# The Science of Autism: Transformative Advances in the Making

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18th Lindamood-Bell Conference

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# Pathophysiology From DNA to Behavior: A Connected Sequence of Mechanisms

Abnormalities in Genetic Code for Brain Development

↓

Abnormal Mechanisms of Brain Development

↓

Structural and Functional Abnormalities of Brain

↓

Cognitive & Neurological Abnormalities

↓

Behavioral Syndrome

# 1. The Main Thing

Define mechanisms of manifestations

# Cause Means Different Things

Etiology-triggering event

Pathophysiology- how event is operationalized

Specific actions: Functional analysis of behavior

# ‘Cause of Autism’

Scientists widely agree there are many etiologies.

Trigger a common pathophysiologic sequence
Of structure function alterations in the brain.

# Treatment Advances Target Mechanisms

Leads to more effective treatments

That are closer to origin of manifestations

Ultimately leads to individualization of treatment as basis for differences understood

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Cognitive & Neurological Abnormalities

↓

Behavioral Syndrome

# How Much Do We Know About What Causes Autism?

A lot.

# 2. DSM-5

# Why Do We Have To Give Up DSM-IV?

Autistic Disorder: DSM-IV

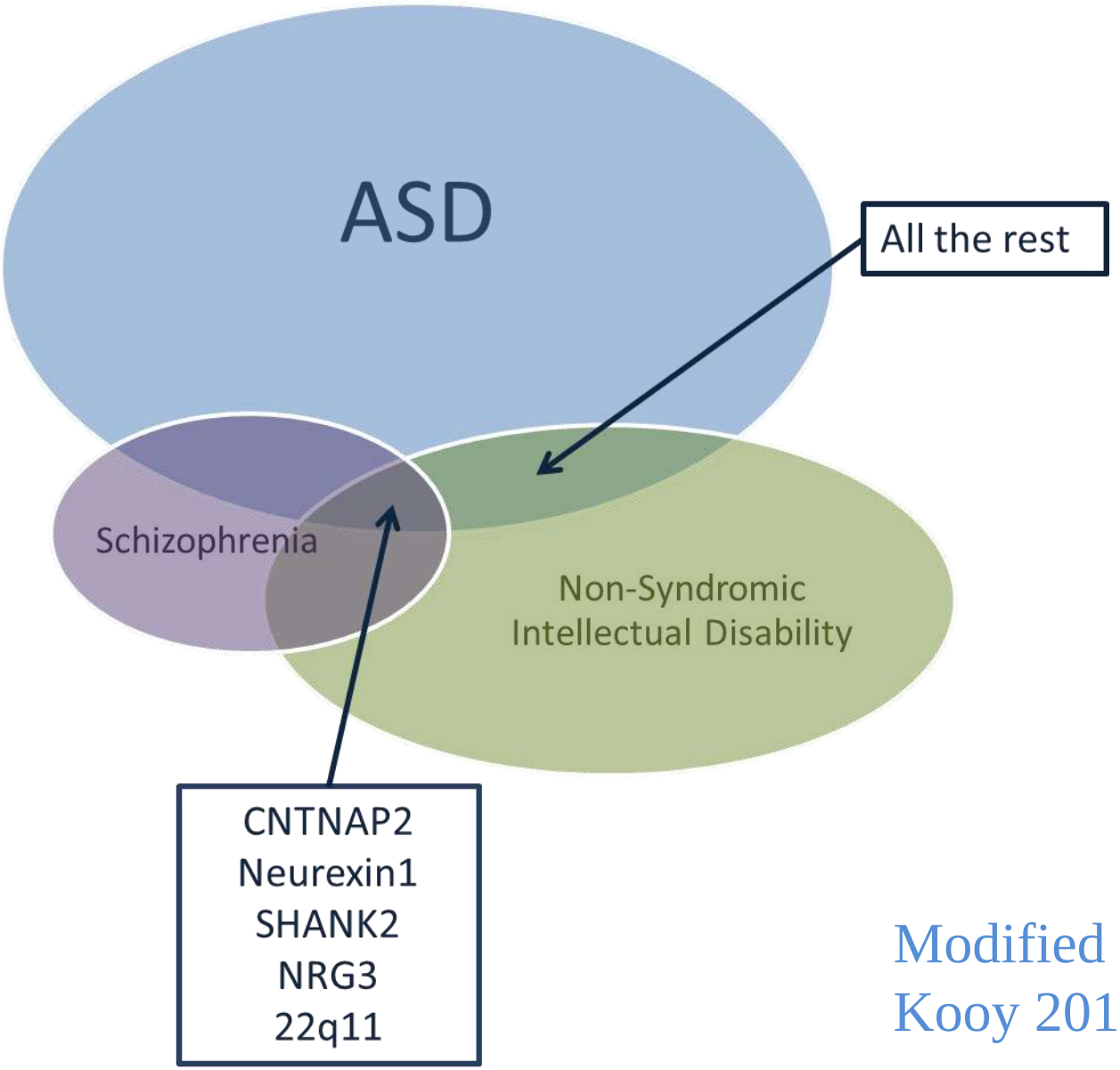
- 3 Core Symptoms
- Associated symptoms: sensory, motor
- Co-morbid Conditions: intellectual disability, ADHD, seizures, mood problems, long list of behavior issues (Pg. 71-72 TR version)

No longer clinically or biologically valid conceptualization of ASD, and confusing to everyone.

# Infant Sibs Research: Entire Range of Behavior Emerges Simultaneously in ASD- One Disorder

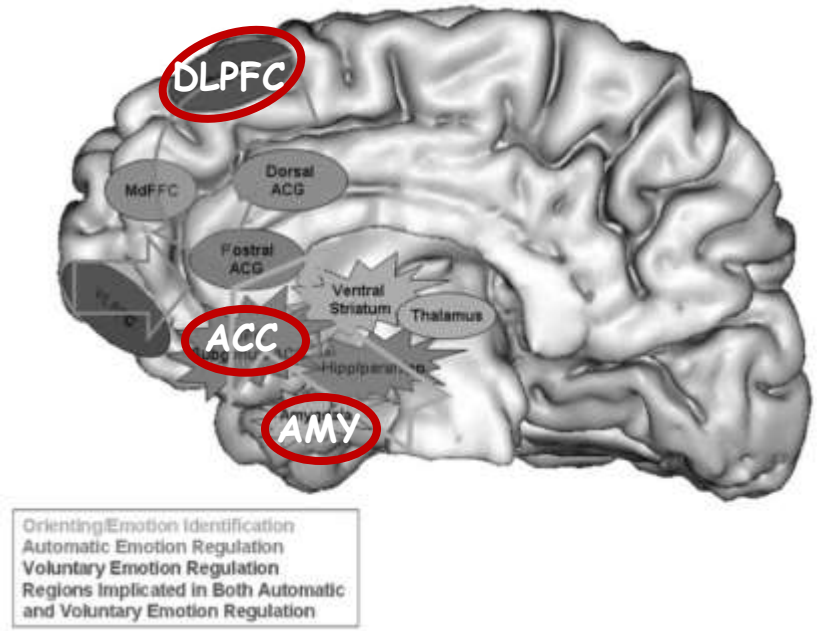
- Manifestations before 12 months are subtle- involve sensory & motor behaviors
- Most appear socially normal at 6 months
- "Associated symptoms" are integral-irritability, altered sensory responsivity & activity level, poor gross motor development emerge together with core deficits
- "These findings 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." Sally Rogers, 2009

# Genes & Brain Circuitry: Alterations Shared Across Disorders




Modified from Kooy 2010

# AMY-ACC-DLPFC are core regions of neural network for identification and regulation of emotion




*Phillips et al, Mol Psy, 2008*

## Role in mood/affect regulation:

- **Amygdala** (**AMY**). Critical to sensing and assessing emotionally-salient stimuli.
- **Anterior cingulate cortex** (subgenual **ACC**; BA 25): integrates information about emotional salience (bottom-up) with cognitive control and motivational states (top-down).
- **Dorsolateral prefrontal cortex**: cognitive assessment of emotional salience (cortical top-down regulation)

**AMY**, amygdala; **ACC**, anterior cingulate cortex; **DLPFC**, dorsolateral prefrontal cortex

# DSM-5: A Monumental Effort

Started 2005

World-wide work of many

A $20 Million investment by APA

18 work groups

International, cross cultural, all genders

# Revision Principles

- DSM is, above all, a manual to be used by clinicians, and changes made for DSM-5 must be implementable in routine specialty practices
- Make revisions that will lead to better clinical diagnostic practice
- Revisions should be guided by research evidence

# Goals For Revisions

- Revisions are designed to lead to:
  - Earlier diagnosis
  - Change in disorder & criteria w/ age
  - Capture variability in expression
  - Earlier treatment
  - More effective treatment
  - Prevention of later complications

# Proposed Major Changes to DSM-5

# Revised DSM Chapter Structure:

Put Disorders With Common Biology and Genes Next To Each Other To Inform Clinicians of Related Disorders and Key Differential Diagnoses

# Revised Chapter Organization

A. Neurodevelopmental Disorders

B. Schizophrenia Spectrum and Other Psychotic Disorders

C. Bipolar and Related Disorders

D. Depressive Disorders

E. Anxiety Disorder

F. Obsessive-Compulsive and Related Disorders

G. Trauma and Stressor-Related Disorders

H. Dissociative Disorders

J. Somatic Symptom Disorders

K. Feeding and Eating Disorders

L. Elimination Disorders

M. Sleep-Wake Disorders

N. Sexual Dysfunctions

P. Gender Dysphoria

Q. Disruptive, Impulse Control, and Conduct Disorders

R. Substance Use and Addictive Disorders

S. Neurocognitive Disorders

T. Personality Disorders

U. Paraphilias

V. Other Disorders

# Proposed Major Revisions to Criteria Format:

- DSM-5 could benefit from offering explicit criteria for both categories and dimensions (not or)
- For any psychiatric disorder, a number of aspects could be conceptualized and assessed dimensionally
- Behavioral dimensions can capture co-occurring disorders & sub-threshold symptoms

Krueger RB, WHO/APIRE Conference on Public Health, Sept .2007

# 6 Cross-Cutting Study Groups

- Diagnostic Spectra Study Group
- Life Span Developmental Approach Study Group
- Gender and Cross-Cultural Study Group
- Psychiatric/General Medical Interface Study Group
- Impairment Assessment and Instruments Study Group
- Diagnostic Assessment Instruments Study Group

# DSM-5 Field Trials

# DSM-5 Field Trials

- **Were Designed To:**
  - examine whether proposed revisions to existing disorders and new disorders are reliable over time
  - assess whether proposed revisions are useful to clinicians and patients
  - determine how proposed changes impact diagnosis and treatment planning

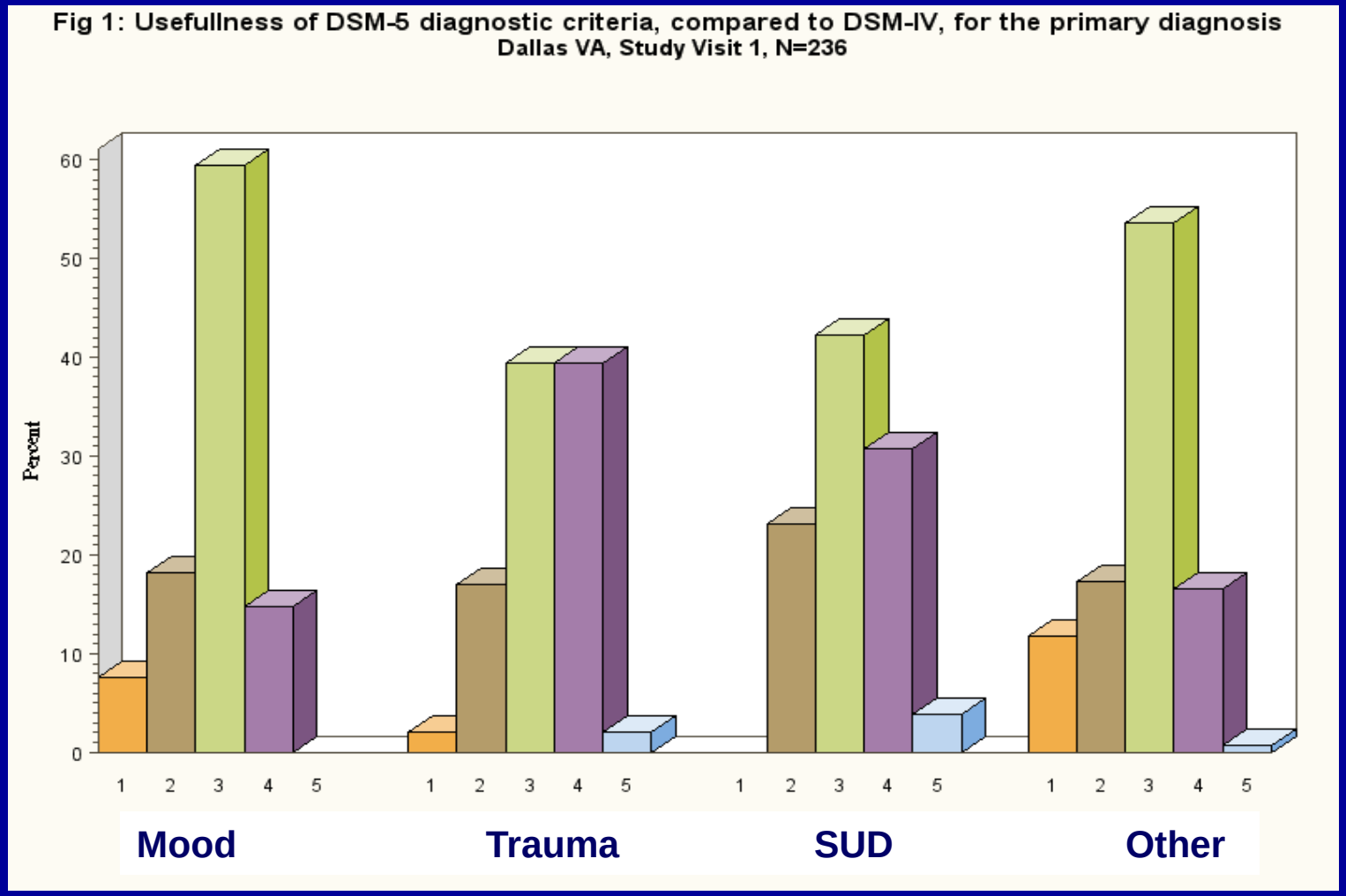
# DSM-5 Field Trials

- Clinical utility and feasibility assessed by:
  - Patient-completed questionnaires as to whether dimensional assessments seemed useful
  - Clinician-completed questionnaires as to whether dimensional assessments and diagnostic checklists were helpful in diagnosis, treatment planning
  - Utility & feasibility of new standardized assessment of disability (WHO-DAS II) in lieu of GAF rating
  - Designed to assess performance of DSM-5 changes in small or solo offices & academic centers

# DSM-5 Field Trials

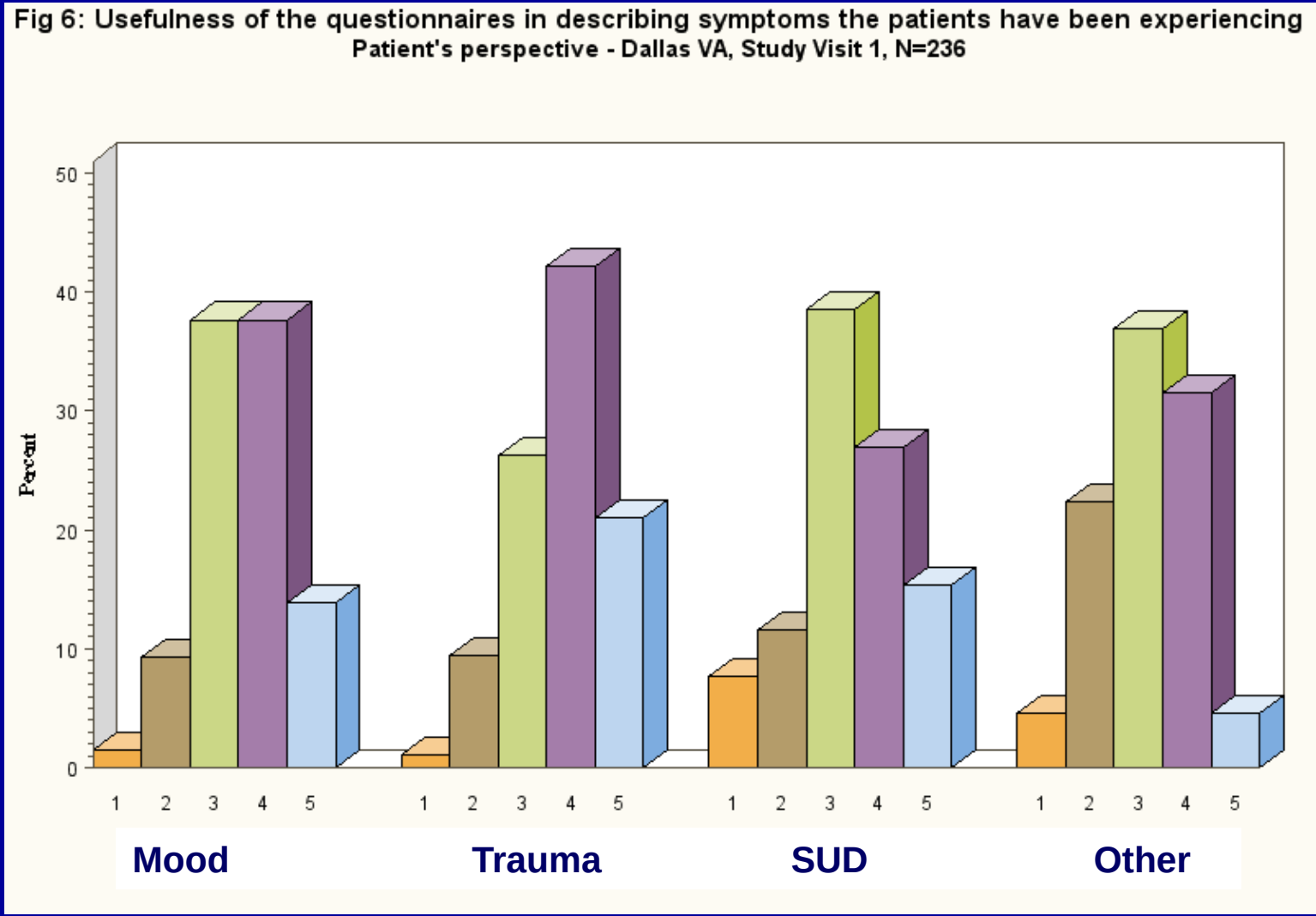
- Large, academic-medical settings
  - Examining proposed changes to DSM-5 in large, diverse samples
  - Includes 11 sites (7 adult, 4 pediatric)
  - Data collection ended in 2011
- Routine clinical practice settings
  - Do “real world” clinicians find DSM-5 diagnoses useful?
  - Psychiatrists plus psychologists, licensed clinical social workers, marriage and family counselors, and advanced-practice mental health nurses
- Data collection ended in 2012

# Clinicians found the DSM-5 diagnostic criteria "moderately to extremely useful" compared to DSM-IV



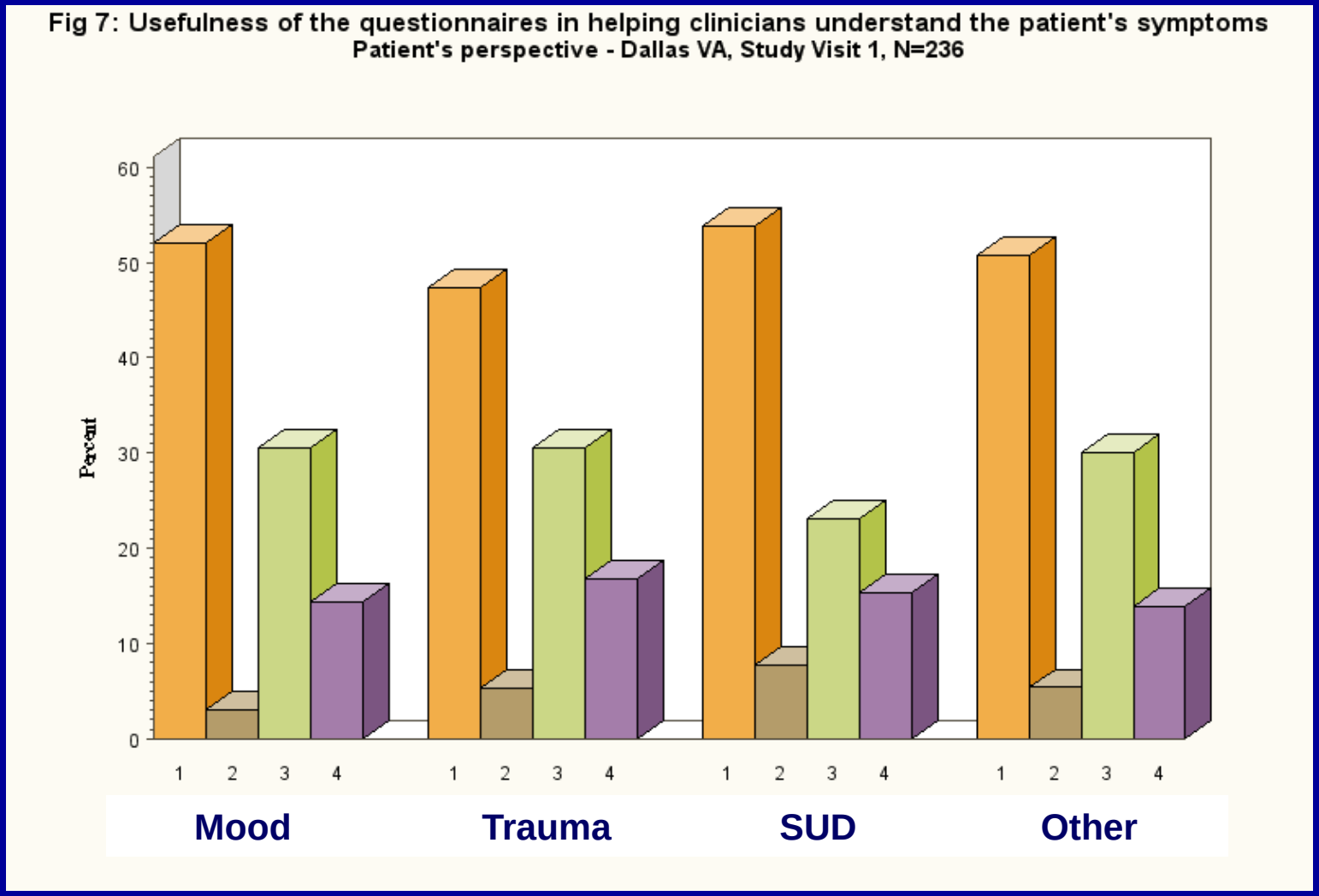

**LEGEND:**
1 = Not at all
2 = Slightly
3 = Moderately
4 = Very
5 = Extremely

# Patients reported that the questionnaires described their symptoms "moderately to extremely well"




**LEGEND:**
1 = Not at all
2 = Slightly
3 = Moderately
4 = Very
5 = Extremely

# Patients believed the questionnaires helped clinicians better understand their symptoms




LEGEND:
1 = Yes
2 = No
3 = Maybe
4 = I don't know

# Current Task Force Efforts:

- Analyze all field trial data and identify needed revisions
- Independent review of proposed criteria by experts not involved in creation of the new criteria
- Review of <u>all</u> public comments

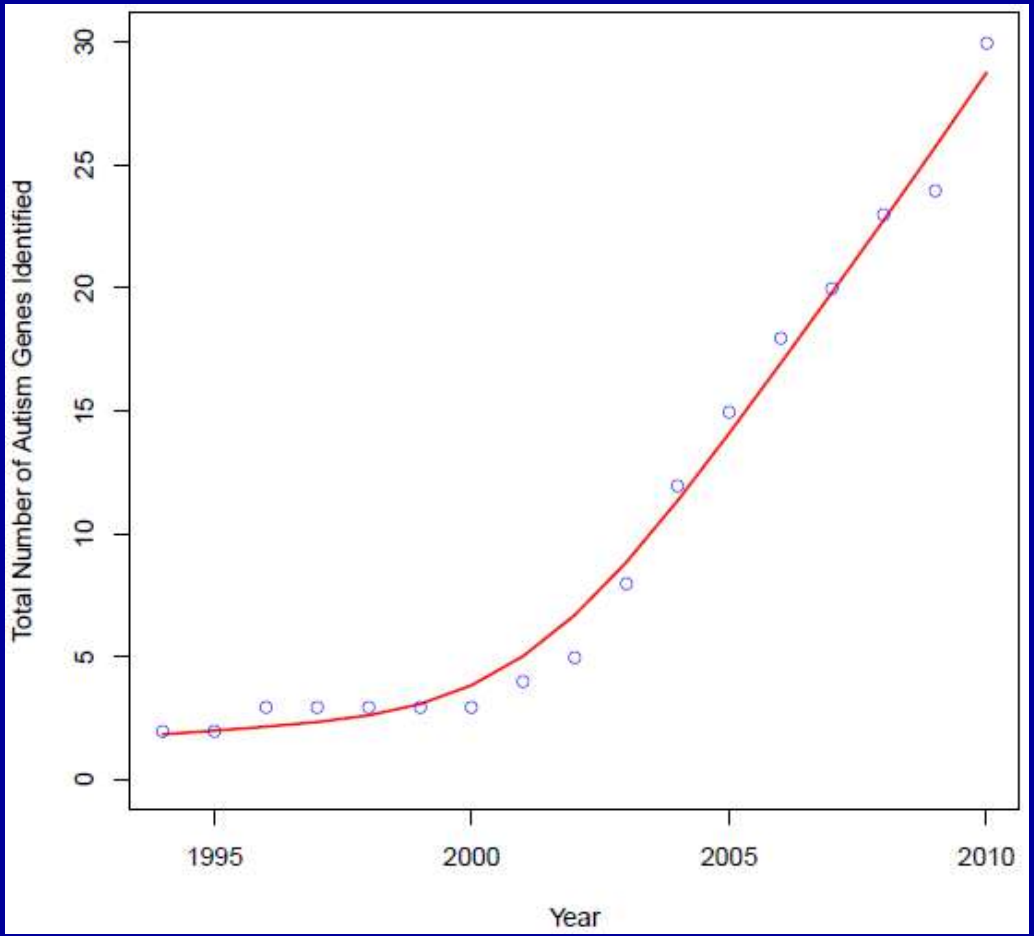
# Future DSM-5 Developments

DSM-5 will go electronic:

- adding links to key supporting documents/evidence/descriptions and
- electronic communications between patients and clinicians

# 3. Genetics Discoveries

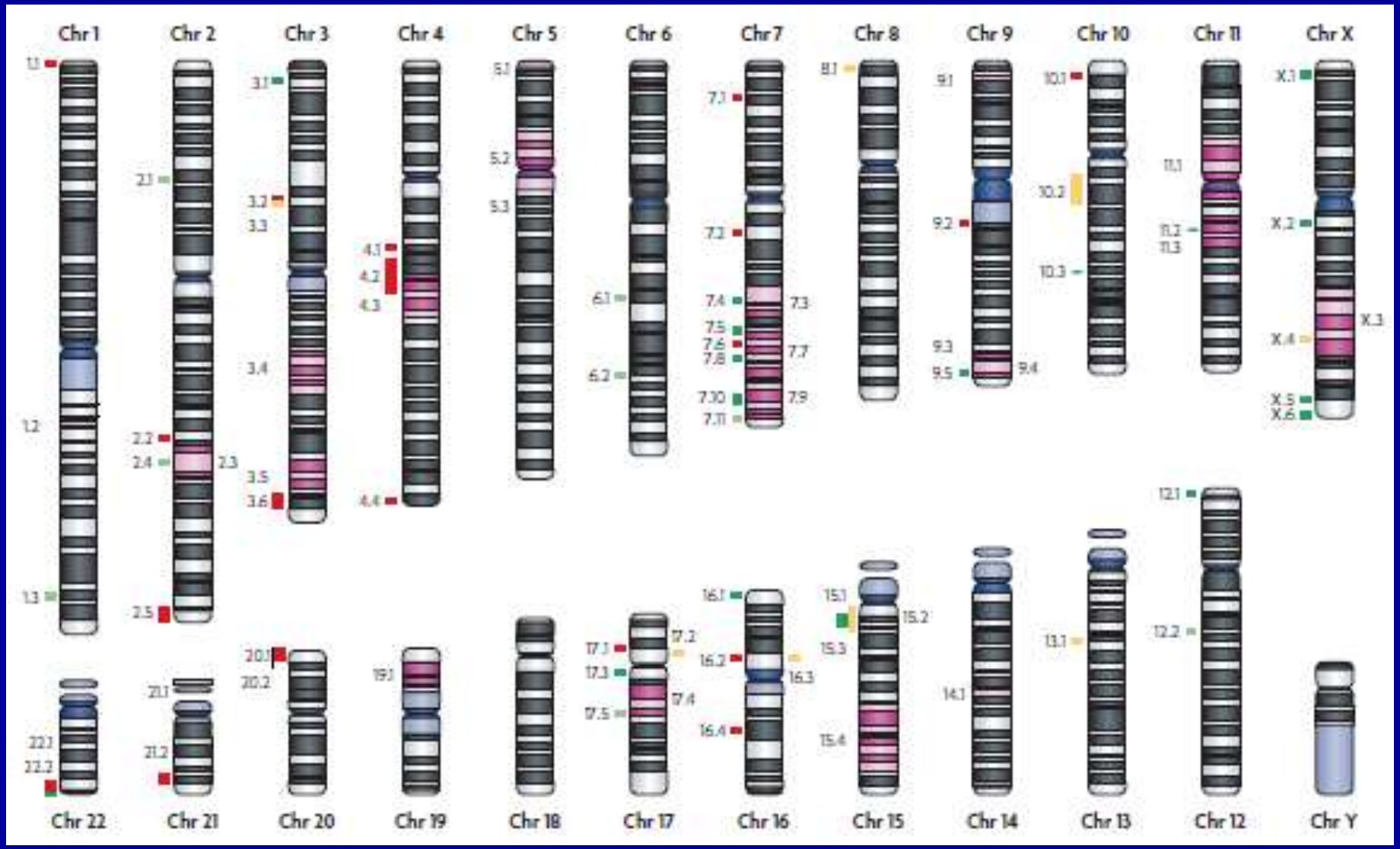
# Exciting times for genetics of Autism Spectrum Disorders




Adapted from Betancur (2011, Brain Res. 1380:42-77)

# Copy Number Variations (CNVs)
# The Awakening to Small DNA Alterations

Small (micro-) deletions or duplications of DNA distributed across chromosomes, inherited and spontaneous, occur constantly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Chr 12
Chr Y

# Another Genomics Technology Advance Leads to Even More Gene Discovery

Fragmentation of chromosome ends during replication and out-of-order recombination:

a new cause of microscopic duplications and deletions in ASD

# Genetic Diagnosis Coming

- But not yet ready for clinical use.
- Ultimately diagnosis will have far greater specificity and will span genes to behavior and account for variability in manifestations and in turn treatments linked to each mechanism.

# 7. Speeding DNA-Based Diagnosis for Newborns

By Alice Park | Dec. 04, 2012 | Add a Comment

DAVID AARON TROY / GETTY IMAGES

Fifty hours. That's how long it now takes to decode and interpret a newborn baby's genome — an undertaking that used to take weeks or even months. And those two days can mean the difference between life and death for a critically ill infant. The speedier genomic analysis is possible thanks to advances in sequencing technology as well as innovative software that links the 3,500 known genetic defects to their childhood diseases, allowing doctors to quickly decide on the right treatment that could save a baby's life. About 30% of babies admitted to the neonatal intensive care unit each year have inherited a genetic disease, and sequencing their genomes may become a critical part of improving their care in coming years — the sooner the better.

# Infant DNA Tests Speed Diagnosis of Rare Diseases

By GINA KOLATA

From the day she was born, the girl had seizure after seizure. Doctors at Children's Mercy Hospital in Kansas City, Mo., frantically tried to keep her alive. Weeks passed and every medication failed. Finally, her family decided to let their baby go, and the medical devices were withdrawn. She was 5 weeks old.

Her doctors suspected a genetic disorder, and as it happened the hospital had just begun a study of a new technique for quickly analyzing the DNA of newborns, zeroing in on mutations that can cause disease.

This new method, published on Wednesday in the magazine Science Translational Medicine, is a proof of concept — a demonstration in four babies that it is possible to quickly scan a baby's entire DNA and pinpoint a disease-causing mutation in a couple of days instead of the more typical weeks or months. The study's investigators said the test could be one of the first practical fruits of the revolution in sequencing an individual's entire DNA.

For the baby with seizures, her doctors provided a sample of her blood. The analysis took only 50 hours and provided an answer. The baby had a mortal gene mutation so rare that it had been reported just once before.

Open

Molecular Psychiatry (2012), 1–7
© 2012 Macmillan Publishers Limited All rights reserved 1359-4184/12
www.nature.com/mp

ORIGINAL ARTICLE

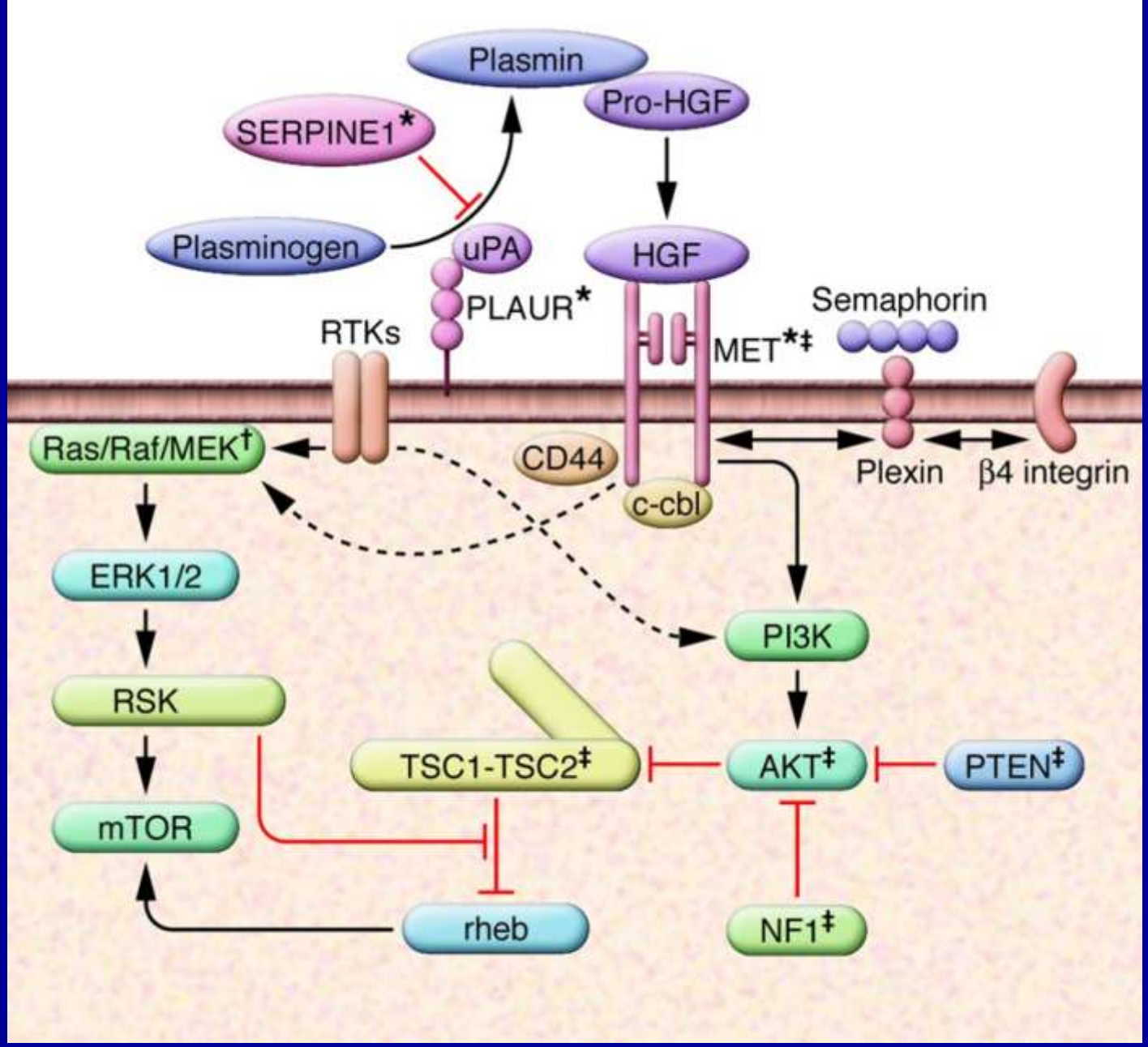
# Predicting the diagnosis of autism spectrum disorder using gene pathway analysis

E Skafidas[1], R Testa[2,3], D Zantomio[4], G Chana[5], IP Everall[5] and C Pantelis[2,5]

# Conclusions

- Understand <u>much</u> about the genetic architecture of autism; will understand <u>much more</u> very soon.
- More genes and more potential drug targets
- Momentum for discovery is huge and due to
  - Pooling data
  - Funding
- 5 years from now gene discovery in ASD will become passé: translation will be the key for ASD in the near future!

# 4. Genes Lead to Signaling Pathways in Brain Cells: New Targets for Brain Treatments




**The genetic and neurobiologic compass points toward common signaling dysfunctions in autism spectrum disorders** P. Levitt, D. B. Campbell. *Clin Invest.* 119, 2009.

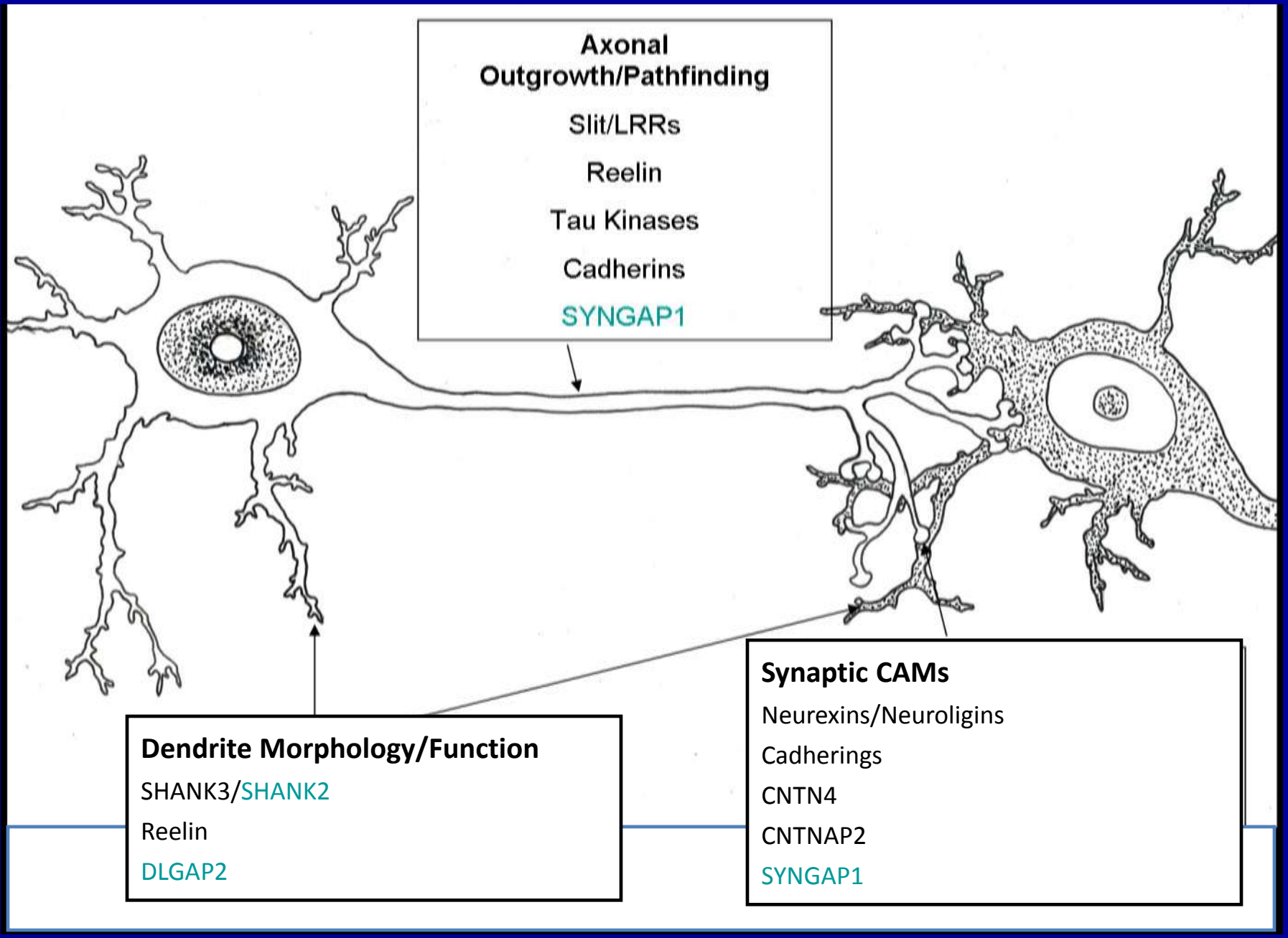
# Can Biological Treatments Change The Brain? In severe cases? At what age?

The first ones exist. Others are entering trials.

Biological interventions impact signaling pathways in brain cells to stop over-growth or start connecting.

# 5. Genes Also Lead to Developmental Neurobiologic Mechanisms: Bridge to Altered Brain Structure

Functional impact of global rare copy number variation in autism spectrum disorder. *Nature*, June 9, 2010 (Epub ahead of print).



# Altered Brain Developmental Mechanisms Lead to Altered Structure and Function of Brain Systems

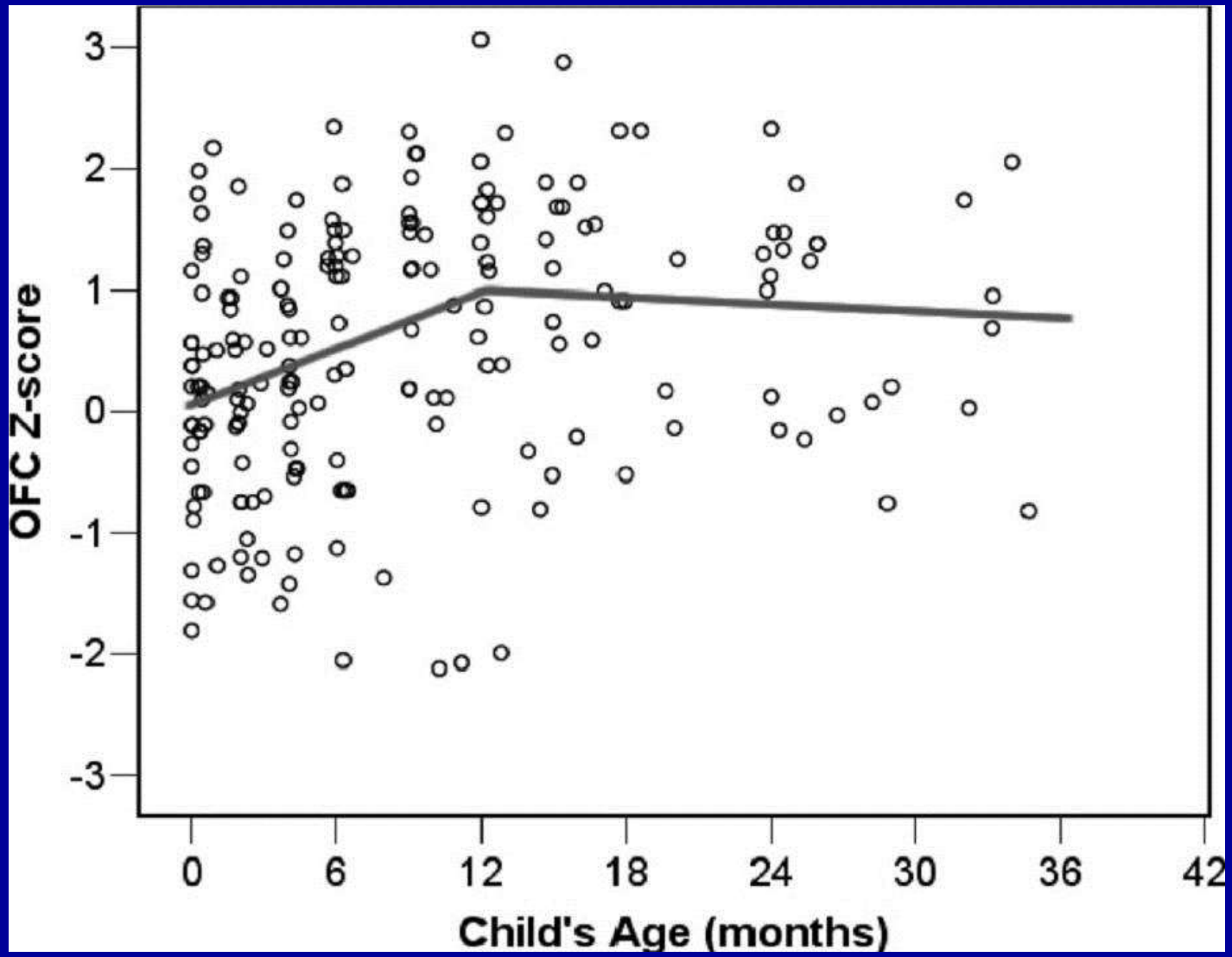



**Figure 2.** Occipital–frontal (OFC) *Z* score measurements (*N* 195) with mean estimated growth trajectory for 28 children with autism spectrum disorder (hierarchical linear model two-piece linearmodel centered at 12 months).

# 6. Advances in Brain Imaging Technology: To See It Is To Measure It

- Improve visualization of micro-alterations in brain circuitry/connections
- Capacity to link brain changes to early alterations in brain development
- Enable detection of change with treatment
- Enhance understanding of heterogeneity
- Forerunner of individualized medicine

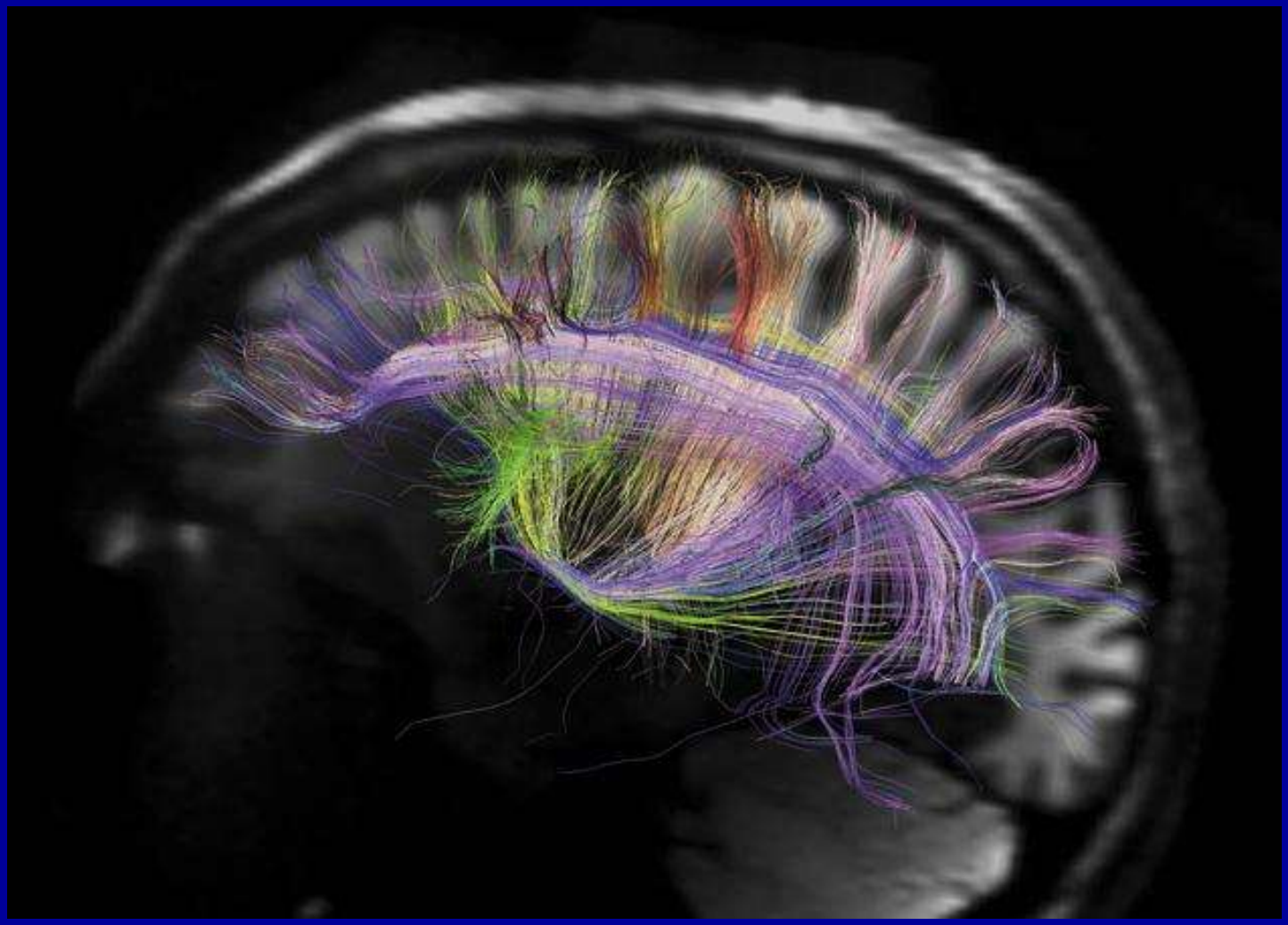
**"Biology gives you a brain. Life turns it into a mind."** *Jeffrey Eugenides*

# ORDER IN THE CORTEX

Scientists have discovered that the brain is even more beautifully organized than they had imagined

**Neurons in the brain zip messages to one another** along long white fibers called axons. Previously scientists traced axon pathways in dissected animal brains, but now they can see the structure of this amazing information superhighway in a living human organ. Using new software with a technique called "diffusion tensor MRI" that tracks water molecules as they move along the axons, Van Wedeen of Massachusetts General Hospital and colleagues found that the fibers are arranged in a surprisingly regular 3-D grid.

BY LAURA HELMUTH

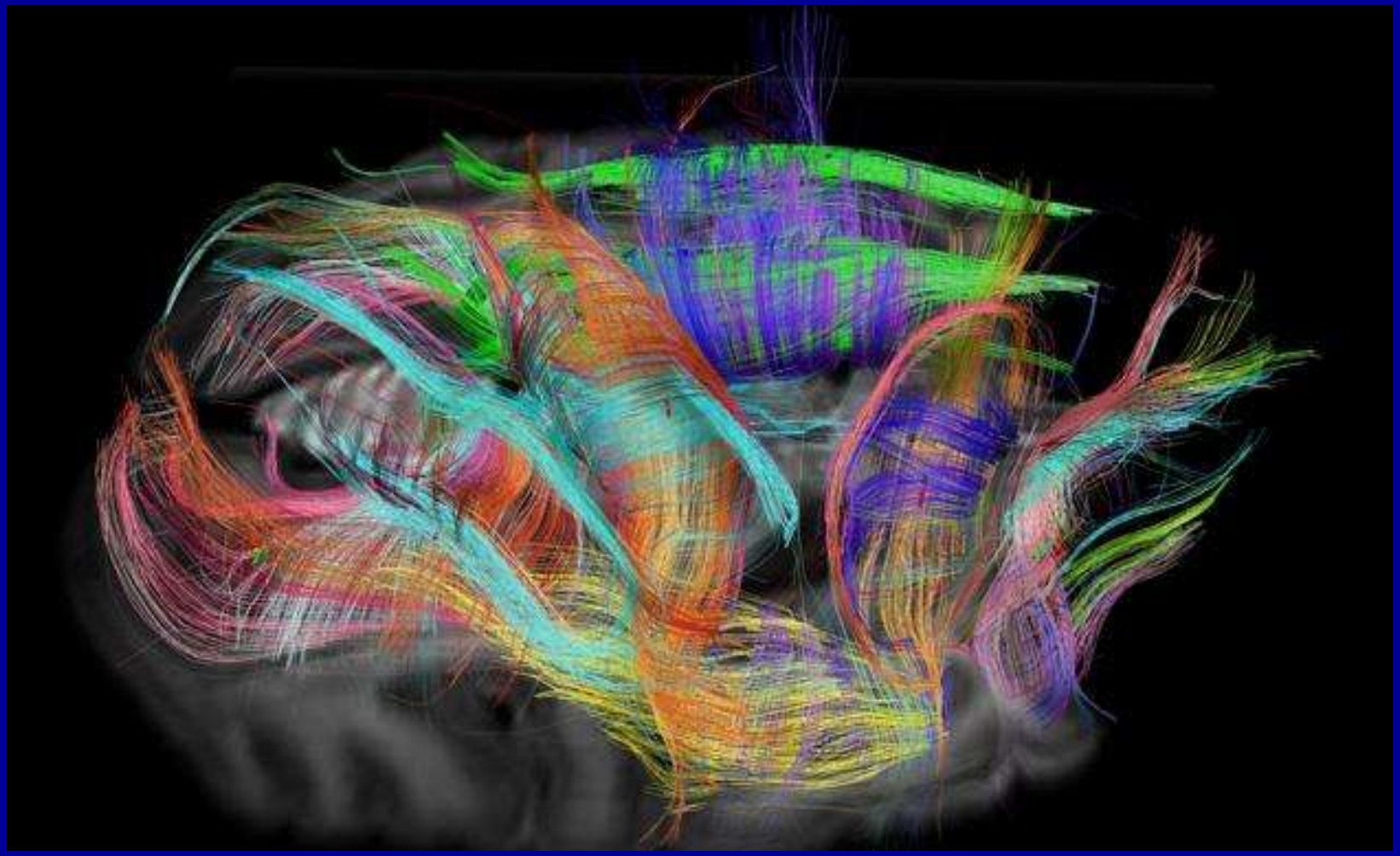


*Martinos Center For Biomedical Imaging, Massachusetts General Hospital*

Neurons in the brain zip messages to one another along long white fibers called axons. Previously scientists traced axon pathways in dissected animal brains, but now they can see the structure of this amazing information superhighway in a living human organ. Using new software with a technique called “diffusion tensor MRI” that tracks water molecules as they move along the axons, Van Wedeen of Massachusetts General Hospital and colleagues found that the fibers are arranged in a surprisingly regular 3-D grid. For instance, the red axons in the image converge on the purple pathway at a 90-degree angle. Axons are interwoven like “the warp and weft of a fabric,” the researchers say, with the pattern bent along the brain’s convolutions. “It’s really pretty, all the little loops and folds,” Wedeen says.

*Martinos Center For Biomedical Imaging, Massachusetts General Hospital*

The technique Wedeen and colleagues use is called "diffusion spectrum MRI," a variation on an existing technique. By monitoring how water moves along axons and at what angle these brain fibers cross one another, the researchers found a surprisingly geometric pattern. The three-dimensional grid is visible in this detail from a rhesus monkey brain.



*Martinos Center For Biomedical Imaging, Massachusetts General Hospital*

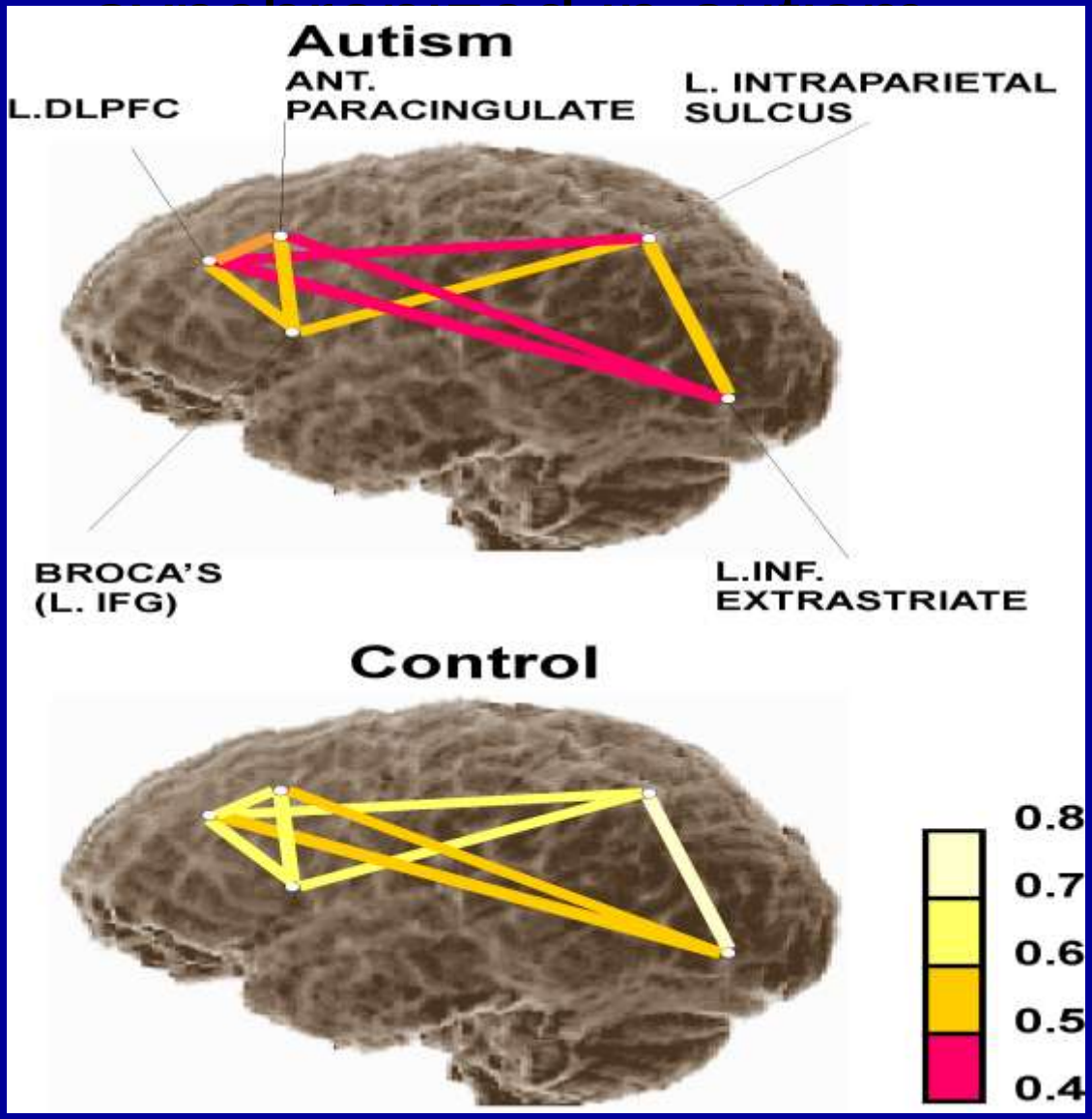
This image from a rhesus monkey shows the larger-scale structure of the grid of axons as they swoop and swirl through the convolutions of the primate's brain.

Images used from:

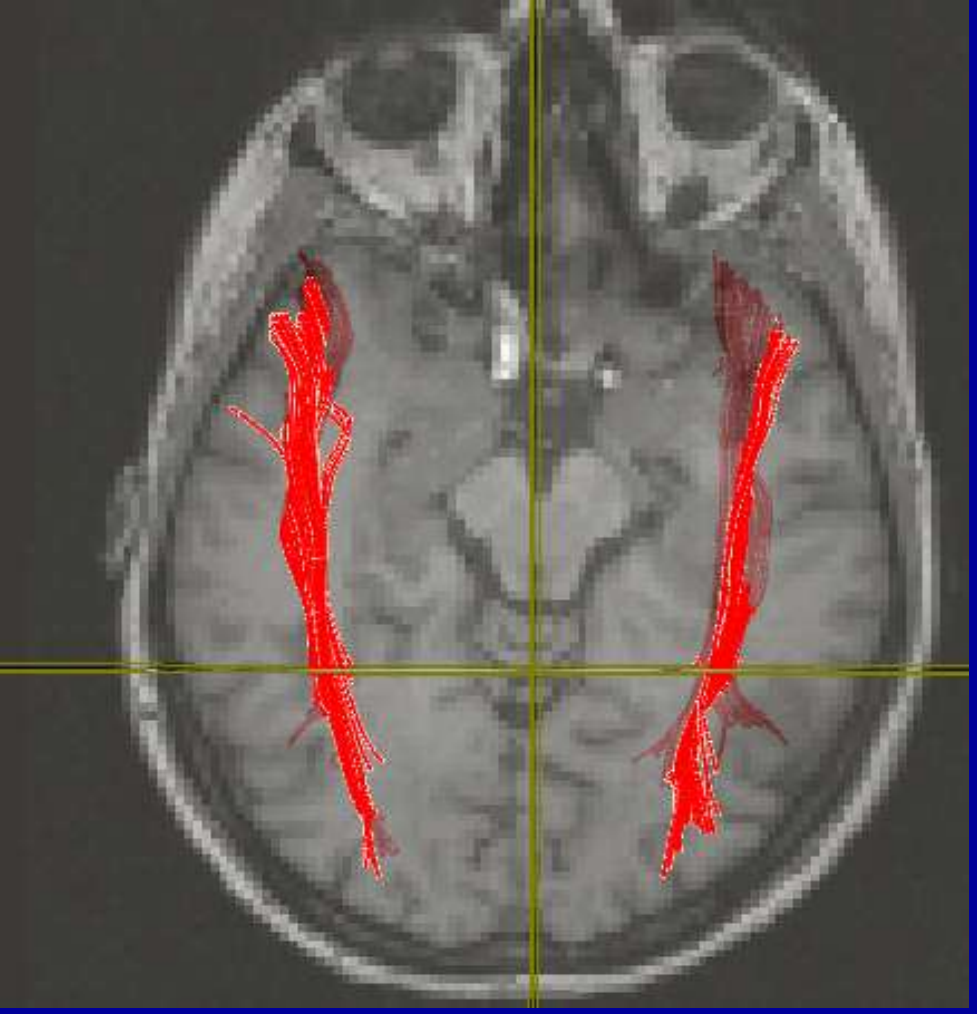
- **Animal Brains, More Beautiful Than You Could Ever Imagine**
- More than just eye candy, these images are teaching scientists new insights into how the brain is organized
- By Laura Helmuth
- *Smithsonian* magazine, July-August 2012

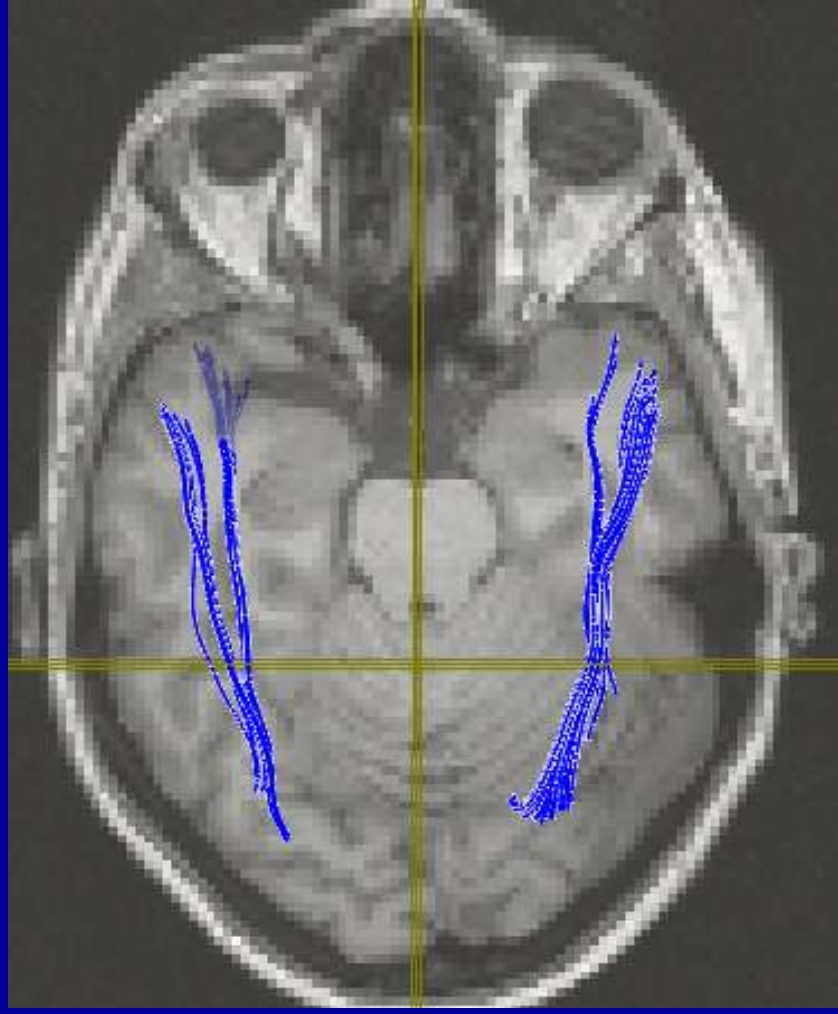
Read more: http://www.smithsonianmag.com/science-nature/Animal-Brains-More-Beautiful-Than-You-Could-Ever-Imagine-160528335.html#ixzz27m1J14ZA

# Pairs of key areas are less



# Mapping Pathways in the Brain





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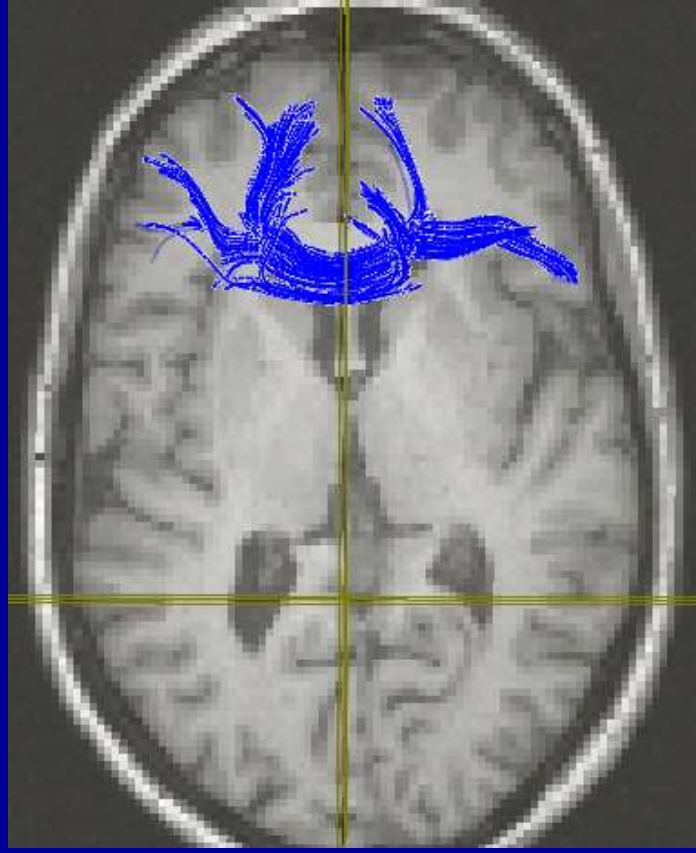
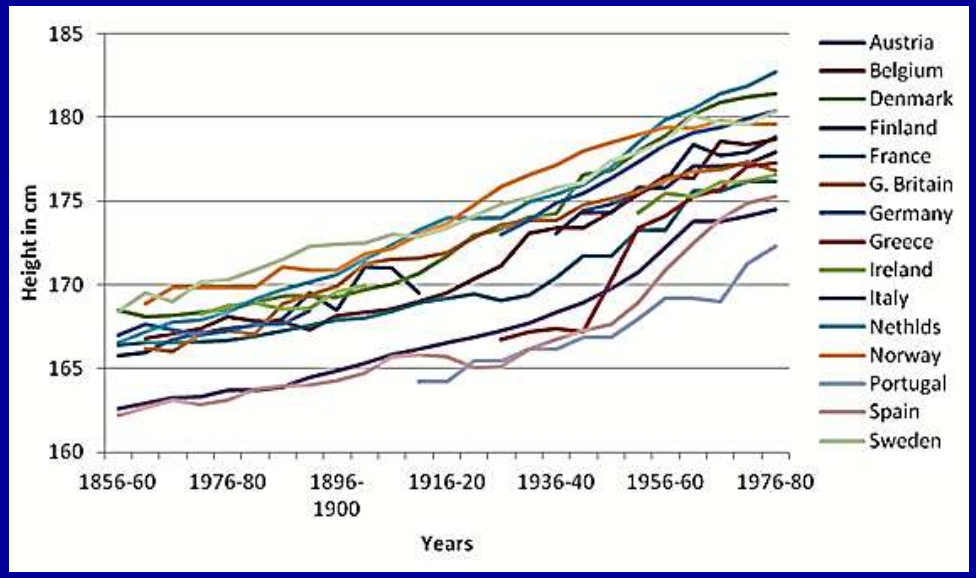


Forceps Minor

# Thing 7. Brain to Cognition & Back Again and Again

# Genes + Environment

- Antiquated notion: G <u>or</u> E, nature or nurture
- e.g., human height: 90% heritable
- Increased immensely over last century
- It's G + E!



# Brain Plasticity Across A Lifetime

# Can Cognitive Treatments Change The Brain? In infants? In adults?

Yes; see Early Start Denver Model

Yes; for less severe ASD.

Intervention is lifelong.

Progress can be lifelong.

# EIBI Changes Brain in Toddlers

# 5. Hope for Reversing Autism

By Alice Park | Dec. 04, 2012 | 2 Comments

GETTY IMAGES

In encouraging news for parents of autistic children, researchers say early behavior therapy can help normalize brain patterns responsible for the symptoms of the condition. Children diagnosed with autism spectrum disorders who participated in the Early Start Denver Model program, which involves intensive social and linguistic engagement with toddlers, showed changes in the way their brains process human faces and objects. Autistic youngsters generally show more brain activity when they view images of an inanimate object like a toy than when they see a picture of a woman's face. But after two years of ESDM therapy, the autistic children showed the opposite response, and these patterns came close to mimicking those found among normally developing children. It's a hopeful sign that it's possible to halt some of the brain changes linked to autism and possibly even reverse them. But the key to the program's success involves early and intensive intervention with properly trained counselors who actively engage the toddlers in several hours of therapy a week.

# Evidence-Based Cognitive Rehabilitation to Improve Functional Outcomes for Adults with Autism Spectrum Disorders

Shaun M. Eack, Ph.D.

Nancy J. Minshew, M.D.

University of Pittsburgh

# Background

- Autism spectrum disorders are characterized by core brain-based impairments in information processing
- Cognitive impairments make the transition to adulthood particularly challenging
- Few interventions exist that successfully target core information processing deficits, and even fewer in adults
- Cognitive rehabilitation has repeatedly shown success at addressing brain-based cognitive impairments:
  - Stroke
  - TBI
  - Alzheimer's
  - Schizophrenia
  - Autism Spectrum Disorder?

# Cognitive Rehabilitation Strategies

- Based on secondary learning
- Learning while doing
- Makes automatic processes explicit with hope that they shift to being automatic
- Target core deficits

# Objectives

- Examine the impact of Cognitive Enhancement Therapy on functional outcome
- Examine the impact of Enriched Supportive Therapy on functional outcome
- Compare the effectiveness of Cognitive Enhancement Therapy vs. Enriched Supportive Therapy
- Examine the neural underpinnings of response

# Design of Trial

- Randomized controlled trial
- 1:1 random assignment to CET or EST
- Treated for 18 months
- Followed post-treatment for 12 months
- Quality of life, functioning, cognitive, and behavioral outcome assessment every 9 months
- Neuroimaging assessments at study baseline and 18 months
- 30 month durability assessment

# Design

- 54 adults with ASD (ADI + ADOS)
  - Autism
  - Asperger's Syndrome
  - PPD-NOS
- Age – 17-45
- "High Functioning" – verbal, IQ > 80
- Significant social and cognitive disability
- Inclusive of those with "comorbid" disorders

# Cognitive Enhancement Therapy

- Aim: To help improve thinking and social wisdom (social cognition)
- Two parts:
  - Neurocognitive Training – Computer-based training in attention, memory, and problem-solving (pairs)
  - Social-Cognitive Groups – Training in perspective-taking, gistfulness, non-verbal communication, emotion perception, and more (small group)
- Conducted in a small group (6-8) individuals with a skilled CET therapist/coach

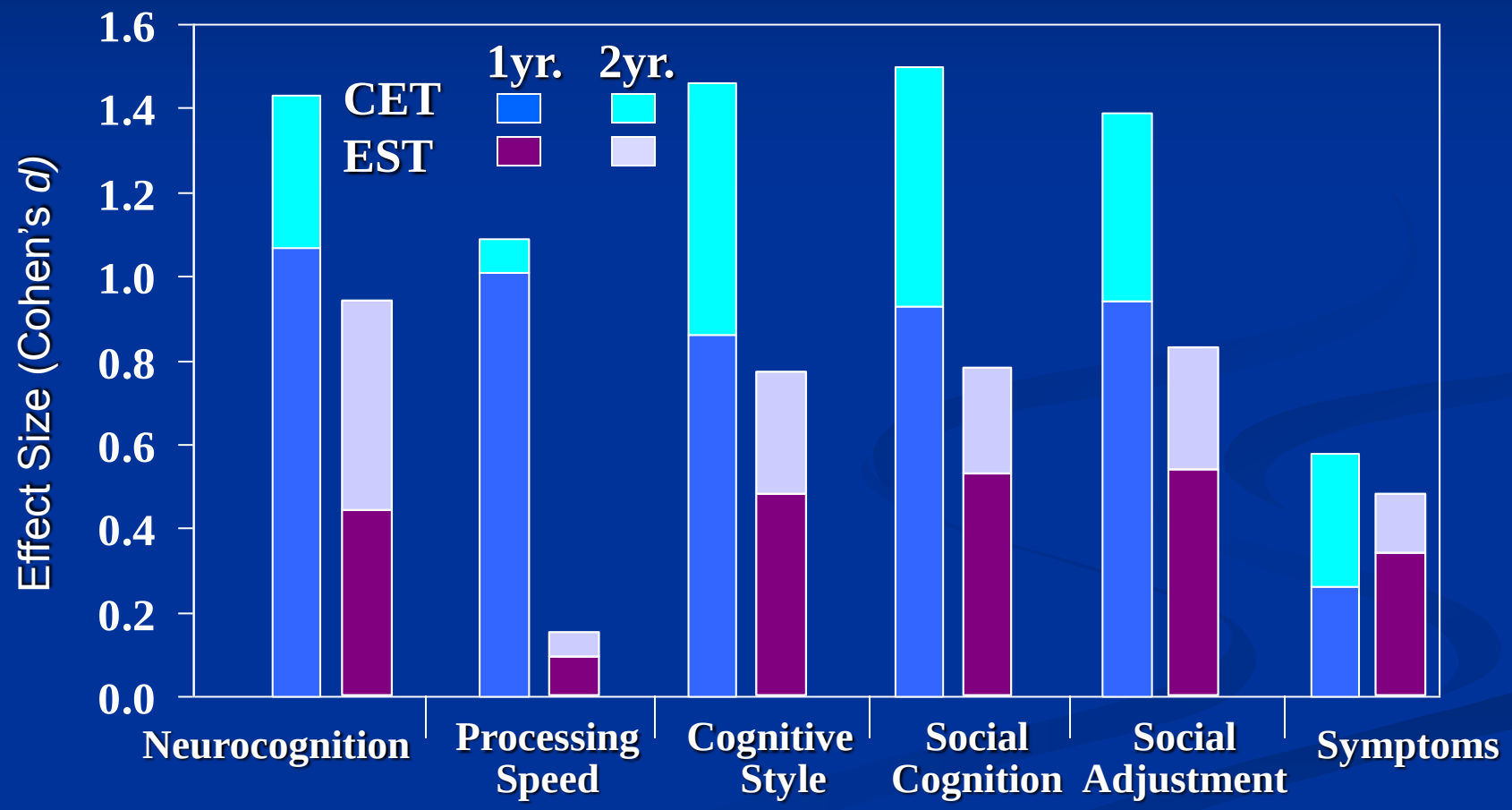
# Enriched Supportive Therapy

- Aim: To help prevent the meltdown
- Teaches individuals:
  - About autism spectrum disorders
  - How to manage emotions and stress
  - How to improve social skills
  - Cope with everyday problems and changes
- Individual therapy approach with a skilled EST therapist

# Best Practices

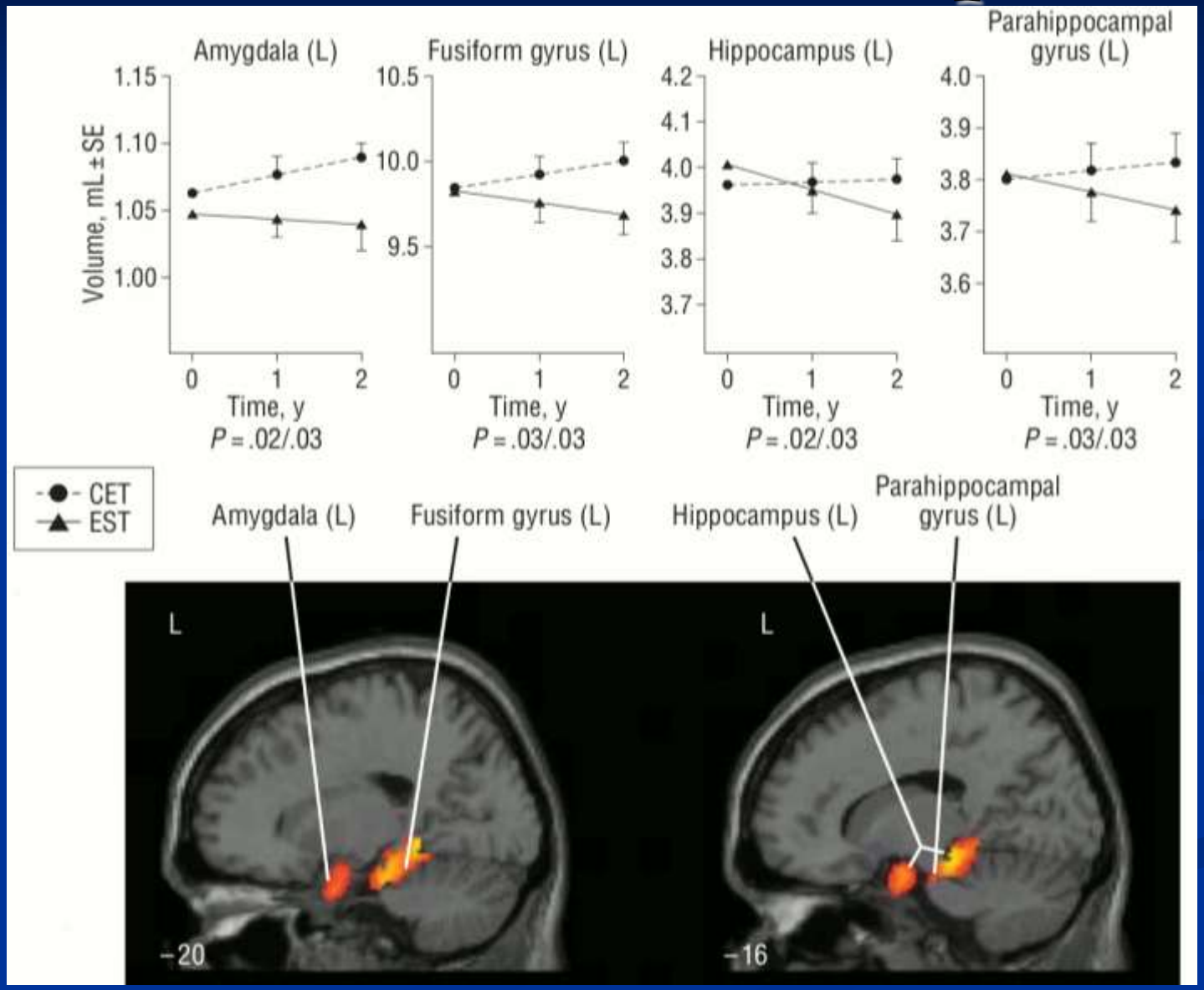
- Cognitive Enhancement Therapy
  - Targeted to the cognitive and neural deficits observed in the disorder
  - Uses evidence-based cognitive rehabilitation established in schizophrenia
- Enriched Supportive Therapy
  - Targeted to remediating the emotional disturbances of autism
  - Uses evidence-based cognitive-behavioral therapy methods established in many conditions

# CET Effects in Schizophrenia



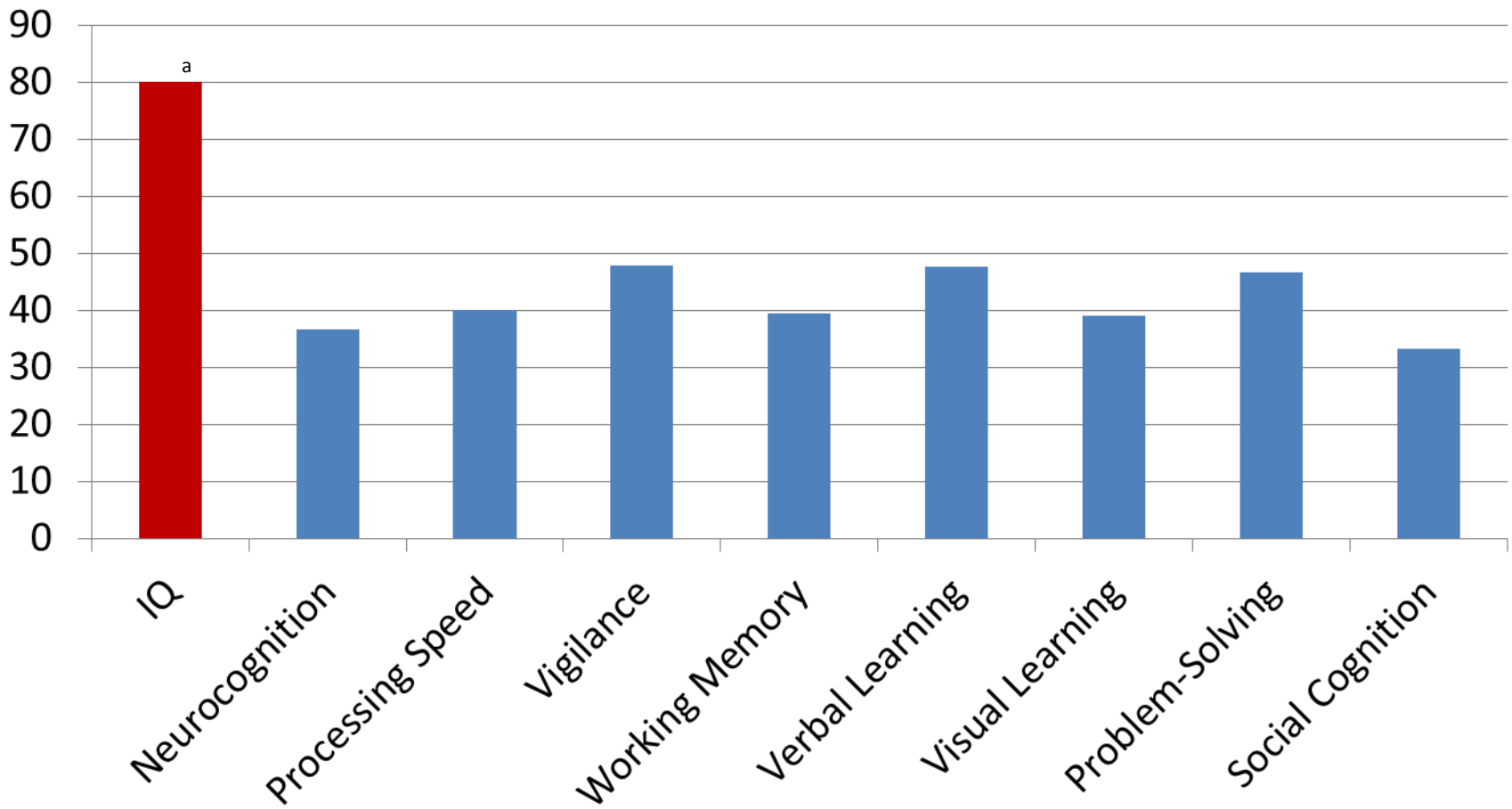

Hogarty et al., 2004. *Arch Gen Psychiatry.* 61:866-876.

# CET Effects in Schizophrenia




Eack et al., 2010. *Arch Gen Psychiatry* 67:674-682.

# Cognition vs. IQ in Adult ASD




Eack et al., under review

[a]Percentile Scores, *N* = 41

# Early Results

- CET is as effective for ASD as for schizophrenia and more effective than EST
- Active ingredients of CET: increased speed of processing and perspective taking

# Recommendations/Implications

- Likely to reduce a significant amount of disability in this population
- Will contribute to increased work and improved relationships.
- Efficacy in two major neuropsychiatric disorders is a first.
- Implies that a domain approach across disorders will be effective.