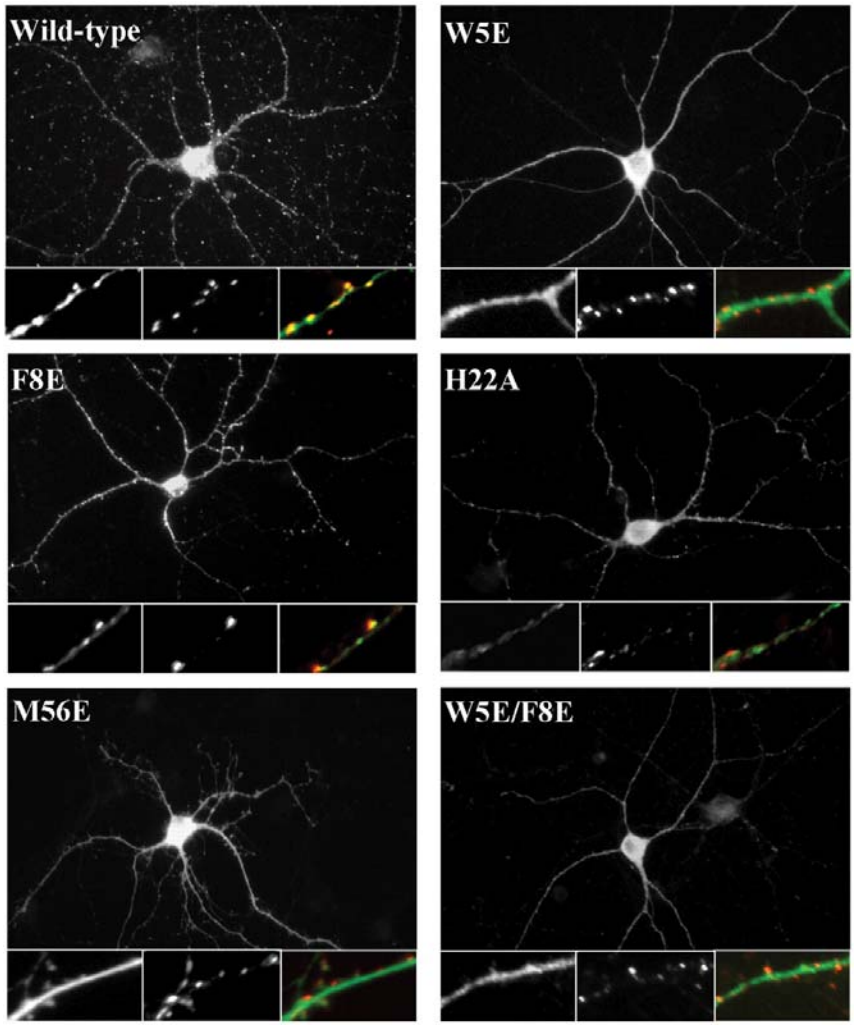
Baron et al, 2006

Mutations of Shank-SAM that disrupt assembly are located in the inter- and intrapolymer interfaces of the sheet



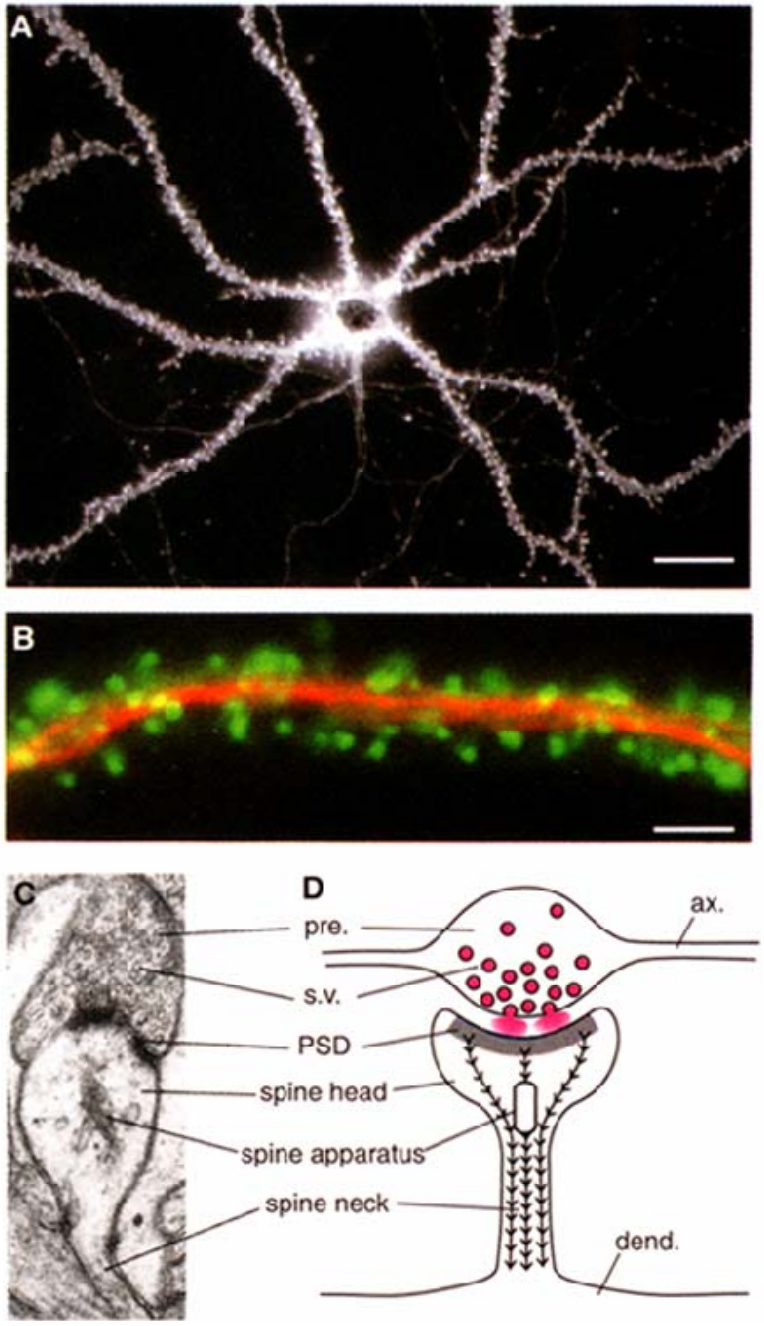
M. K. Baron et al., Science 311, 531 -535 (2006)

Assembly mutants prevent the localization of Shank to the synapse



M. K. Baron et al., Science 311, 531 -535 (2006)

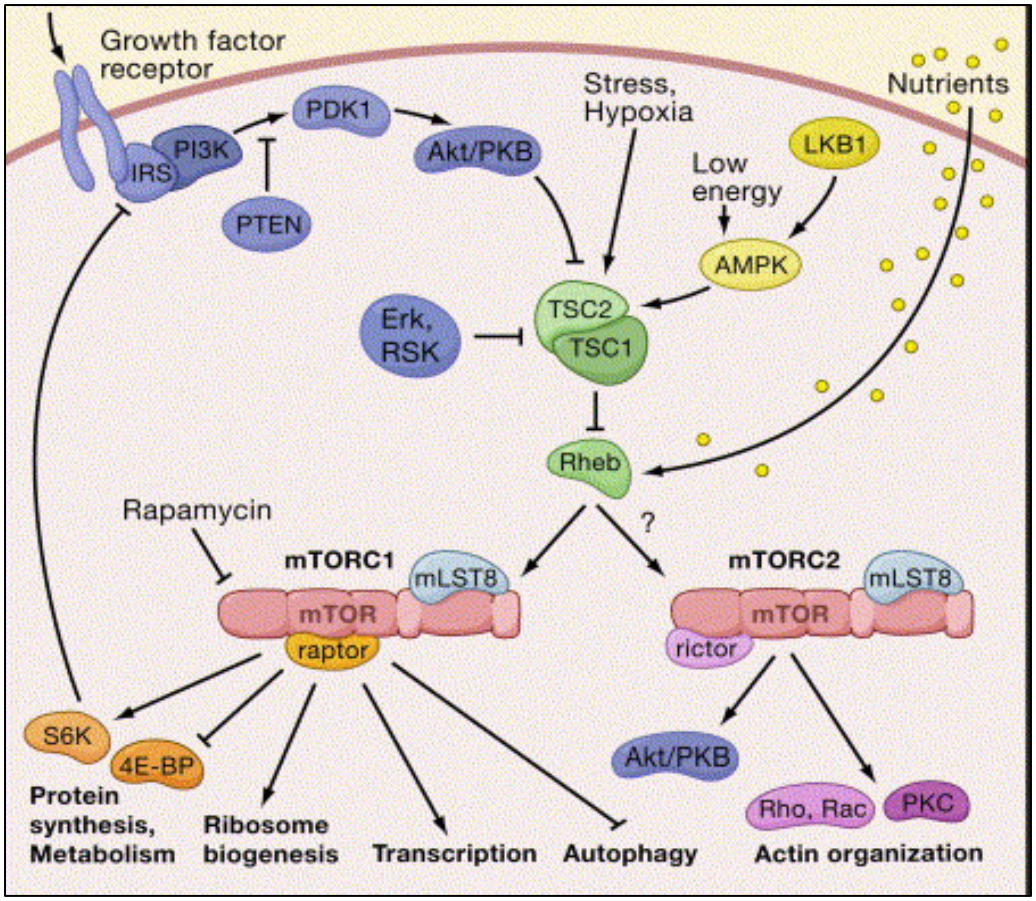
Published by AAAS



Andrew Matus, Science 2000

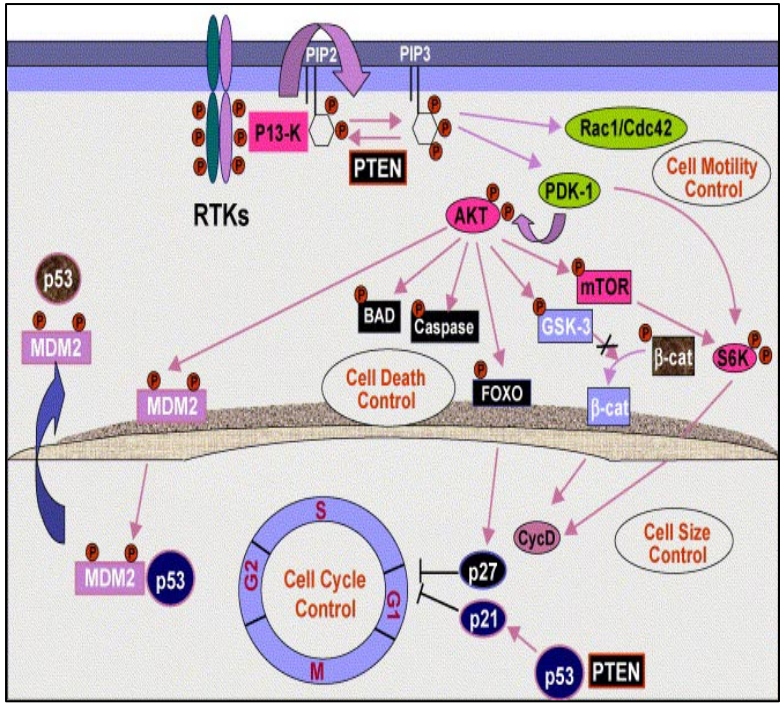
Cancer Biology & Autism

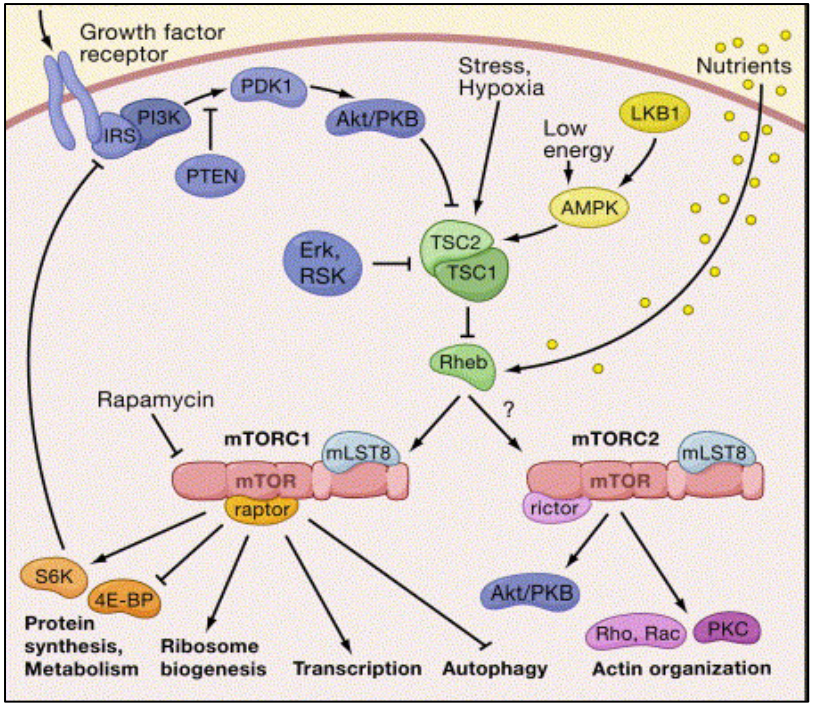
Cancer Biology & Autism



Wullschleger, Loewith & Hall (2006)

Cancer Biology & Autism





Wullschleger, Loewith & Hall, Cell 2006

Cancer Biology & Autism

Pten +/-

QuickTime™ and a
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are needed to see this picture.

Pten: phospholipid phosphatase

Kwon et al.(2006)

Tumor Suppressors & Autism

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

TSC1/TSC2 stress sensors

Tavazoie et al, 2007

PAK Inhibition Reverses Fragile-X Phenotype

QuickTime™ and a
TIFF (Uncompressed) decompressor
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Spine density

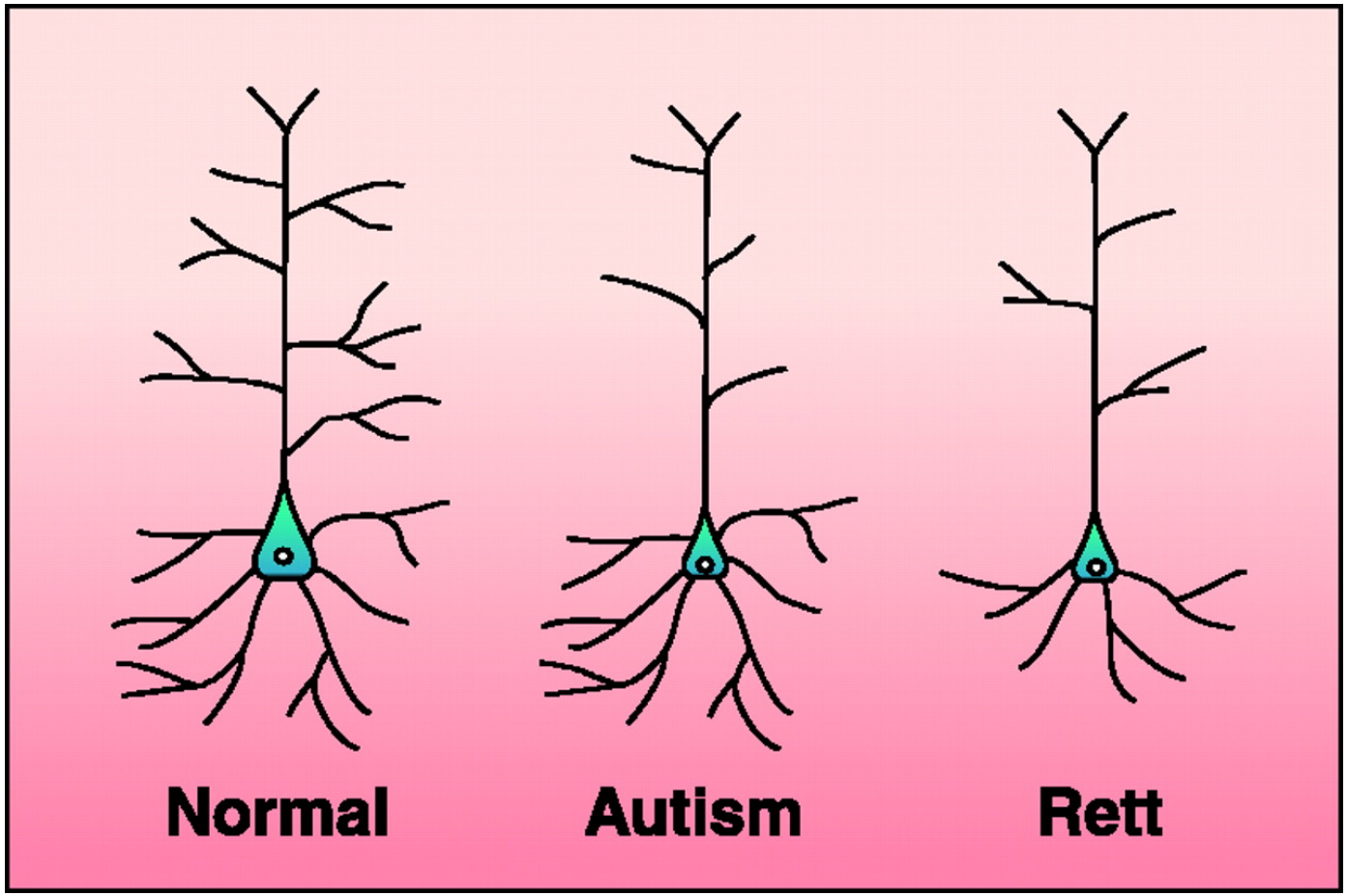
Long Term Potentiation (LTP)

Hayashi et al. (2007)

IV

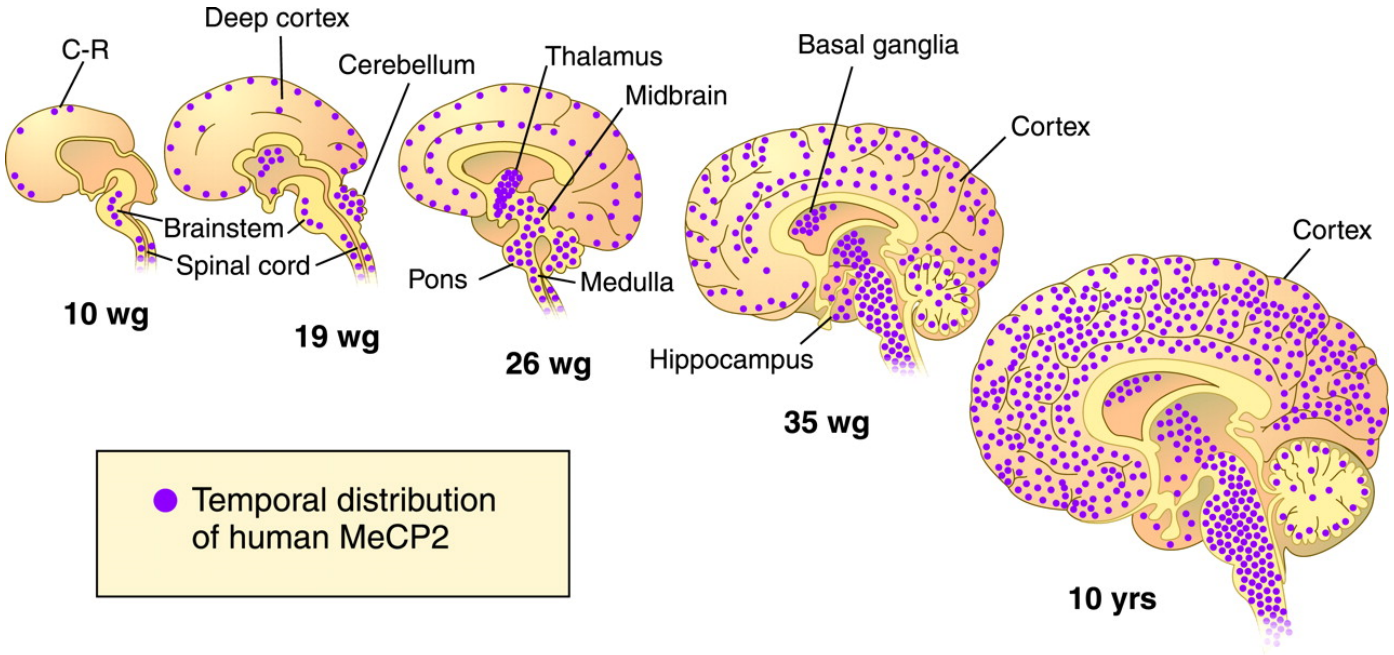
Can the Effects of Autism be Reversed?

Schematic representation of pyramidal neurons from control, autism, and Rett brains



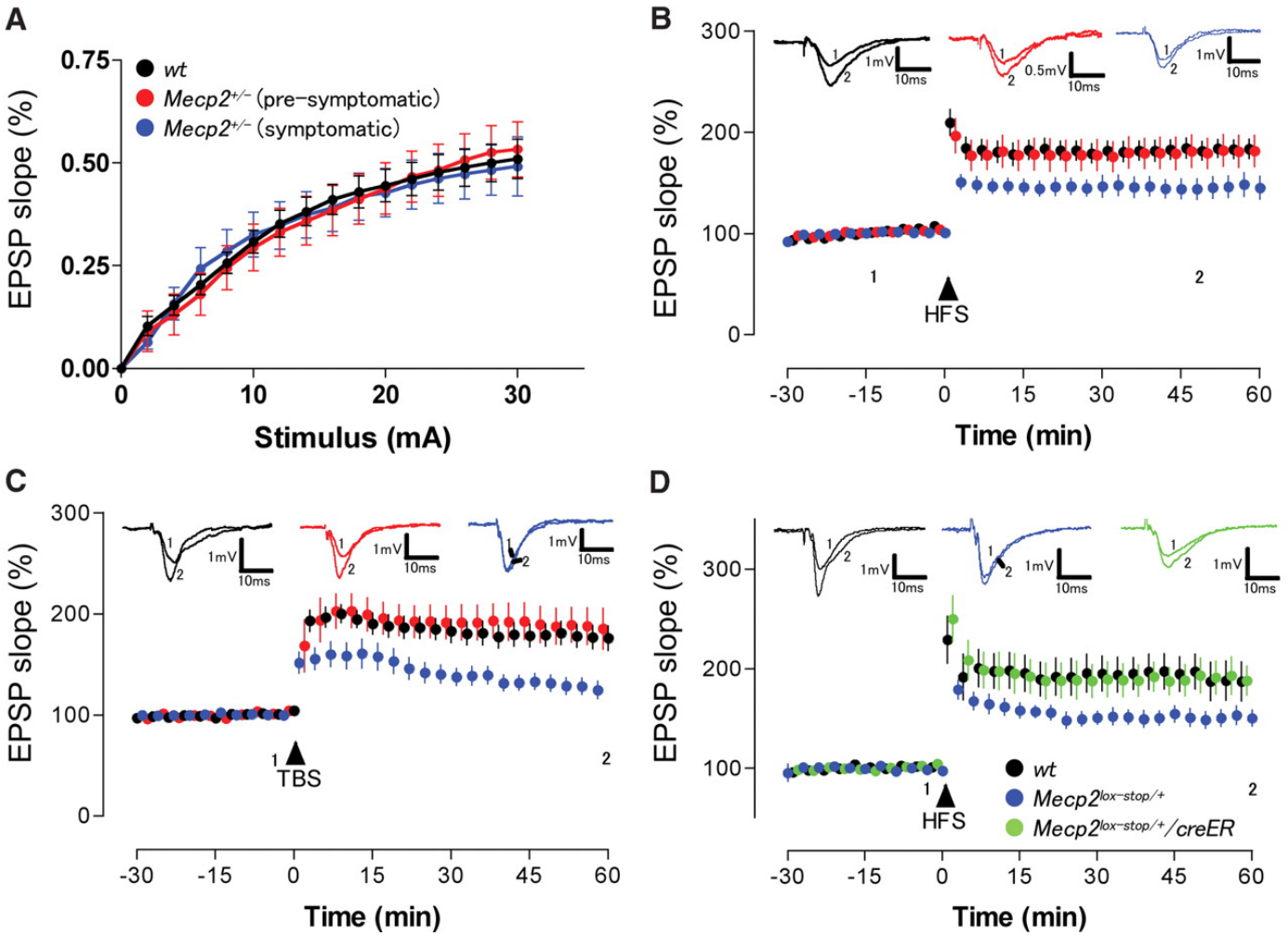
H. Y. Zoghbi Science 302, 826 -830 (2003)

Spatial and temporal distribution of MeCP2 during human development



H. Y. Zoghbi Science 302, 826 -830 (2003)

A deficit in long-term potentiation (LTP) accompanies onset of symptoms in mature adult Mecp2lox-Stop/+ heterozygous females and is reversed by Mecp2 reactivation



J. Guy et al., Science 315, 1143 -1147 (2007)

Neurological Deficits of Autism are Reversible

"In conclusion, our study shows that RTT-like neurological defects due to absence of the mouse *Mecp2* gene can be rectified by delayed restoration of that gene. The experiments do not suggest an immediate therapeutic approach to RTT, but they establish the principle of reversibility in a mouse model and therefore *raise the possibility that neurological deficits seen in this and related disorders are not irrevocable*". (italics mine)

Guy, J. et al. published on-line 8 February 2007 (www,Scienceexpress.org)

Debunking the Myth of Mental Retardation

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

“…y aún no puede resolverse.”

QuickTime™ and a
decompressor
are needed to see this picture.

“So many feet, poor thing, and still it can’t
make up its mind. And, seeing it
stunned at such a critical moment,
today what worry that traveler brought me.”

César Vellejo (“La araña”, verse 4)

Michael Wigler's Unified Genetic Model

"We therefore propose the following unified model for sporadic and inherited autism. The majority of autisms are a result of *de novo* mutations, occurring first in the parental germ line. For reasons yet to be determined, female offspring are considerably more resistant to displaying the effects of such mutations than are males. Resistant individuals, but females in particular, carrying the mutation may marry, and with a probability of 50% pass the mutation to their offspring, who will display the symptoms with high priority if male".

PNAS 104, 12831-12836 (2007)

New Directions in Autism Research

1. Cancer Biology & Autism (PTEN, IGF-1, mTOR).

2. Gut Microflora (clostridial overabundance).

3. MEG Imaging (sensory, linguistic, motor planning - 'neuroendophenotype').

4. Oxidative Stress (biomarkers)

5. Rhythmicity, synchrony, timing, E/I

Fragile-X & Loss of Synaptic Plasticity

"Fragile-X syndrome, a common form of inherited mental retardation, is caused by the loss of fragile-X mental retardation protein (FMRP), an mRNA binding protein that is hypothesized to regulate local mRNA translation in dendrites downstream of gp-1 metabotropic receptors (mGluRs)."

"Quantitative analysis of mRNA levels in FMRP-specific immunoprecipitates from synaptoneurosomes demonstrated the association of FMRP with CAMKIIα, PSD-95, and GluR1/2 É causing the impairments of synaptic plasticity observed in Fmr1 knockout miceÉ ".

R.S. Muddashetty et al., J. Neuroscience 27, 5338-5348 (2007)