

ASD: Research to Practice in the 21st Century

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Progress Comes From Participation

We wish to honor those individuals and families who have believed in research and been committed to participating again and again.

A Few of the Many Scientists



Nancy Minshew, MD



William Eddy, PhD



Marcel Just, PhD



Marlene Behrmann, PhD



John Sweeney, PhD



Beatriz Luna, PhD



Mark Strauss, PhD



Tom Mitchell, PhD

A Few of the Many Scientists (cont'd)



Diane Williams, PhD



Suzy Scherf, PhD



Carla Mazefsky, PhD



Kate McFadden, MD



Shaun Eack, PhD



Tim Keller, PhD



Ilan Dinstein, PhD



Uri Hasson, PhD

What does 'cause' mean?

Etiology

Pathophysiology

Functional analysis of behavior

From DNA to Behavior: A Connected Sequence of Mechanisms At All Levels

Abnormalities in Genetic Code for Brain Development



Abnormal Mechanisms of Brain Development



Structural and Functional Abnormalities of Brain



Cognitive & Neurological Abnormalities



Behavioral Syndrome

Defining Cause Means

Defining Mechanisms

Within & between levels

Developing treatments that specifically
target mechanisms

Autism: Neurobiology in the 21st century

- “New” Neurobiologic Findings
- Lead to New Account for ASD
- More Fundamental Mechanisms
- New Conceptual Formulations
- New Targeted Interventions

Autism is the result of alterations in how the brain processes information which alters how the mind sees, thinks and feels at conscious & nonconscious levels

Autism is the result of altered processing & integration of information in the brain, & as a consequence, in the mind.

Brain Processes Information

- Brain does not “care” what the information is
- Brain has specialization for different functions
- Emotions are the product of brain circuitry
- As are social interactions.
- What functions are affected depends on what brain connections have been altered & by what molecular pathophysiologic mechanism. This produces the disorder specific pattern

These alterations are the result of altered development of the connections (of cerebral cortical neurons) that form cortical networks or systems.

Disruption in brain development in ASD occurs during three phases of brain development:

- Neuronal organization- most cases
- Neuronal migration- severe seizures
- Neuronal proliferation- extreme premies

15-20 genes or chromosomes account for about 20% of ASD cases- about 1% of cases each.

These genes direct development of connectivity among cortical neurons.

Discovery of these genes led to definition of molecular events, which led to use of a biologic (drug) treatment to prevent the development of intellectual disability, seizures, & ASD in tuberous sclerosis.

Understanding the basis of alterations in thinking and feeling has led to new neurocognitive interventions designed to promote secondary growth of brain connections.

Understanding the basis of alterations in thinking and feeling and in the brain has also led to more accurate functional analysis of behavior and in turn to more effective clinical approaches.

Autism is a synapse-opathy?

At some point in the future, ASDs will be classified according to the disrupted developmental neurobiologic event and the gene(s) responsible, & symptoms will be defined in terms of connectomes, proteomes, RNA expression profiles.

State of science hypothesis, 2006

Technology Enables Advances

- Technology has a mathematical basis
- Gains based on math are exponential not linear
- Future advances in ASD will be exponential
(BBC, 2010)

Most Important Unanswered Question?

Q: What is the basis of heterogeneity?

A: Variability in genetic cause of the disorder & variability in familial inheritance

Progression of Science and Its Understanding of Altered Function

- Behavioral psychology approach: looking for explanations of brain dysfunction in behavior
- Neurology approach: looking for explanations of behavior in neurobiology of the brain
- Genetics approach: looking for cause of brain dysfunction in genes regulating its development

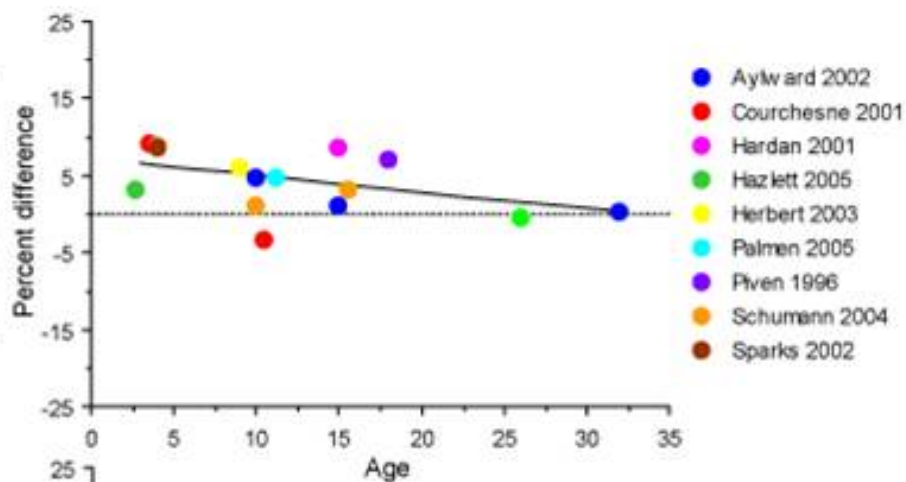
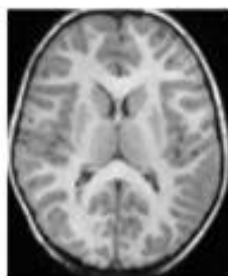
Autism: From the 20th to the 21st century

- New Findings Demanded New Account
- A New Way of Understanding Cause
- New Mechanisms

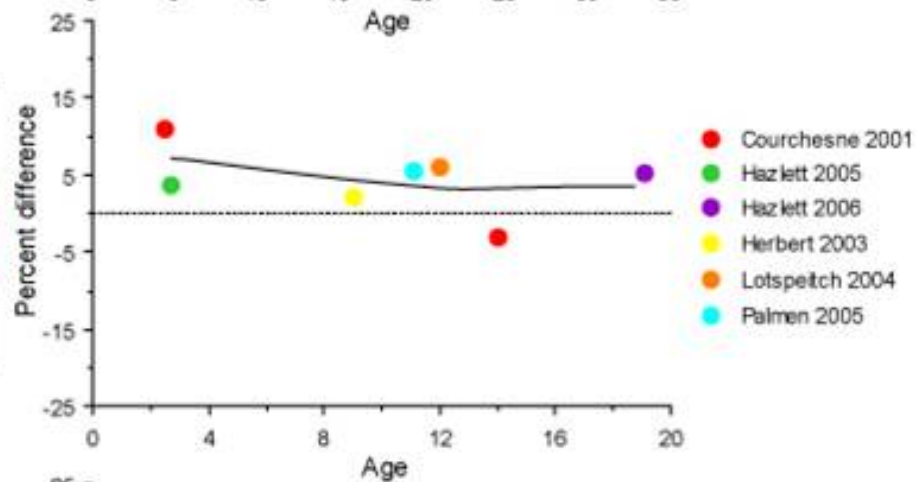
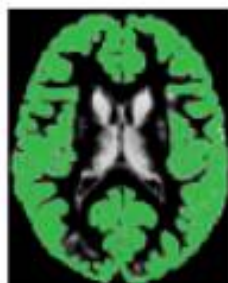
Evolving Interpretations of Brain Dysfunction in ASD: End of the 20th Century

- Social impairment: “pathognomonic” & inferred to be the cause of syndrome- social primacy
- Alternative: No primary or unifying core deficit(s); each sign inferred to be independent (dimensional approach) & independent genes
- Pitfall: expecting the brain to act according to human logic applied to behavior- rather than seeking out neurological mechanisms & principles that govern presentation & expression of neurodevelopmental disorders

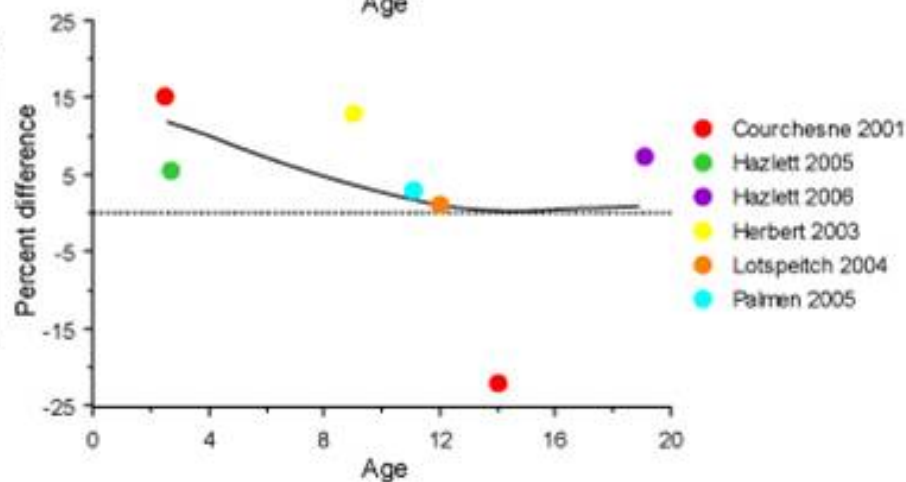
A Total Brain



B Gray Matter



C White Matter



Brain Growth Dysregulation

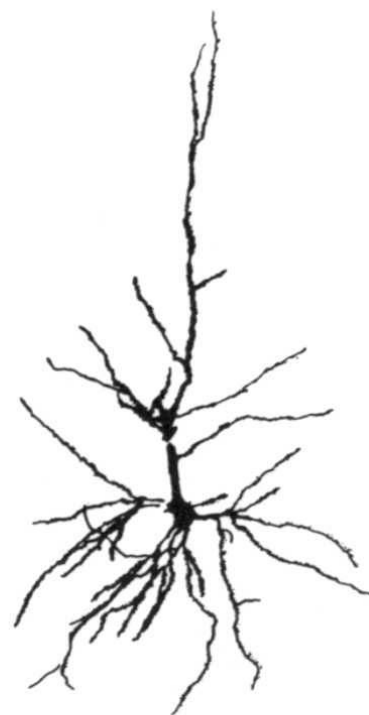
Properties of developmental neurobiologic processes:

- Repeated cycles of overgrowth and remodeling
- Results in a more compact brain with greater skills

Q: Other Signs of Disturbances in Developmental Neurobiologic Mechanisms

Histopathology of autism

CA₁



Control

Autism

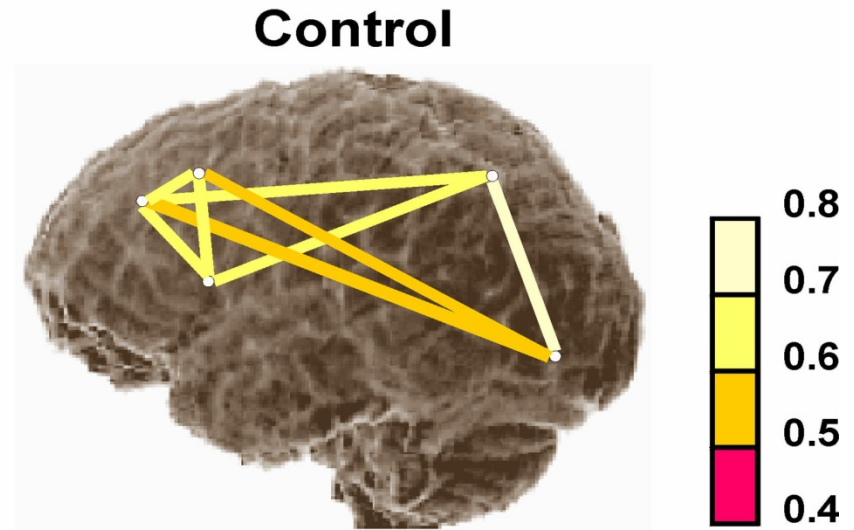
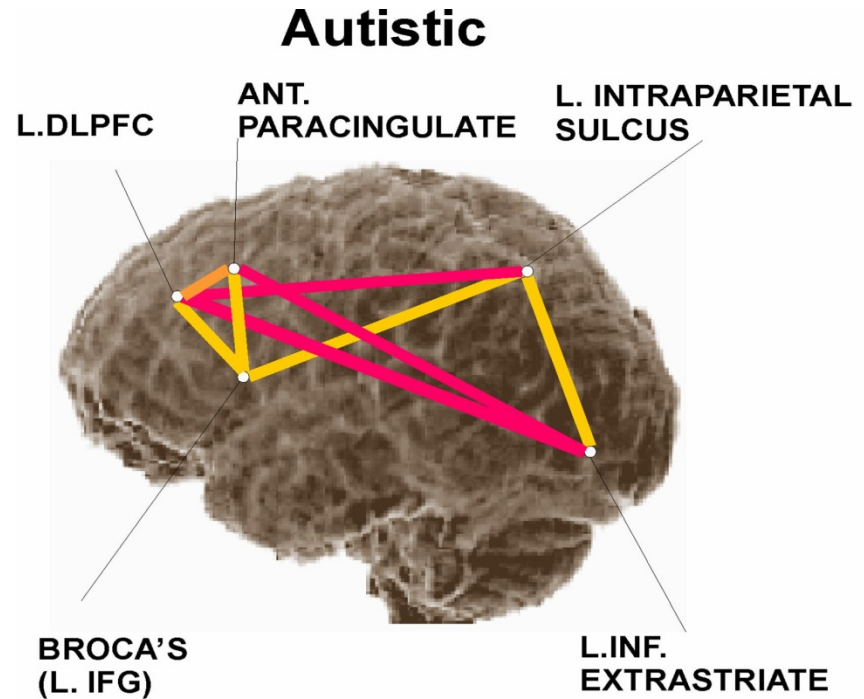
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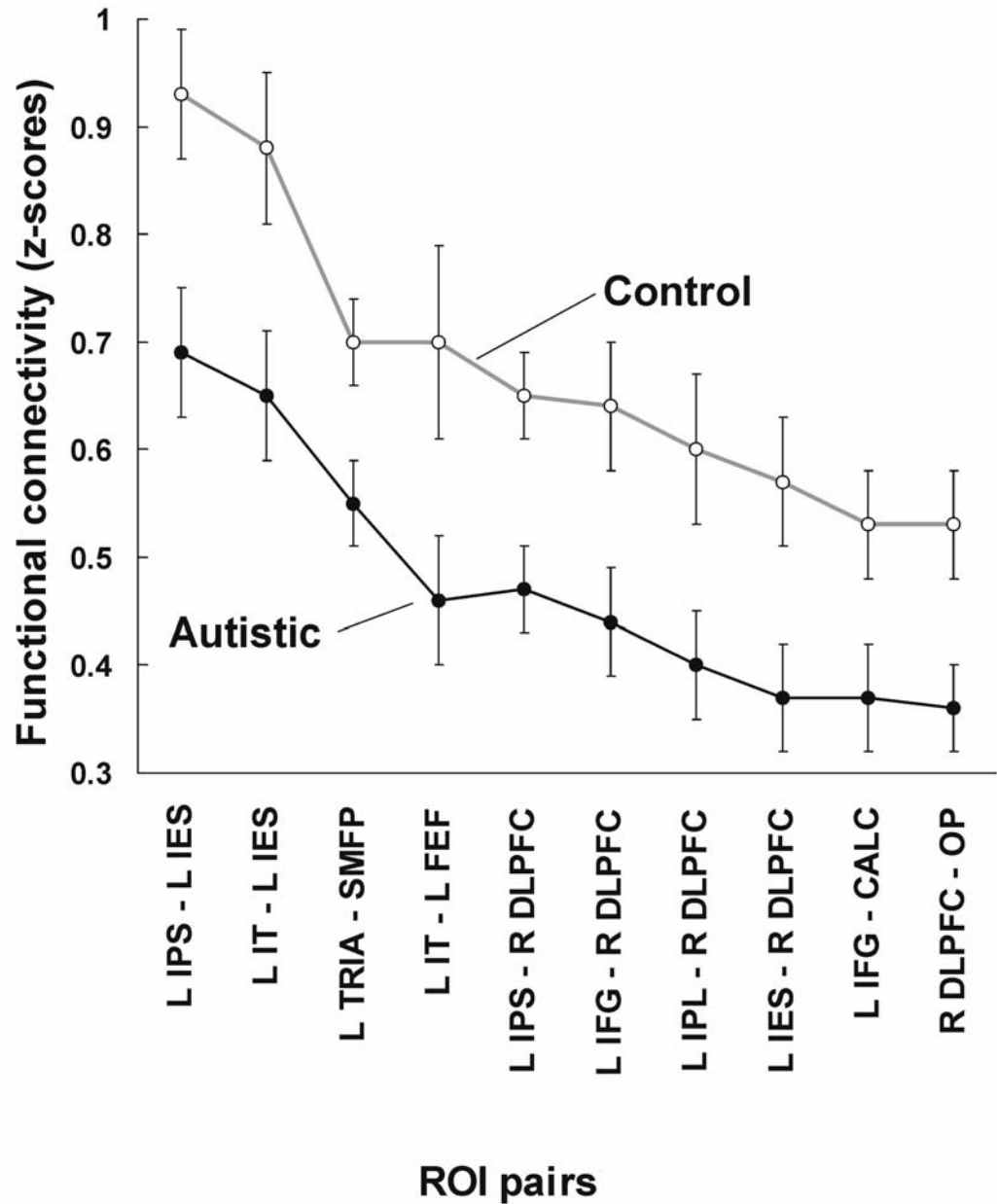
And there was underconnectivity of brain networks...

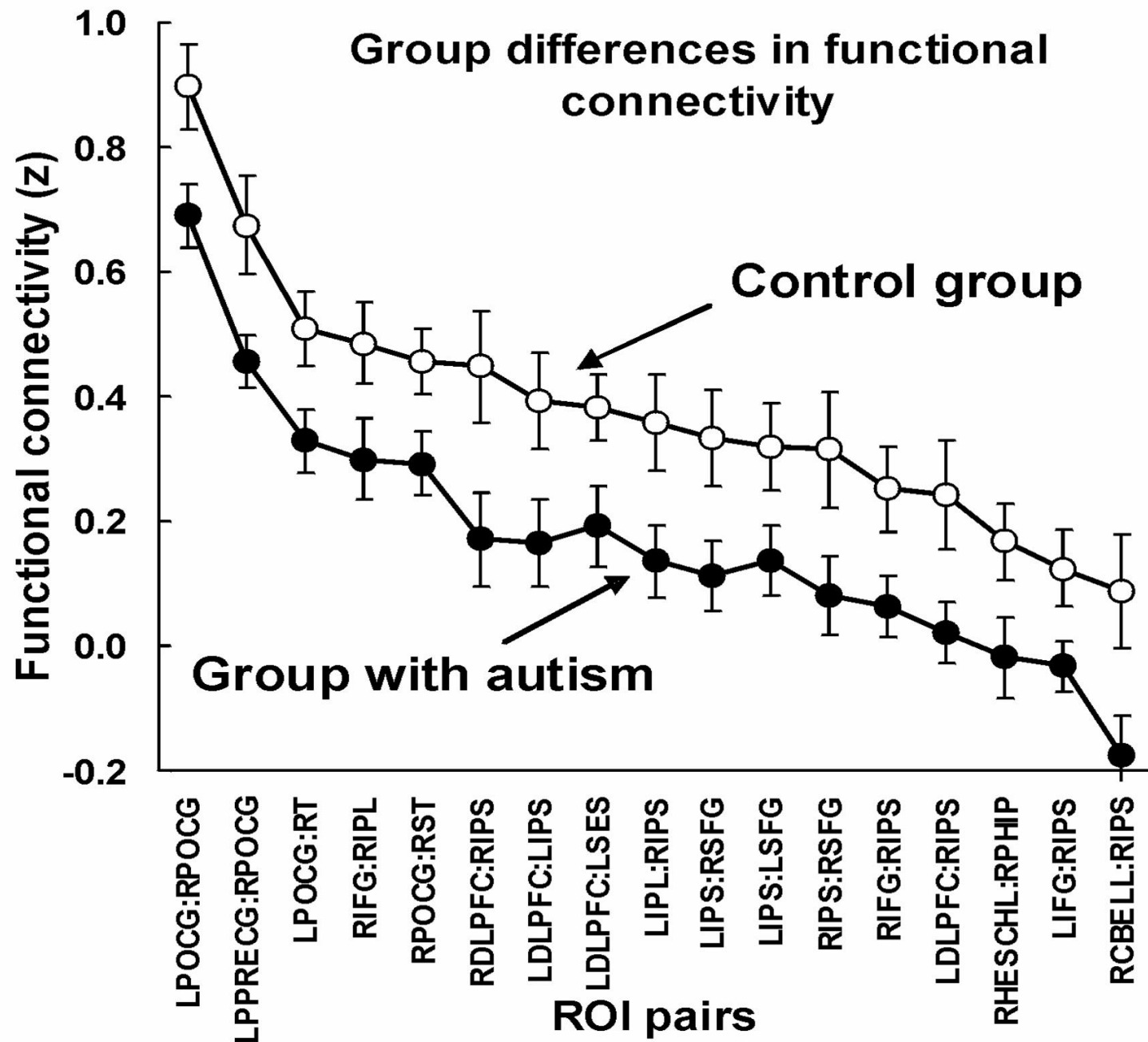
- Under connectivity among brain regions
- Corticocortical underconnectivity
- Underconnectivity with frontal cortex
- Anterior posterior asynchrony
- Enhanced local posterior connections- even language tasks processed by visual system rather than language system

Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)



Reliable differences
in functional
connectivity: autism
group has lower
functional
connectivity but
same rank order





And then there were genes associated with ASD- some part of chromosomal syndromes

- Syndromic autism
- And there were many genes without separable phenotype:
- Non-syndromic autism & then
- A new genetic mechanism (CNV)

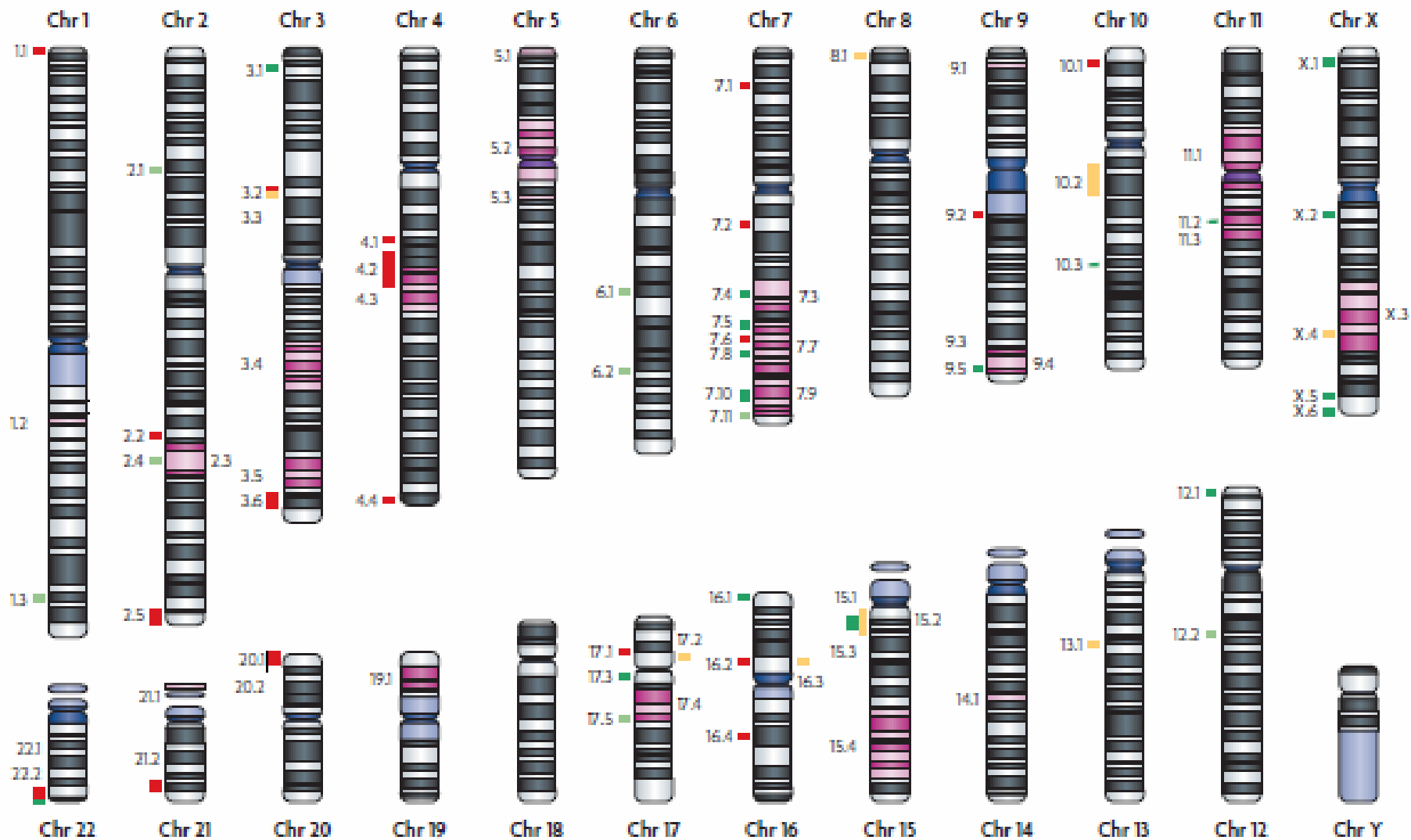
Table 1 | **ASD-related syndromes**

Syndrome	Gene(s) associated with the syndrome	Proportion of patients with the syndrome that have an ASD	Proportion of patients with an ASD that have the syndrome	Refs
15q duplication — Angelman syndrome	<i>UBE3A</i> (and others)	>40%	1–2%	101–103
16p11 deletion	Unknown	High	~1%	20, 35, 44
22q deletion	<i>SHANK3</i>	High	~1%	21, 22, 104
Cortical dysplasia-focal epilepsy syndrome	<i>CNTNAP2</i>	~70%	Rare	37
Fragile X syndrome	<i>FMR1</i>	25% of males; 6% of females	1–2%	105
Joubert syndrome	Several loci	25%	Rare	106
Potocki–Lupski syndrome	Chromosome position 17p11	~90%	Unknown	107
Smith–Lemli–Optiz syndrome	<i>DHCR7</i>	50%	Rare	108
Rett syndrome	<i>MECP2</i>	All individuals have Rett syndrome	~0.5%	109
Timothy syndrome	<i>CACNA1C</i>	60–80%	Unknown	24
Tuberous sclerosis	<i>TSC1</i> and <i>TSC2</i>	20%	~1%	110

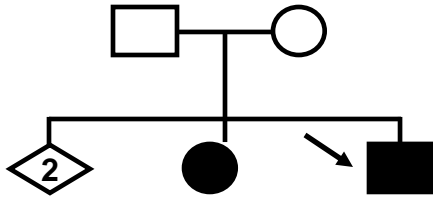
The rates quoted in the table depend on the population that is being evaluated. For example, rates are higher in individuals from simplex families compared with multiplex families, and are higher in dysmorphic and mental retardation populations compared with idiopathic populations. 'High' is used for syndromes in which no good estimates exist (that is, only a handful of individuals with the syndrome in question have been identified). It should also be noted that none of the studies cited here indicates that assessment for the autism spectrum disorder (ASD) was performed blind to a patient's primary diagnosis. An expanded version of the table with additional variables can be found in [Supplementary information S1](#) (table). *CACNA1C*, calcium channel voltage-dependent L type alpha 1C subunit; *CNTNAP2*, contactin associated protein-like 2; *DHCR7*, 7-dehydrocholesterol reductase; *FMR1*, fragile X mental retardation 1; *MECP2*, methyl CpG binding protein 2; *SHANK3*, SH3 and multiple ankyrin repeat domains 3; *TSC1*, tuberous sclerosis 1; *TSC2*, tuberous sclerosis 2; *UBE3A*, ubiquitin protein ligase E3A.

Table 2 | Evidence scores for ASD gene candidates

Gene	Syndrome or mutation(s)	Replicated association	Analysis of variant	Mouse model	Other evidence	Total score
<i>Promising</i>						
AVPR1A	0	0	0	1	0	1
DISC1	0	0	0	1	0	1
ITGB3	0	1	0	0	0	1
AHI1	2	0	0	0	0	2
EN2	0	1	0	1	0	2
GRIK2	0	1	0	0	1; homozygous mutation results in non-syndromic mental retardation	2
NRXN1	2	0	0	0	0	2
SLC25A12	0	1	0	0	1; associated with neurite outgrowth, expression is upregulated in ASD brain	2
<i>Probable</i>						
CACNA1C	2	0	1	0	0	3
CNTNAP2	2	1	0	0	0	3
MET	0	1	1	0	1; expression reduced in brains of cases versus controls	3
OXTR	0	1	0	1	1; expression reduced in blood of cases versus controls	3
SHANK3	2	0	0	0	1; modulates glutamate-dependent reconfiguration of dendritic spines	3
SLC6A4	0	1	1	0	1; clinical benefit from inhibitors, variation linked to gray-matter volume	3
CADPS2	2	0	1	1	0	4
DHCR7	2	0	1	0	1; hypocholesterolaemia in a proportion of probands	4
FMR1	2	0	1	1	0	4
NLGN3	2	0	1	1	0	4
NLGN4X	2	0	1	1	0	4
PTEN	2	0	0	1	1; mutations result in abnormal structure and function of the synapse	4
TSC2	2	0	1	0	1; regulates dendrite morphology and function of glutamatergic synapses	4
GABRB3	2	1	0	1	1; expression is dysregulated in pervasive developmental disorders	5
MECP2	2	0	1	1	1; MECP2 deficiency causes reduced expression of UBE3A and GABRB3	5
TSC1	2	0	1	1	1; regulates dendrite morphology and function of glutamatergic synapses	5
UBE3A	2	0	1	1	1; expression is dysregulated in pervasive developmental disorders	5
RELN	2	1	1	1	1; levels reduced in brains of cases versus controls	6

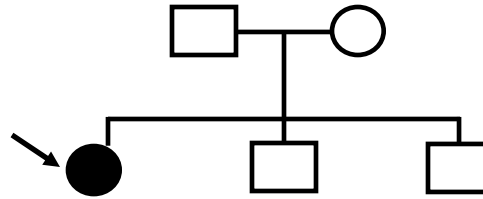


A. Multiple de novo events
SK0152



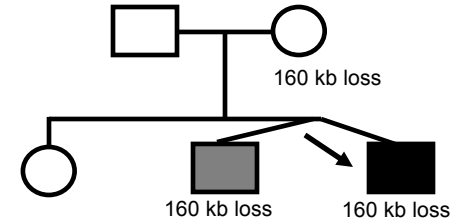
T(5:7>[p15p 13]
1.2 Mb loss 3p25.1
3.4 Mb loss 5p 15
423 kb loss 12p 12

B. SHANK3 deletion & de novo gain
MM0109

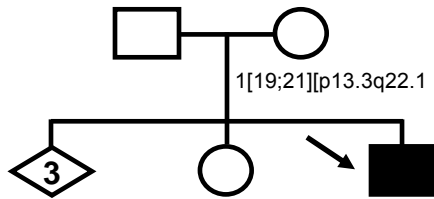


277 kb loss at SHANK3
1.4 Mb gain at 20q 13.33

C. Inherited loss at Xp22.11 (PTCHD1)
SK0186

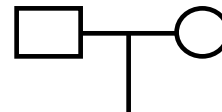


D. Inherited and de novo event
SK0215



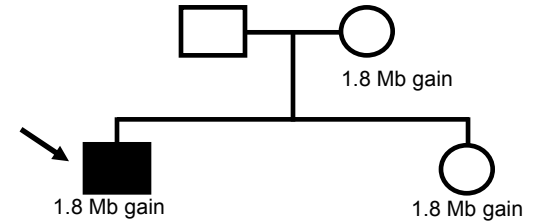
160 kb loss
1[19;21][p13.3q22.1]
1.1 Mb loss 1p21.3

E. De novo loss at 7q36.2 (DPP6)
NA0002



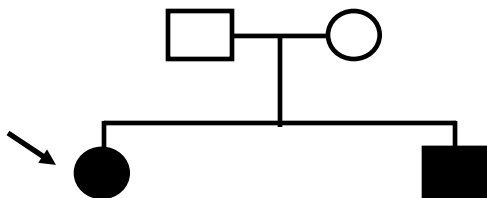
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F. Inherited gain at 7q36.2 (DPP6)
SK0190



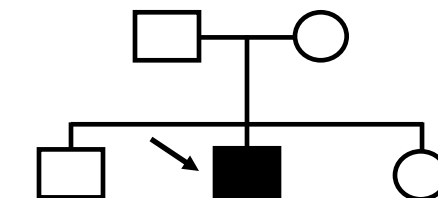
1.8 Mb gain
1.8 Mb gain

G. De novo loss at 16p11.2
MM0088



676 kb loss

H. De novo gain at 16p11.2
SK0102

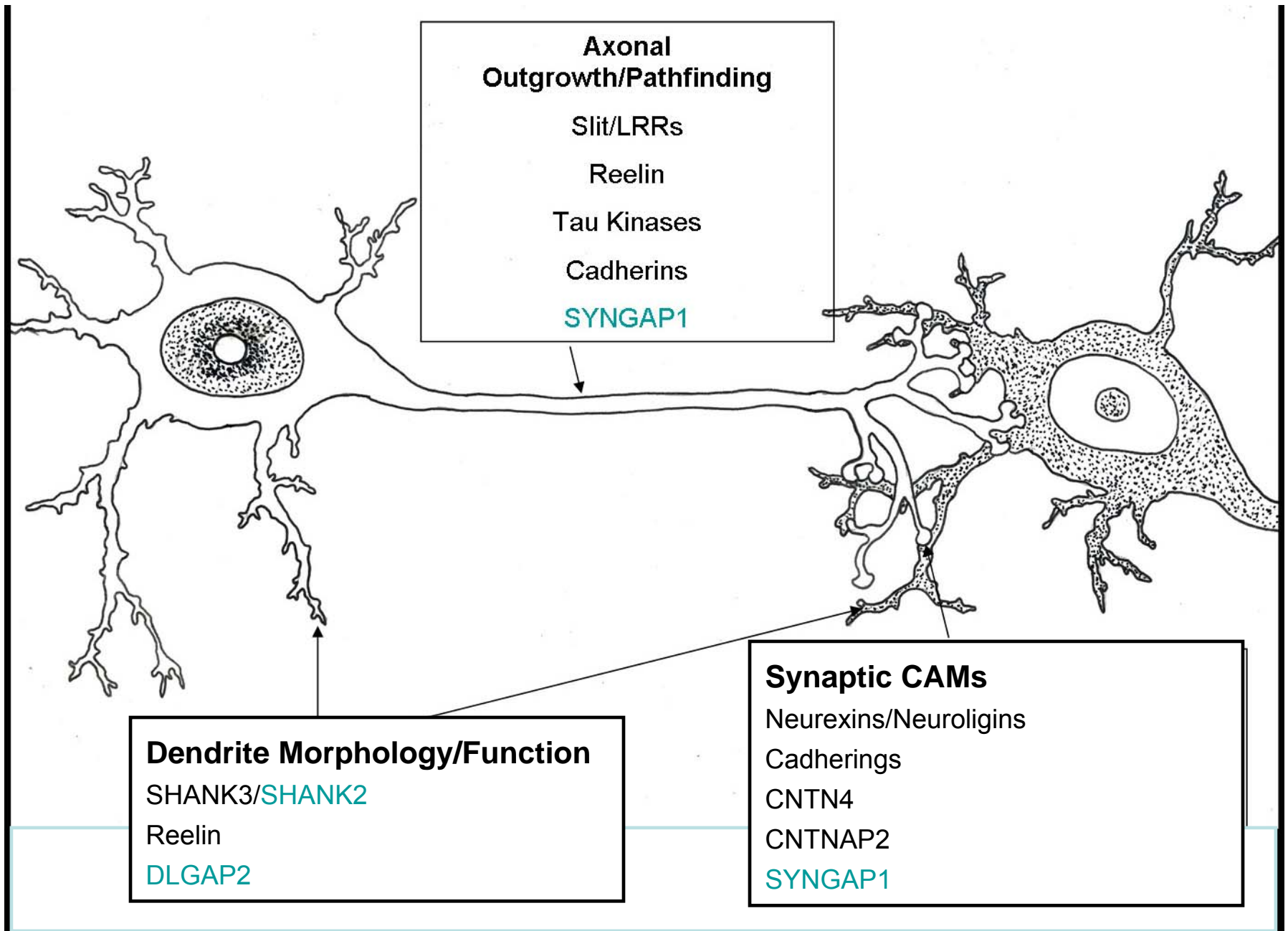


500 kb gain

Genes involved in autism code for development of connections between neurons

- Axonal outgrowth & pathfinding
- Synapse formation & maintenance
- Dendritic connections

Circle From Gene to Brain to “Cognition” to Behavior Completed



Understanding What You Can't See

Brain development is exceedingly complex and dynamic. Mechanisms begin with DNA program, its selective decoding, with molecular events driving its construction and function. It is what you can't see that is leading to dysfunction and disorder in many many cases.

Define A Pathophysiologic Sequence For ASD

Abnormalities in Genetic Code for Brain Development



Abnormal Mechanisms of Brain Development



Structural and Functional Abnormalities of Brain



Cognitive & Neurological Abnormalities



Behavioral Syndrome

What Are Infant Siblings Teaching Us About Autism in Infants?

Rogers, 2009

- Began with: home video movies showed symptoms of autism long before diagnosis
- Key Q: What are the first behavioral characteristics that predict the development of autism?
- Method: study of infants with an older sibling diagnosed with autism
- This strategy is proving invaluable in bringing new insights to autism

Developmental Characteristics of Infant Sibs: Onset > 6 mos; Motor & Balance First

- No developmental differences at 6 mos
- Developmental differences at 12 mos on standardized tests- a developmental deceleration
- Gap widens between 12 & 24 months and beyond
- Differences in fine and gross motor- early
- Less mouthing of objects-less vocalizations
- Truncal instability when sitting- early

Developmental Characteristics of Infant Sibs: Sensory-Repetitive-Visual Regard

- Unusual visual regard & Repetitive waving of arms and hands at 12 and 18 mos
- Sensory-related behaviors: under and over responsiveness at 12 months but not 6 mos
- Social emotional: no temperamental differences at 6 mos, over time temperamentally more difficult with more intense distress and more time fixating on objects; accompany- don't predate- sx
- At 24 months, emotional and behavioral self-dysregulation distinguished infant sibs dx ASD

Developmental Characteristics of Infant Sibs: Social Realm

- No social signs at 6 months don't predate other sx
- Delays in verbal and nonverbal language at 12 months but not earlier
- Best predictor of response to name at 14 mos- child's self initiated and spontaneous gaze shifts from toy to parent- joint attention- this is a social impairment (acts as if deaf)

Developmental Characteristics of Infant Sibs: Overview Thus Far: Surprises

- Lack of behavioral markers at 6 months; earliest differences are subtle, involve a few behaviors or small differences
- Socially normal at 6 months
- Onset: not early or regressive but rather slower or faster mounting of symptoms- a deceleration of development: core symptoms present at 12 mos and grow more severe over time
- “Associated symptoms” are integral-irritability, sensory responsivity, activity level, poor gross motor development

Developmental Characteristics of Infant Sibs: Conclusions

- “These findings do not support the view that autism is primarily a social-communicative disorder and instead suggest that autism disrupts multiple aspects of development rather simultaneously.”
- “Children’s developmental rates are decelerating markedly in a 12 month period, with IQs dropping from average to below 50 for some children.”

Sally Rogers, 2009

What is happening in the BRAIN in infant sibs?

- Onset of acceleration of brain growth at 9-12 months- coincident with onset of symptoms.
- Brain growth in ASD is inverse of Retts syndrome.

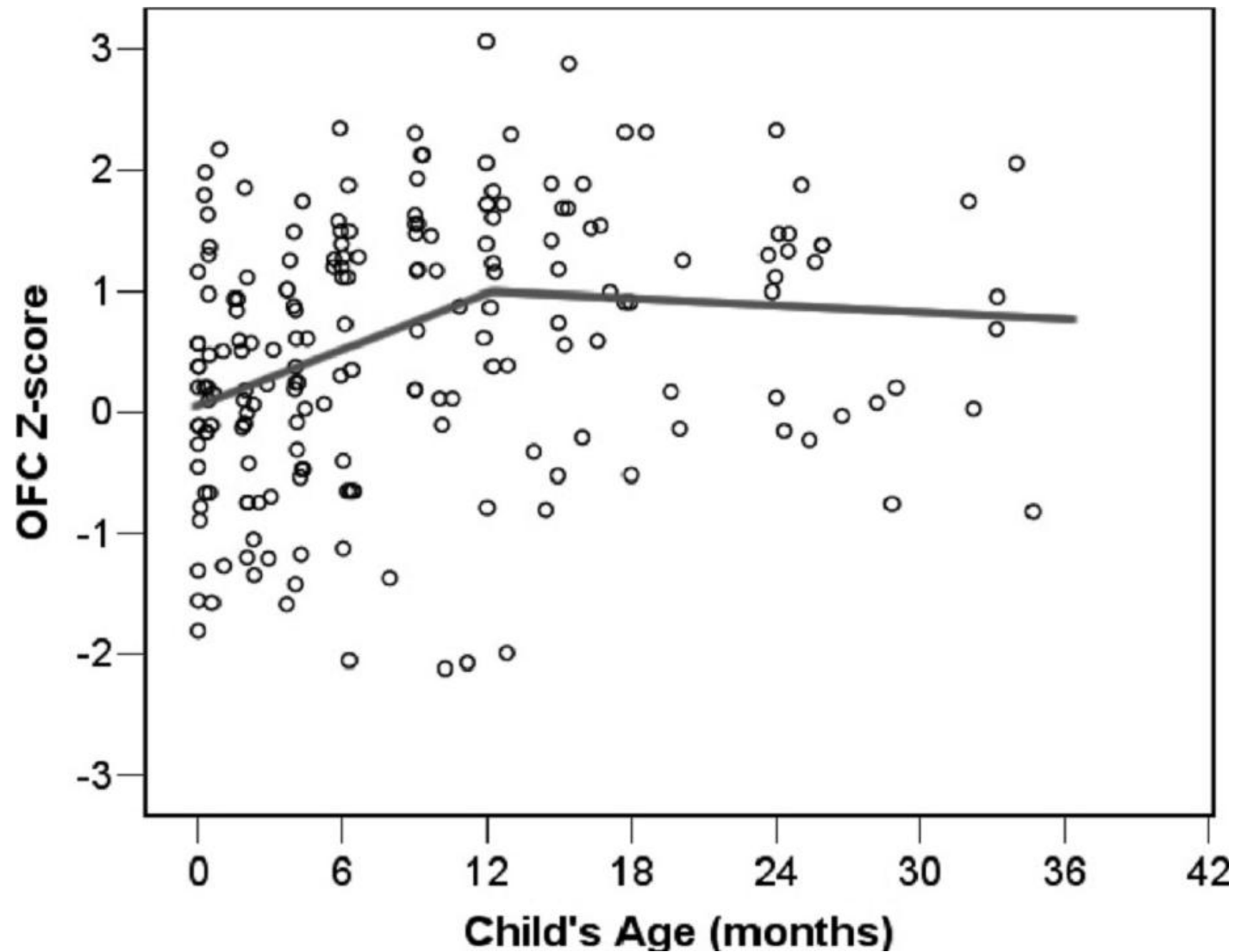


Figure: Occipital–frontal (OFC) Z score measurements ($N = 195$) with mean estimated growth trajectory for 28 children with autism spectrum disorder (hierarchical linear model two-piece linear model centered at 12 months).

Brain Affected Broadly in ASD

From the beginning
Many domains, not one

Brain Affected Broadly But Selectively in ASD

From the beginning
Clinical expression is broad but specific.

Signs appear in child development as brain development reaches the point at which the affected structure (s) develops. See cerebral palsy- signs not obvious until voluntary movement should be developing

Brain Affected Broadly But Selectively in ASD

The selectivity reflects the genes and developmental neurobiologic mechanisms that are responsible—those that relate to cortical systems development. This is the common underlying connection among the symptoms. They don't occur independently and by chance produce ASD by co-occurring. They co-occur because genes code for specific aspects of brain development in specific areas.

Behaviorally Defined Syndrome With No Known Connection Between “Core”, “Associated” “Comorbid”

FROM: 3 Core Symptoms +

- Associated Symptoms: sensory, motor
- Co-morbid Conditions: intellectual disability, ADHD, seizures, regulation disorders

TO: integrated relationship of all manifestations- whatever mechanism causes one causes all; neurologic or developmental neurobiologic disorders w/ organizing principles at original events

Neurologic Principles of Disease

- Brain disturbances produce a constellation of neurologic signs & symptoms: symptoms/signs equally important
- The constellation & mode of presentation reflect the underlying brain mechanism and its location
- Impairments present when the time in development comes for that skill to appear

Developmental Neurobiologic Processes

- Organogenesis
- Neuronal proliferation*
- Glial proliferation, migration
- Neuronal migration**
- Neuronal organization***
- Myelination

TABLE 2-24 Organization

Peak Time Period

5 months' gestation–years postnatal

Major Events

Subplate neurons: establishment and differentiation

Lamination: alignment, orientation, and layering of cortical plate neurons

Neurite outgrowth: dendritic and axonal ramifications

Synaptogenesis

Cell death and selective elimination of neuronal processes and of synapses

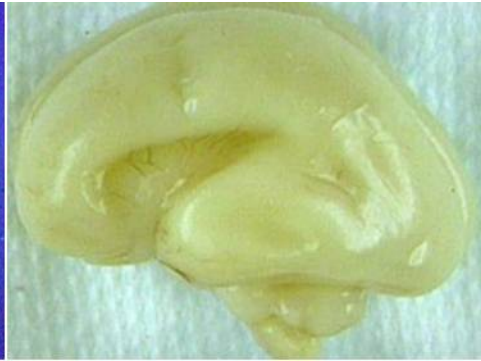
Glial proliferation and differentiation

How the Brain Develops

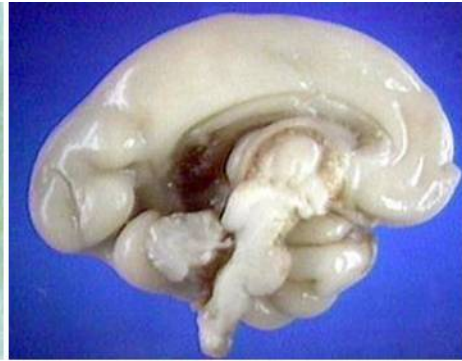
15-1/2 wks



22 wks



23 wks



~25 wks



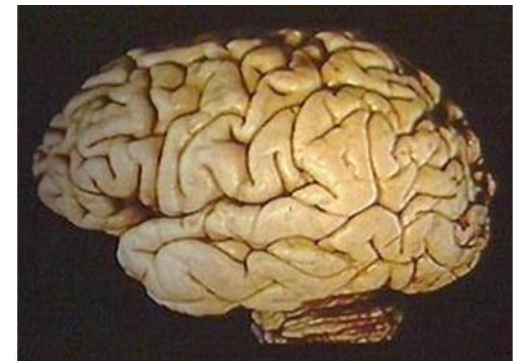
27 weeks

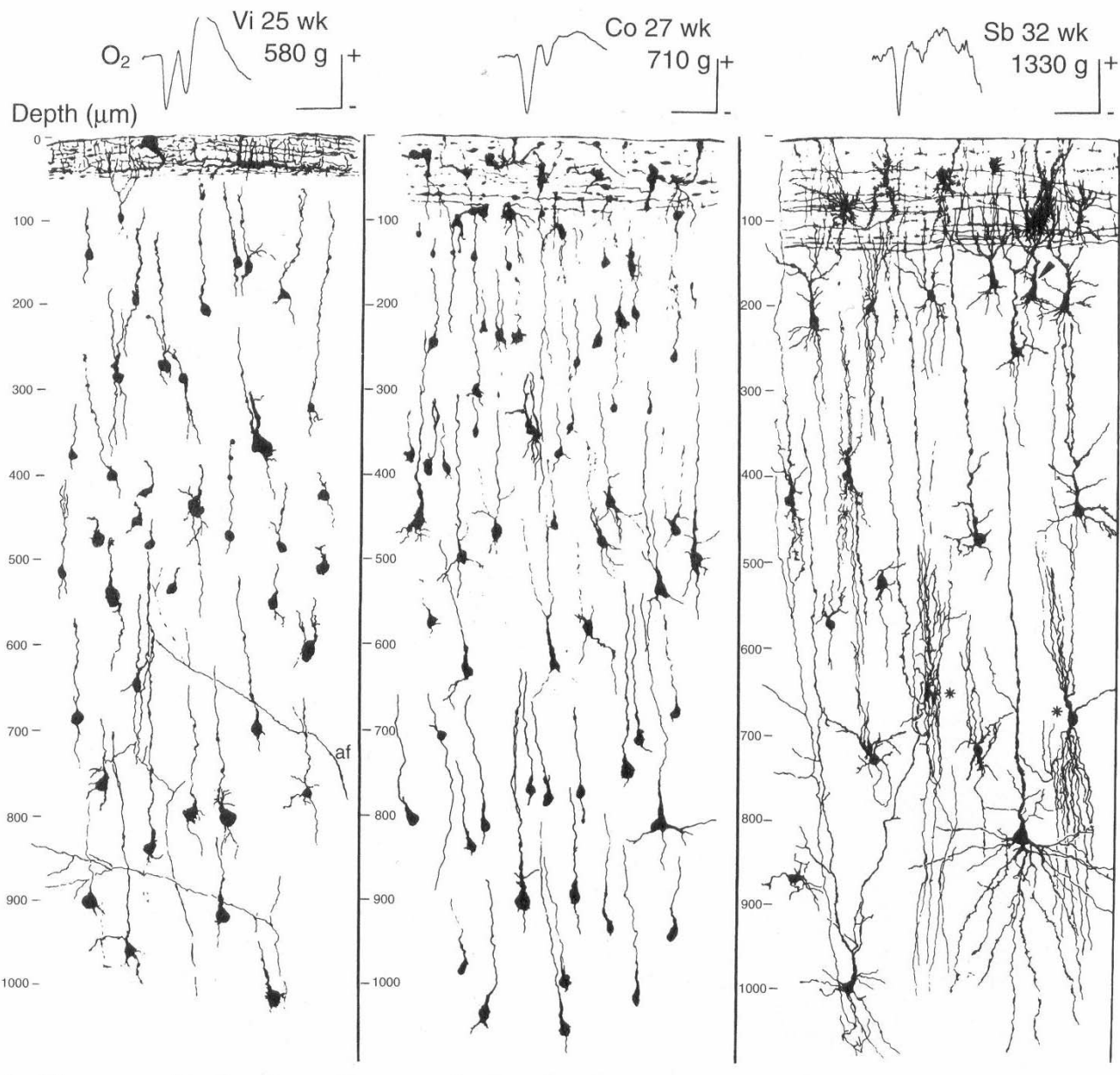


Full term brain



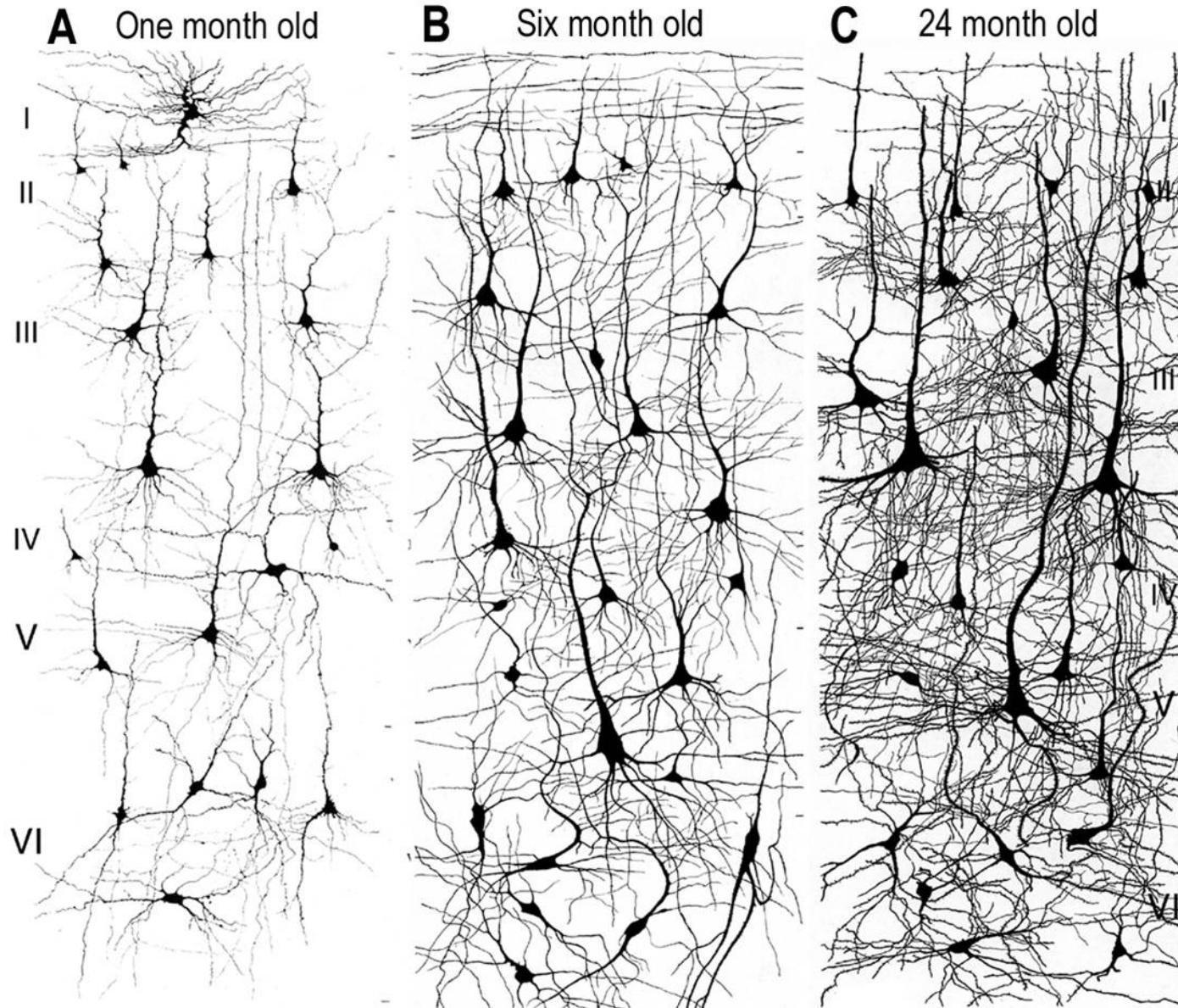
Adult

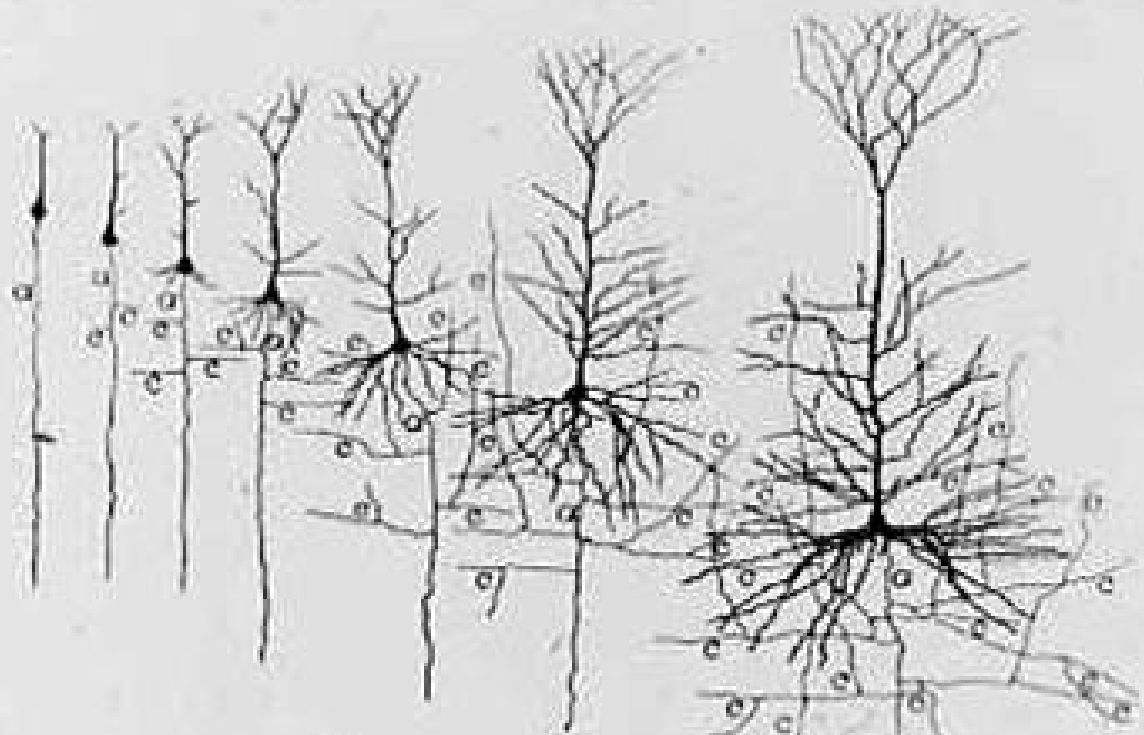




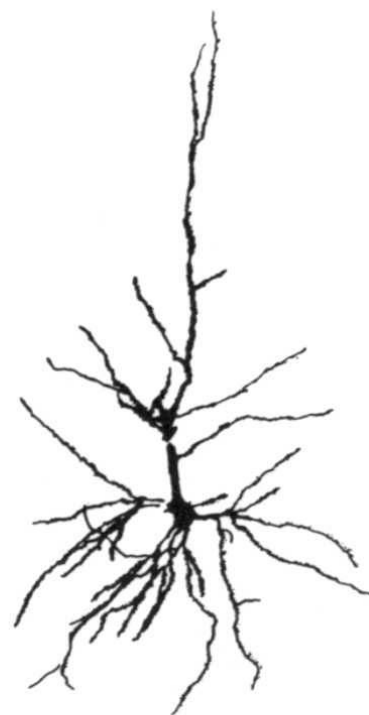
Camera Lucida composite drawings of neurons in the visual (calcarine) cortex of human infants indicated gestational ages. Note the appearance and elaboration of basilar dendrites and the tangential spread of apical dendrites, as well as the accompanying maturation of the visual evoked response (top). (Courtesy of Dr. Dominick Purpura).

How the Brain Develops





CA₁

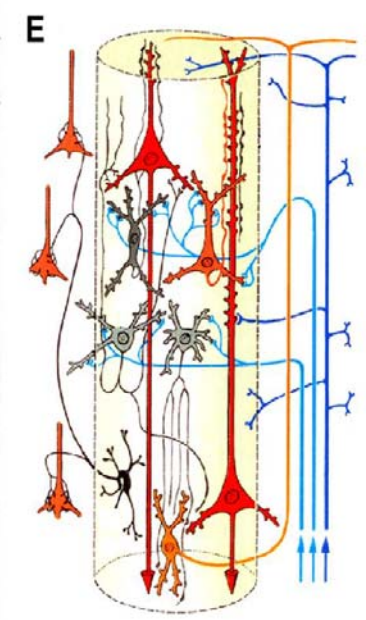
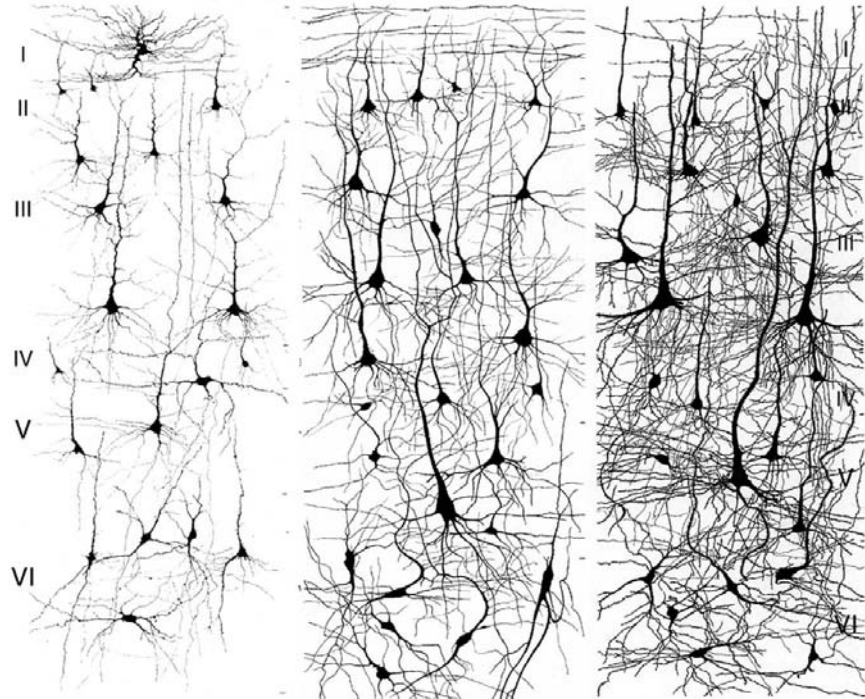
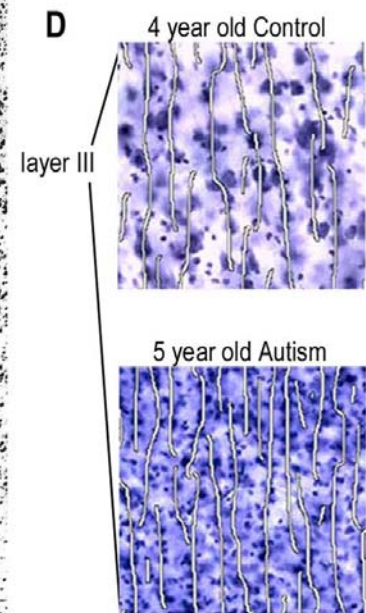
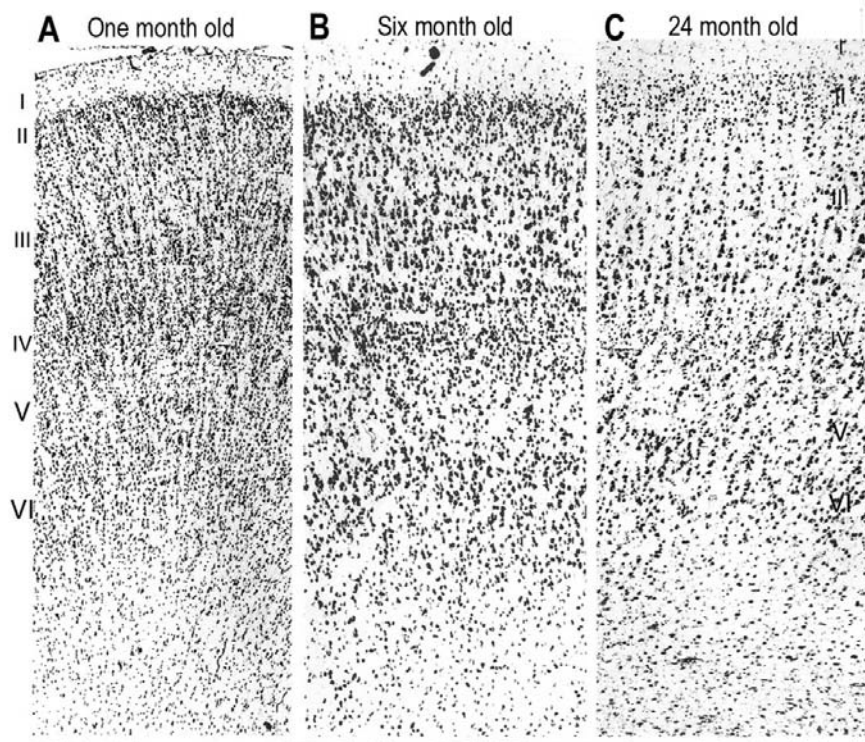


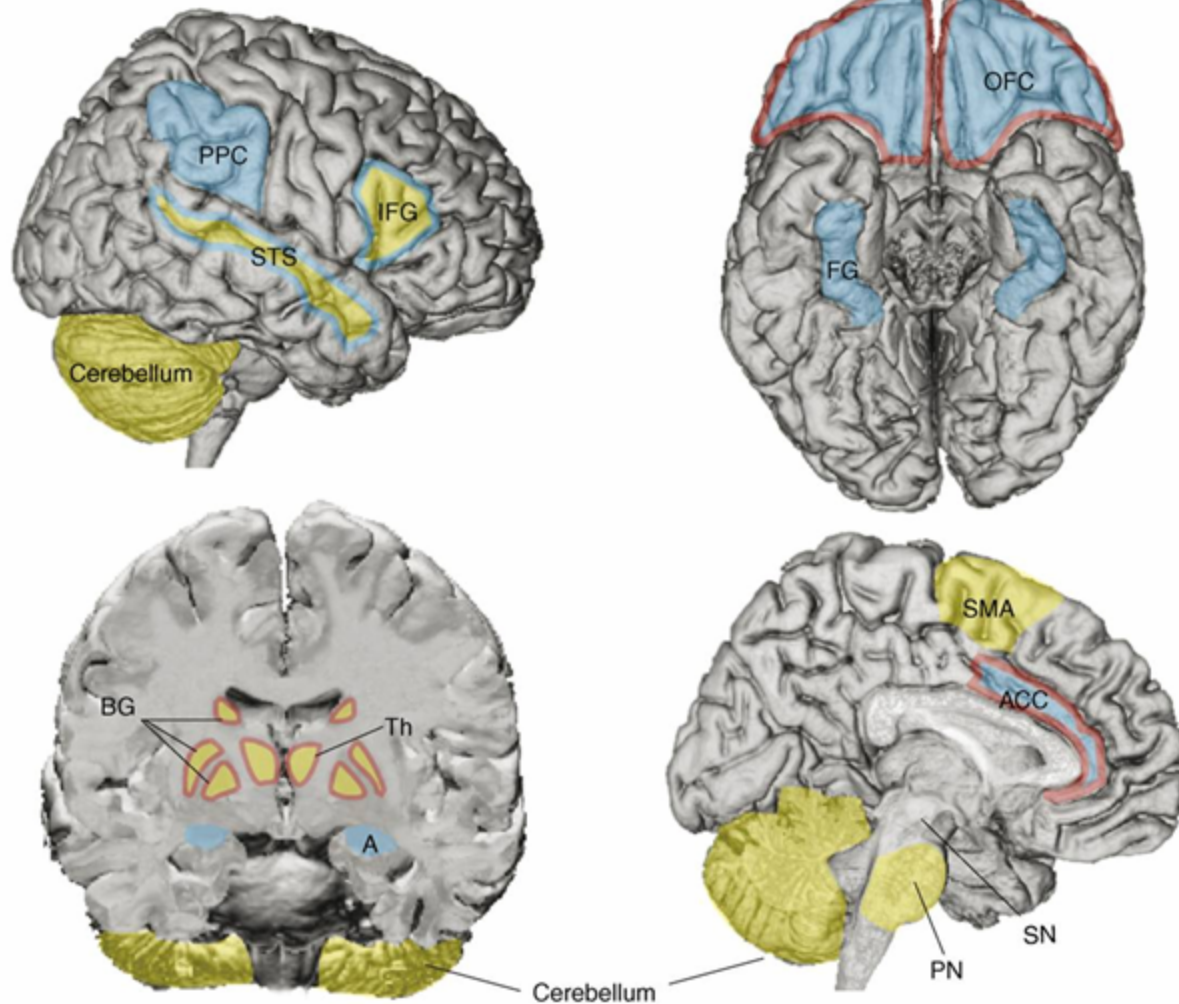
Control

Autism

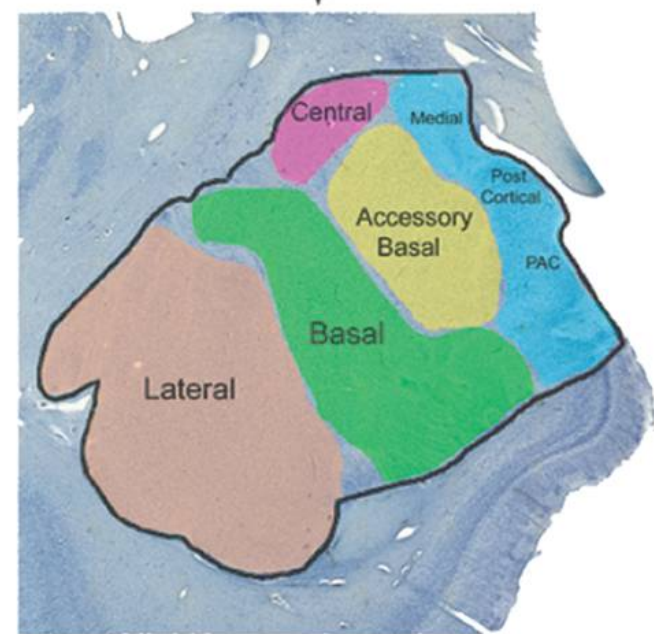
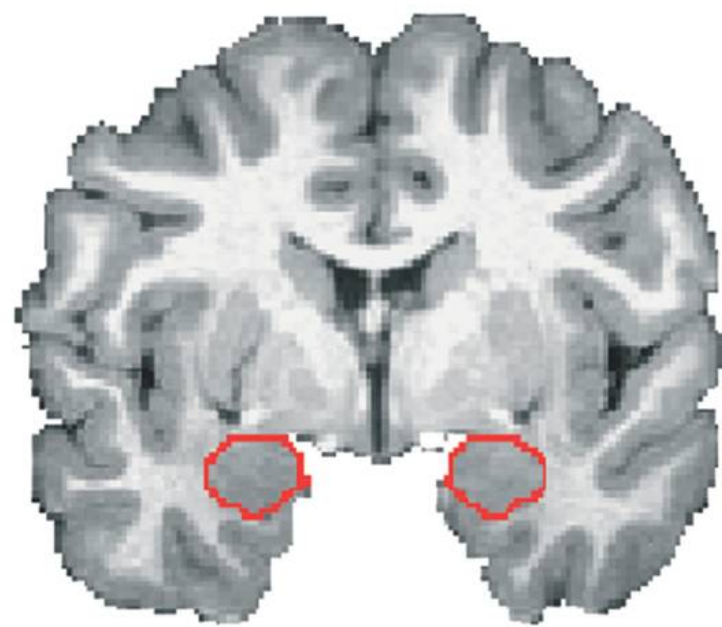
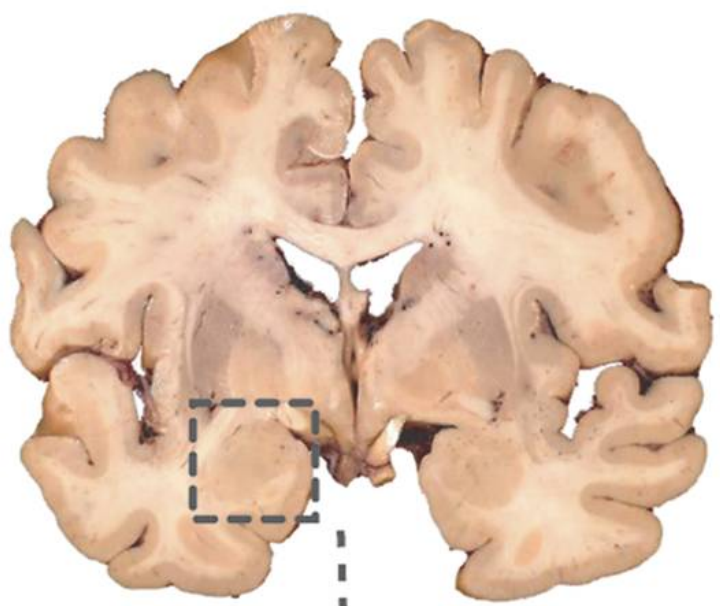
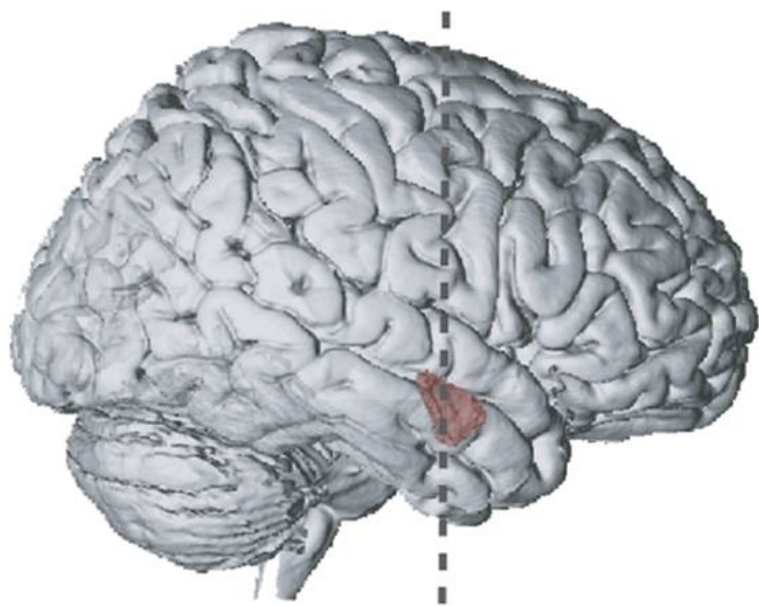
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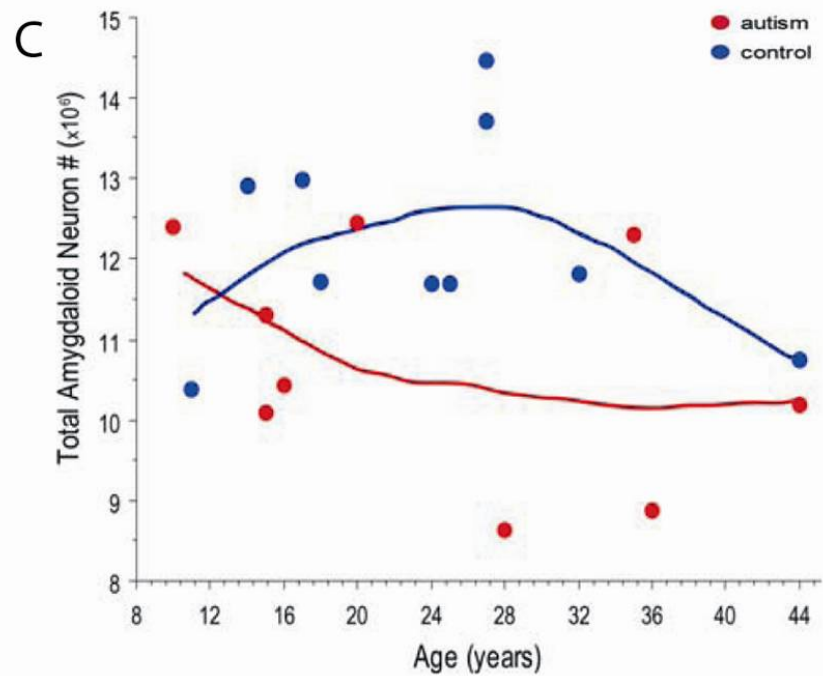
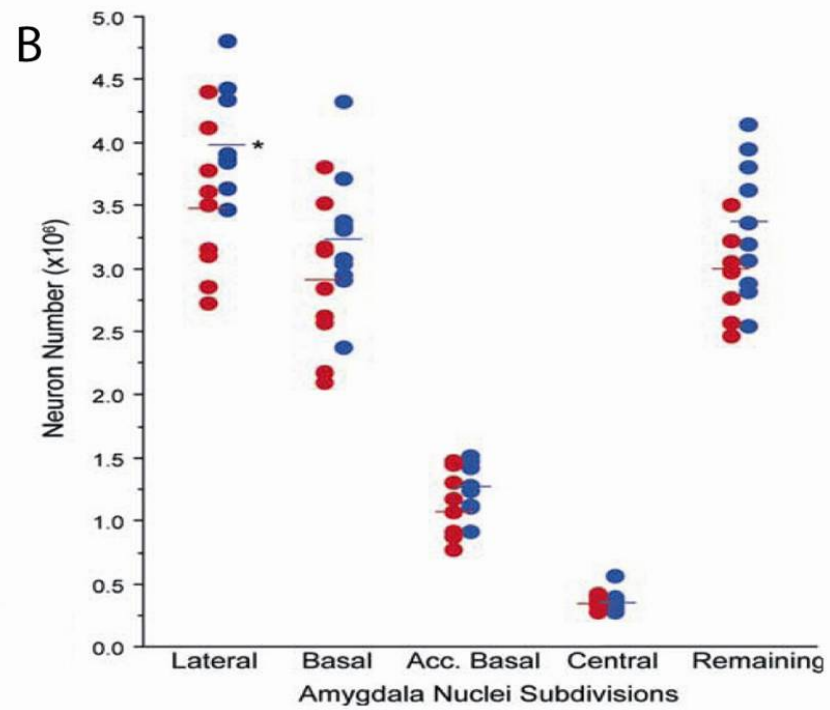
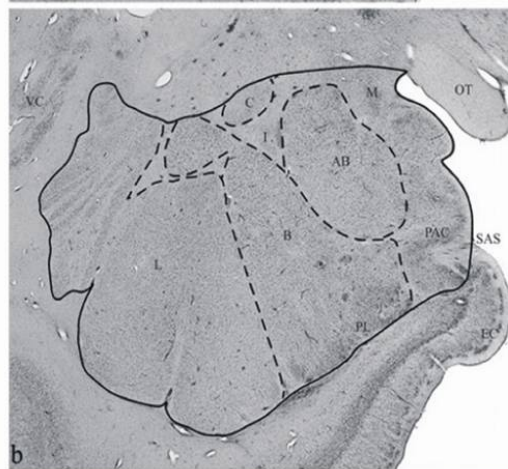
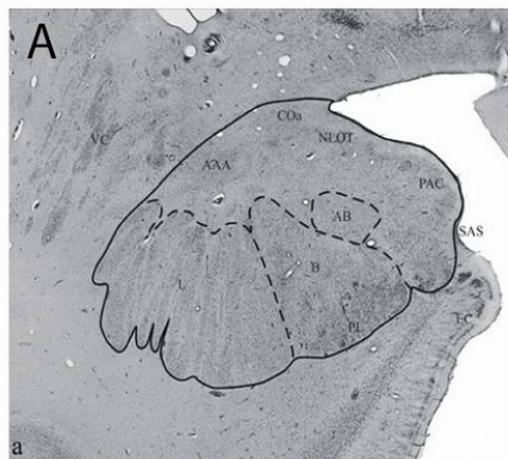






Social impairment	Communication deficits	Repetitive behaviors
OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex FG – Fusiform gyrus STS – Superior temporal sulcus A – Amygdala IFG – Inferior frontal gyrus PPC – Posterior parietal cortex	IFG- Inferior frontal gyrus (Broca's area) STS – Superior temporal sulcus SMA – Supplementary motor area BG – Basal ganglia SN – Substantia nigra Th – Thalamus PN – Pontine nuclei	OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex BG – Basal ganglia Th – Thalamus





Altered Connections Alter Thinking, Feeling & Personal Experience

Autism is the result of alterations in how the brain processes information, which alters how the mind sees the world.

The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

Intact or Enhanced

- Attention
- Sensory Perception
- Elementary Motor
- Simple Memory
- Formal Language
- Rule-learning
- Visuospatial processing

Cognitive Weaknesses

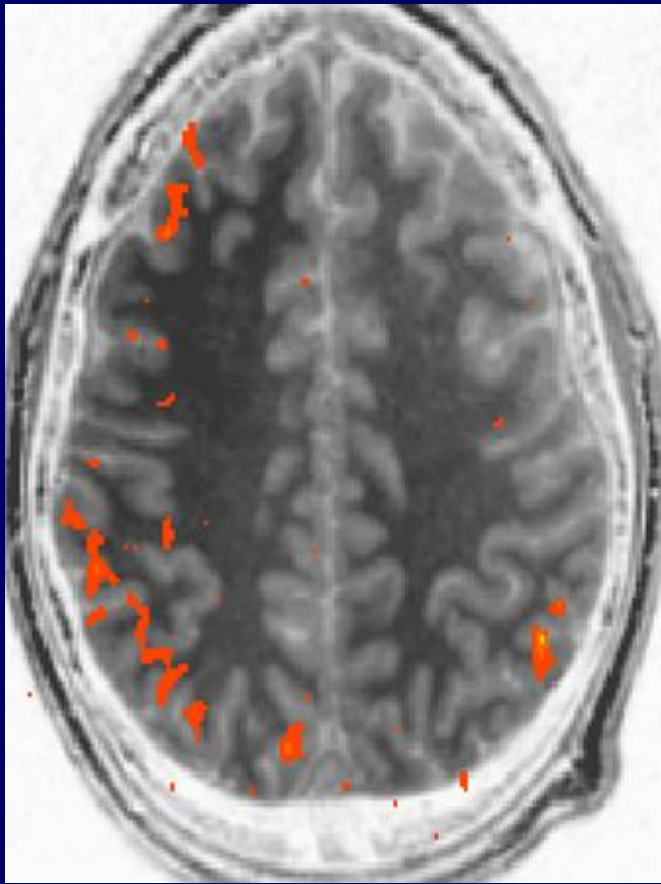
- Complex Sensory
- Complex Motor
- Complex Memory
- Complex Language
- Concept-formation
- Face Recognition

What Does The Profile Mean?

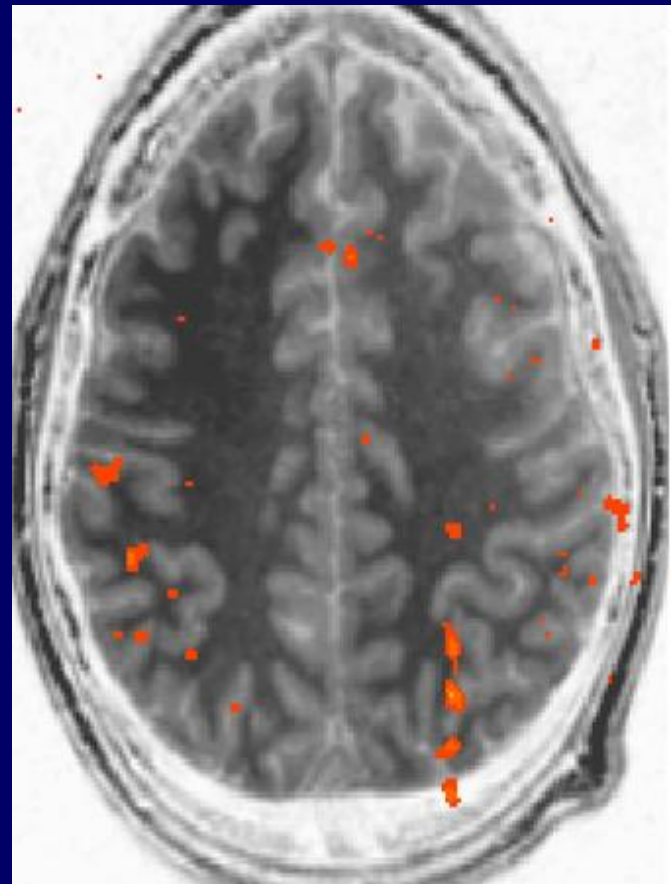
- Elementary abilities intact or enhanced
- Information processing capacity limited- integrative processing disproportionately impaired
- Inference: higher order brain circuitry is under developed- over-reliance or over-development of lower order visual circuitry to function.

fMRI Activation During a Spatial Working Memory Task

(Courtesy John Sweeney)



Healthy Group



Autism Group

Current Work

RESULTS

- Complexity a common denominator of deficits
- Now revealed to be related to deficit in integrative circuitry

A Disorder of Brain Connectivity: Explaining the Cognitive & Neurologic Profile

- Underconnectivity of cortical networks
- Excessive local connections
- Anterior-posterior connectivity gradient

Neuroimaging of the functional and structural networks underlying visuospatial vs. linguistic reasoning in high-functioning autism

Sahyoun CP, Belliveau JW, Soulières I, Schwartz S, Mody M.

High-functioning individuals with autism have been found to favor visuospatial processing in the face of typically poor language abilities. We aimed to examine the neurobiological basis of this difference using functional magnetic resonance imaging and diffusion tensor imaging. We compared 12 children with high functioning autism (HFA) to 12 age- and IQ-matched typically developing controls (CTRL) on a pictorial reasoning paradigm under three conditions: V, requiring visuospatial processing; S, requiring language (i.e., semantic) processing; and V+S, a hybrid condition in which language use could facilitate visuospatial transformations. Activated areas in the brain were chosen as endpoints for probabilistic diffusion tractography to examine tract integrity (FA) within the structural network underlying the activation patterns. The two groups showed similar networks, with linguistic processing activating inferior frontal, superior and middle temporal, ventral visual, and temporo-parietal areas, whereas visuospatial processing activated occipital and inferior parietal cortices. However, HFA appeared to activate occipito-parietal and ventral temporal areas, whereas CTRL relied more on frontal and temporal language regions. The increased reliance on visuospatial abilities in HFA was supported by intact connections between the inferior parietal and the ventral temporal ROIs. In contrast, the inferior frontal region showed reduced connectivity to ventral temporal and middle temporal areas in this group, reflecting impaired activation of frontal language areas in autism. The HFA group's engagement of posterior brain regions along with its weak connections to frontal language areas suggest support for a reliance on visual mediation in autism, even in tasks of higher cognition.

Altering cortical connectivity: remediation-induced changes in the white matter of poor readers

Keller TA, Just MA

Neuroimaging studies using diffusion tensor imaging (DTI) have revealed regions of cerebral white matter with decreased microstructural organization (lower fractional anisotropy or FA) among poor readers. We examined whether 100 hr of intensive remedial instruction affected the white matter of 8- to 10-year-old poor readers. Prior to instruction, poor readers had significantly lower FA than good readers in a region of the left anterior centrum semiovale. The instruction resulted in a change in white matter (significantly increased FA), and in the very same region. The FA increase was correlated with a decrease in radial diffusivity (but not with a change in axial diffusivity), suggesting that myelination had increased. Furthermore, the FA increase was correlated with improvement in phonological decoding ability, clarifying the cognitive locus of the effect. The results demonstrate the capability of a behavioral intervention to bring about a positive change in cortico-cortical white matter tracts.

How Does the Brain Classify Words? Results of Recent fMRI Studies

- Encoding by the brain is distributed- involves multiple brain regions- leads to flexibility
- Each word encoded according to four attributes in adults:
 - Eating
 - Shelter
 - Manipulation
 - Number of characters in word
- Vital to design of early interventions

Reward Mechanisms

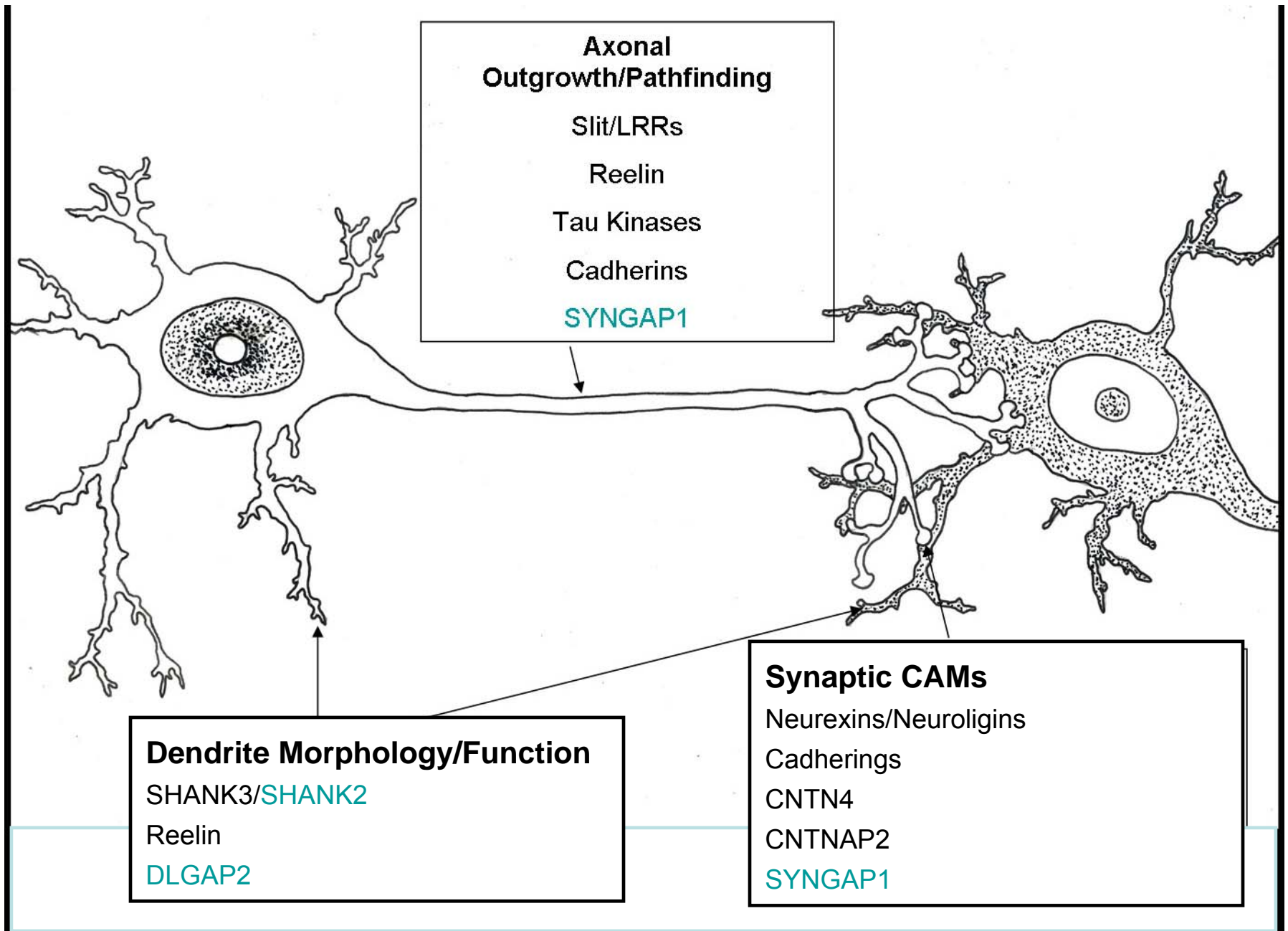
Implicit Learning Mechanisms

All are automatic, non-conscious & rapid

20-25 Genes Identified So Far
More As We Speak

Many Mostly Rare Genes Found In ASD

- No single or even few genes implicated. Rather, numerous candidates with a modest at best increased risk for autism.
- Tend to have one thing in common: are involved in determining **where and how brain cells (neurons) are connected and talk to each other.**



Autism Candidate Genes

1. Genes whose products affect **axonal targeting and pathfinding** i.e. getting neurons connected in the right way

Cadherins and leucine-rich repeat proteins

which are cell surface proteins expressed in neuronal processes - thought to be important for establishing connections between cells in the developing brain

Autism Candidate Genes

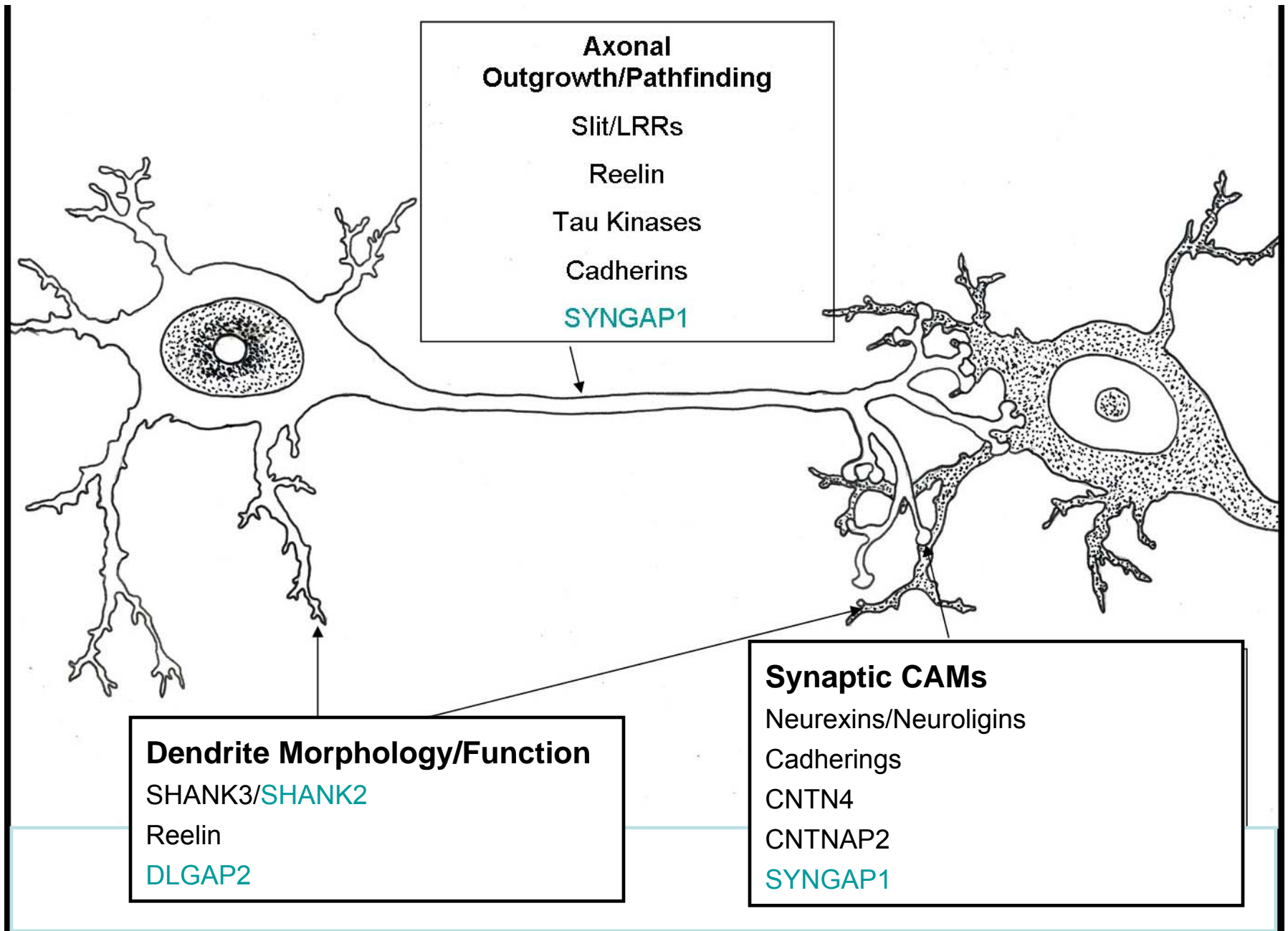
2. Those that affect synaptic functioning:

Neurexins and neuroligins bind each other across the synapse (i.e. glue neurons together) and mediate signaling across the synapse, and affect the properties of neural networks by specifying synaptic functions (i.e. excitatory versus inhibitory)

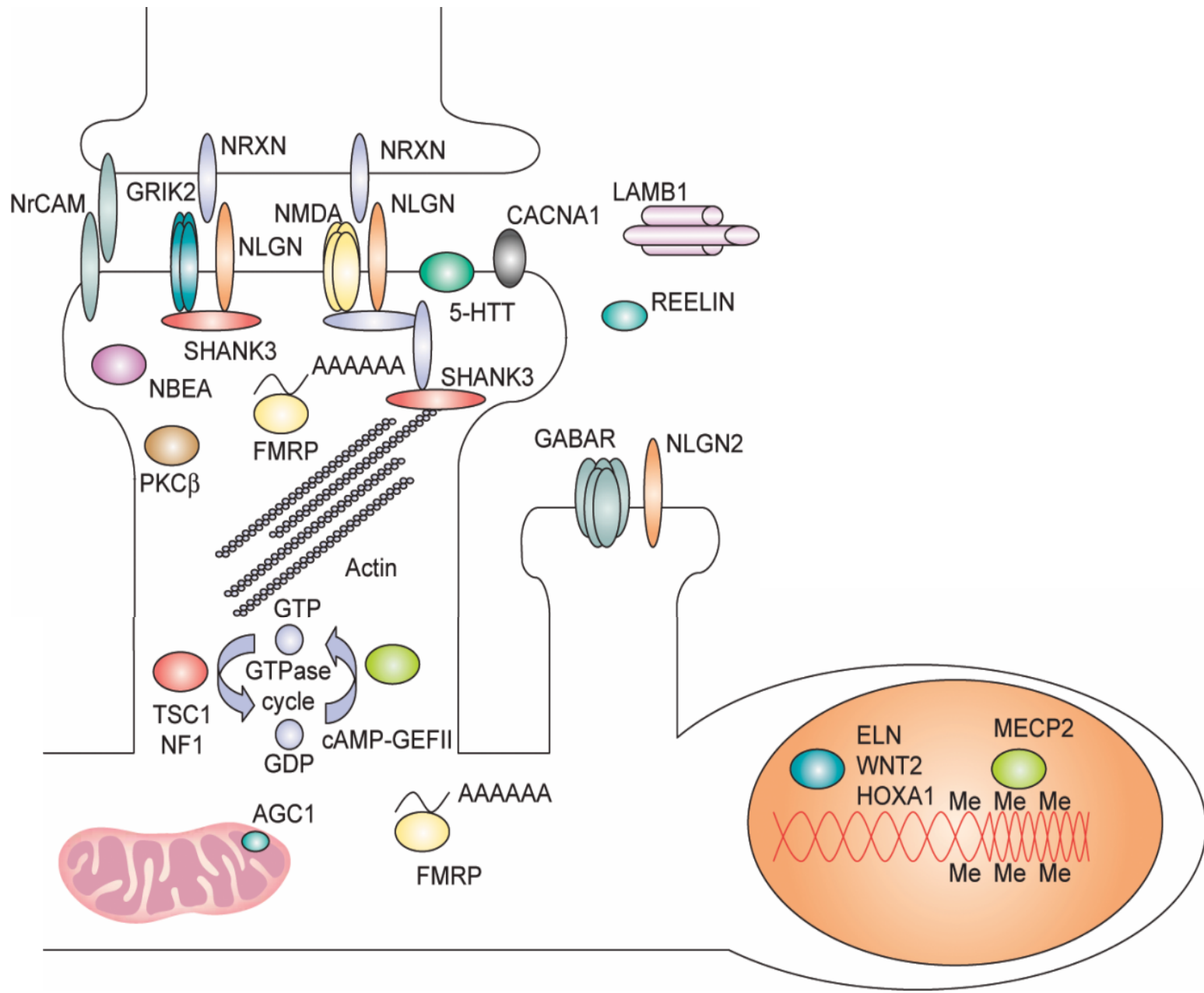
Autism Candidate Genes

3. Those that appear to affect **dendritic function**:

Shank family of synaptic proteins function as molecular scaffolds at the post synaptic density and promote the maturation and enlargement of dendritic spines.



Identification of Genes Leads to
Definition of Molecular Mechanisms



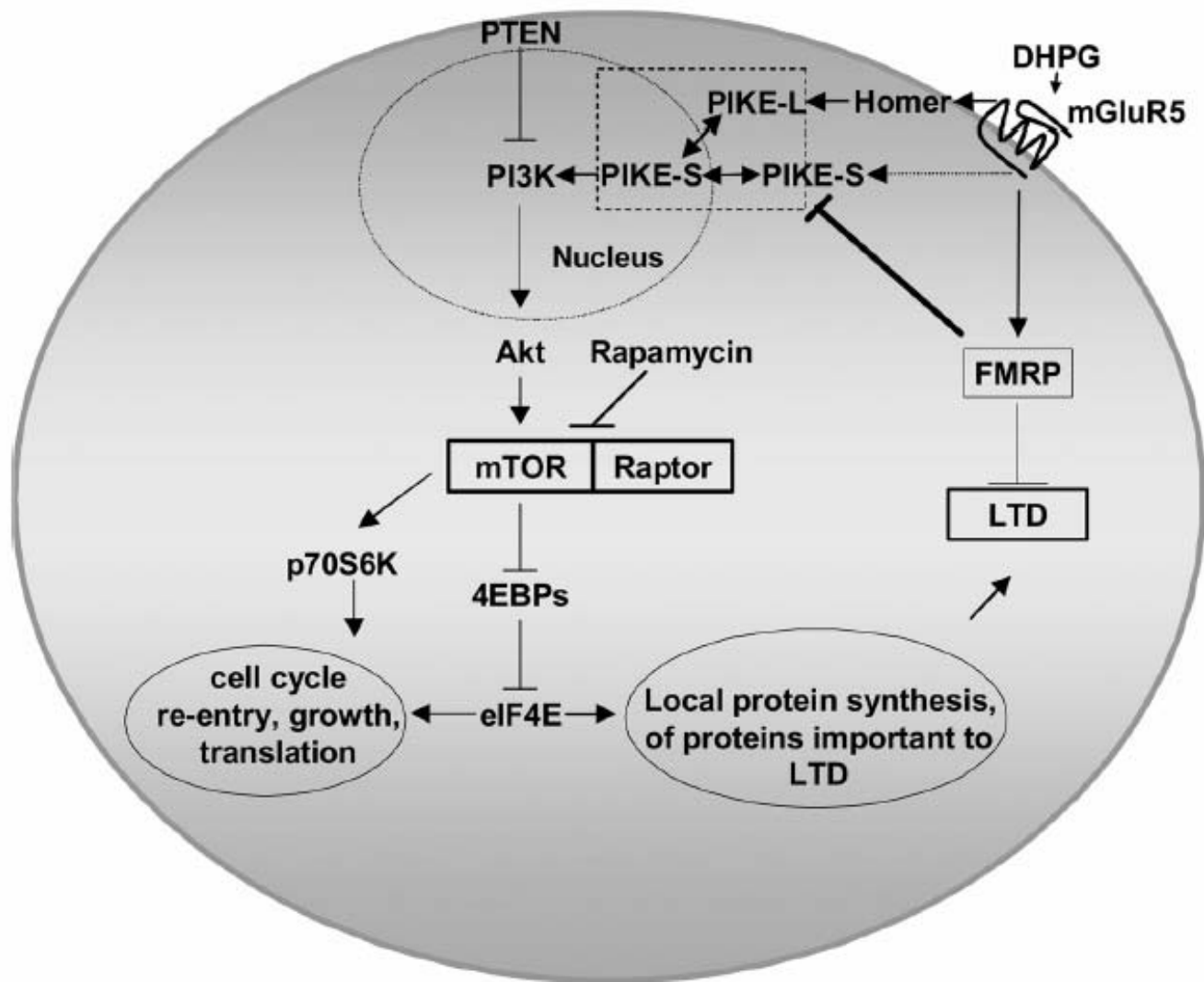


Figure 7. Model showing possible interaction of FMRP with the mTORC1 complex. In wild-type mice, FMRP represses PIKE or other endogenous activator of PI3K/Akt signaling and thereby exerts a negative regulatory effect on mTOR signaling. Activation of group I mGluRs by the agonist DHPG promotes formation of an mGluR-Homer-PIKE complex, which engages PI3K/Akt signaling (Rong et al., 2003). PI3K/Akt in turn stimulates mTOR signaling, initiation of translation of synaptic proteins in dendrites, and mGluR-LTD. In FMRP-deficient mice, the positive effector (PIKE) is upregulated and mTOR signaling is overactivated and DHPG insensitive, leading to aberrant synthesis of synaptic proteins and exaggerated protein synthesis-independent mGluR-LTD. The PI3K inhibitor LY294002 reduces p-mTOR to wild-type levels and restores DHPG sensitivity.

A Molecular Pathophysiology Emerges

- Defining molecular mechanisms empowers a new world of interventions
- mTor inhibitor Rapamycin to prevent development of seizures, intellectual disability and ASD in infants and toddlers diagnosed with TSC gene tuberous sclerosis; clinical trials in progress

Curr Opin Neurol. 2010 Jan 16. [Epub ahead of print]

Tuberous sclerosis complex: a brave new world?

Ess KC.

Department of Neurology and Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, Tennessee, USA.

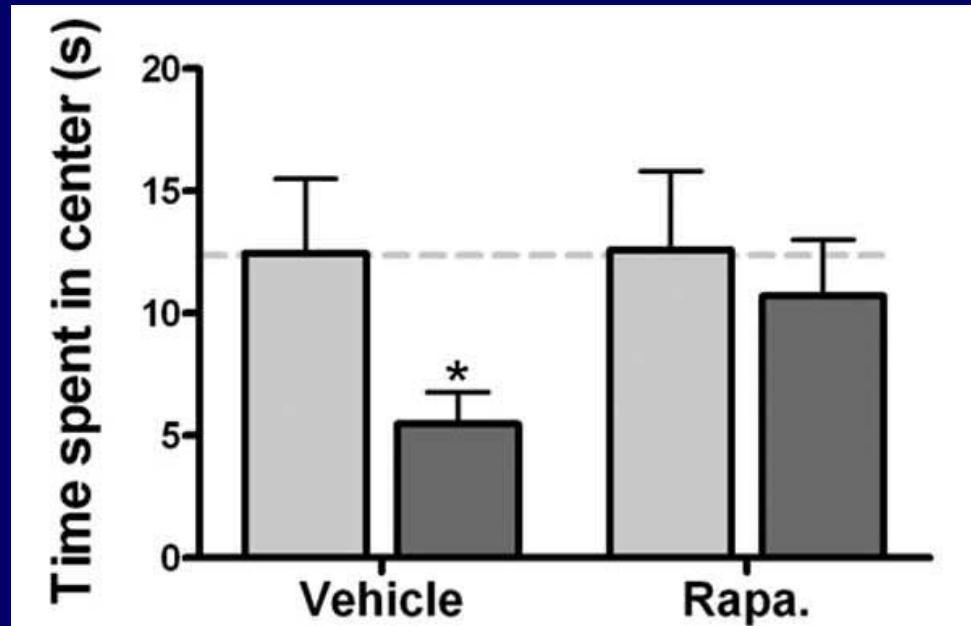
PURPOSE OF REVIEW: Tuberous sclerosis complex (TSC) is a multiorgan genetic disease caused by mutations in the TSC1 or TSC2 genes. TSC has been recognized for many years as an important cause of severe neurological disease with patients suffering from epilepsy, developmental delay, autism, and psychiatric problems. During the last year, there have been enormous advances in basic and translational research pertaining to TSC. **RECENT FINDINGS:** In this review, I discuss the basic science findings that position the TSC1 and TSC2 genes as critical regulators of the mammalian target of rapamycin kinase within mammalian target of rapamycin complex 1. In addition, I will discuss the development of new animal models, translational data, and recent clinical trials using mammalian target of rapamycin complex 1 inhibitors such as rapamycin. **SUMMARY:** The past few years have seen spectacular advances that have energized TSC-related research and challenged existing symptomatic treatments. Although it remains to be seen whether use of mammalian target of rapamycin complex 1 inhibitors will revolutionize the care of patients with TSC, the application of basic and translational research towards a specific clinical disorder emphasizes the potential and promise of molecular medicine.

PMID: 20087180 [PubMed - as supplied by publisher]

Animal Models of ASD Genes

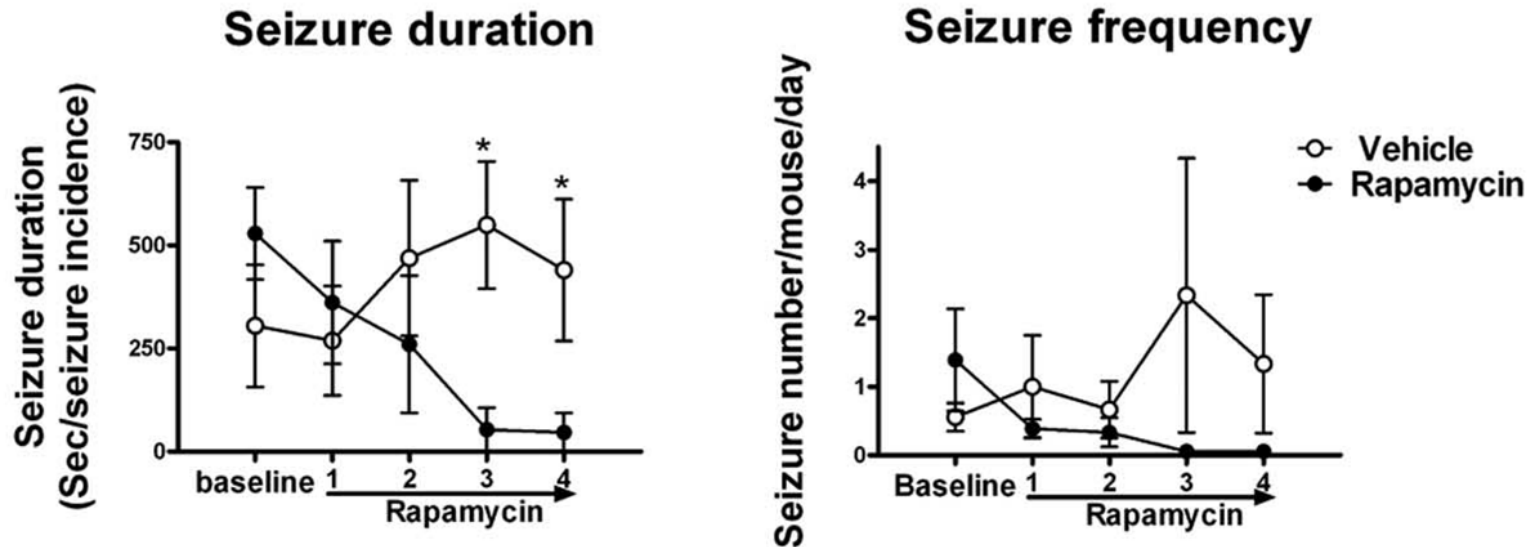
Play a major role in defining genes, what they do, how they do it, and how outcome can be changed

Rapamycin Treatment of Mouse PTEN



Rapamycin treatment reduces anxiety, improves social activity, and controls seizures. In the open-field test, rapamycin (Rapa)-treated *Pten* mutant mice showed no significant difference from rapamycin-treated controls, whereas vehicle treated *Pten* mutants showed statistically significant decrease in center time compared with vehicle-treated control mice.

Rapamycin Treatment of Mouse PTEN



Rapamycin injection progressively reduces seizure duration and frequency of *Pten* mutant mice. $n = 6$ mice per group. $*p < 0.05$ compared between vehicle- and rapamycin-treated mutants. Data are mean \pm SEM and were analyzed by ANOVA, followed by *post hoc t* test.

Deregulation of *EIF4E*: a novel mechanism for autism

M Neves-Pereira,¹ B Müller,² D Massie,³ J H G Williams,¹ P C M O'Brien,⁴ A Hughes,¹ S-B Shen,² David St Clair,¹ Z Miedzybrodzka^{1,3}

ABSTRACT

BACKGROUND: Autism is a common childhood onset neurodevelopmental disorder, characterised by severe and sustained impairment of social interaction and social communication, as well as a notably restricted repertoire of activities and interests. Its aetiology is multifactorial with a strong genetic basis. EIF4E is the rate limiting component of eukaryotic translation initiation, and plays a key role in learning and memory through its control of translation within the synapse. EIF4E mediated translation is the final common process modulated by the mammalian target of rapamycin (mTOR), PTEN and fragile X mental retardation protein (FMRP) pathways, which are implicated in autism. Linkage of autism to the EIF4E region on chromosome 4q has been found in genome wide linkage studies.

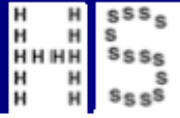
CONCLUSIONS: These observations implicate EIF4E, and more specifically control of EIF4E activity, directly in autism. The findings raise the exciting possibility that pharmacological manipulation of EIF4E may provide therapeutic benefit for those with autism caused by disturbance of the converging pathways controlling EIF4E activity.

Process of CET

- Starts with basic socialization and attention training in pairs (3mo to 6mo)
- Moves to small group-based social-cognitive training (6mo to 18mo)
- Simultaneously moves to executive function and problem-solving training (6mo to 18mo)
- All provided in the context of meaningful functional goals (e.g., work, school, girlfriend)

Intervention to Enhance Face Recognition and Brain Plasticity in Autism

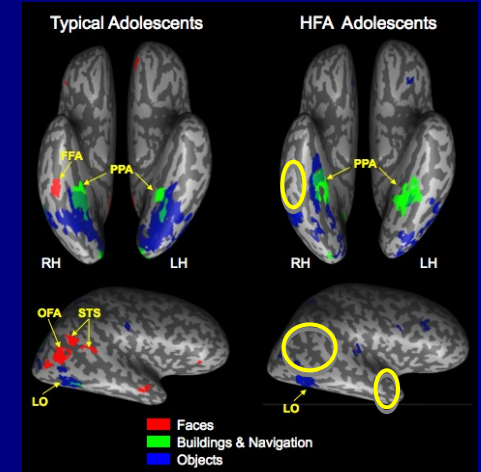
Perceptual Bias to Focus on Local Elements



Especially Difficult for Recognition of Individual Faces



Atypical Development of Face-Related Cortex



Whole is more than sum of parts!



Toddler viewer with autism: focus on non-essential inanimate details

Aversion to Faces?

Greeble Intervention – Learning to Integrate the Elements



Intervention to Enhance Face Recognition and Brain Plasticity in Autism

Perceptual Bias to Focus on Local Elements

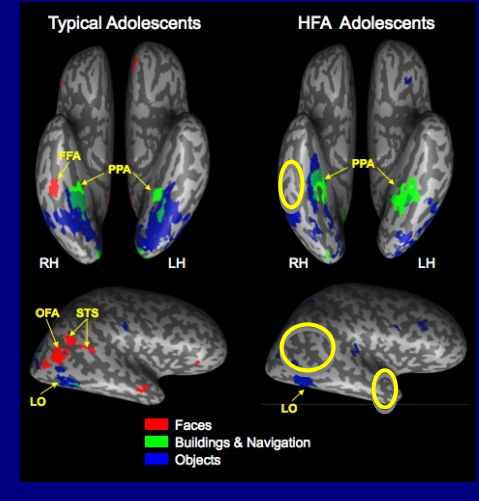


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Especially Difficult for Recognition of Individual Faces



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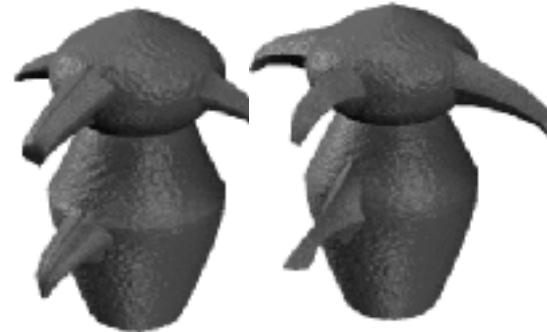


Whole is more than sum of parts!



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Progress Comes From Participation

We wish to honor those individuals and families who have believed in research and been committed to participating again and again.