Understanding ASD in the 21st Century

ICDL Conference

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November 6, 2009

Autism Spectrum Disorder
DSM-V Coming 2012

- Note ASD
- Continue to be behaviorally based
- No separate category for cases due to underlying conditions such as tuberous sclerosis, NF, fragile-x syndrome, PTEN, metabolic disorders, etc
- Practical implications for screening for associated disorders: when and why to do scans, blood & urine; ATN is developing PCP friendly guidelines

Brain Affected Broadly in ASD

From the beginning

Many domains, not one

A Disorder of Brain Connectivity

Underdevelopment of network connections

Excess local connections

Latest Specification of Brain Neurobiology

Autism is a disorder of connectivity
of *cortical neurons*.

20-25 Genes Identified So Far
More As We Speak

Share mechanisms for connecting neurons together

A Molecular Pathophysiology Emerges

With this, comes the beginning of biologic interventions targeting mTor, which is in clinical trials for MR, Seizures, & ASD secondary to overgrowth disorders like TS.

More Accurate Understanding of Brain & Cognitive Mechanisms Also Brings New Interventions

- Cognitive Enhancement Therapy for adults
- Griebles: building integration skills in the mind & connections in the brain of 10-15 year olds
- Iconz: all ages, broader ability; building functional capacity and thinking in daily life
- Coming soon: new approach to early intervention & approaches to emotion regulation

Pathophysiologic Sequence of Neurodevelopmental Disorders

Abnormalities in Genetic Code for Brain Development

↓

Abnormal Mechanisms of Brain Development

↓

Structural and Functional Abnormalities of Brain

↓

Cognitive & Neurological Abnormalities

↓

Behavioral Syndrome

BRAIN AFFECTED BROADLY in ASD

From the beginning

Many domains, not one

Common Principles of Neurology

- Brain disturbances produce a constellation of cognitive & neurologic deficits, not a single deficit
- The constellation & mode of presentation reflect the underlying brain mechanism and its location
- Vascular, infectious, traumatic, autoimmune, developmental-maturational-degenerative

Discriminant Function Analysis: Domains Without Deficits[3]

Domain	Tests Passing Tolerance	Percent Correct	Kappa[1]
Attention	Letter Cancellation; Number Cancellation	66.70	0.33
Sensory Perception	Finger Tip Writing; Luria-Nebraska Sharp/Dull Tactile Scale item	64.40	0.29
Simple Language	K-TEA Reading; K-TEA Spelling WRMT-R Attack; Controlled Oral Word Association	71.20	0.42[2]
Simple Memory	CVLT Trial 1	65.20	0.30
Visuo-Spatial	WAIS-R Block Design	56.10	0.12

[1]Kappa below .40 indicates poor agreement beyond chance
[2]Significant *Kappa* reflects superior performance by autistic subjects
[3] Based on 33 individually age, IQ, gender matched pairs of subjects

Discriminant Function Analysis[1]: Domains With Deficits

Domain	Tests Passing Tolerance	Percent Correct	Kappa
Motor	Grooved Pegboard; Trail Making A	75.80	0.52
Complex Language	K-TEA Reading Comprehension; Verbal Absurdities; Token Test	72.70	0.45
Complex Memory	Nonverbal Selective Reminding-Consistent Long Term Retrieval; WMS-R Story Recall-Delayed Recall; Rey-Osterrieth Figure-Delayed Recall	77.30	0.55
Reasoning	20 Questions; Picture Absurdities; Trail Making B	75.8	0.52

[1]Based on 33 individually matched pairs of autistic & control subjects (Neuropsychologic Functioning in Autism: Profile of a Complex Information Processing Disorder, *JINS*, 3:303-316, 1997)

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

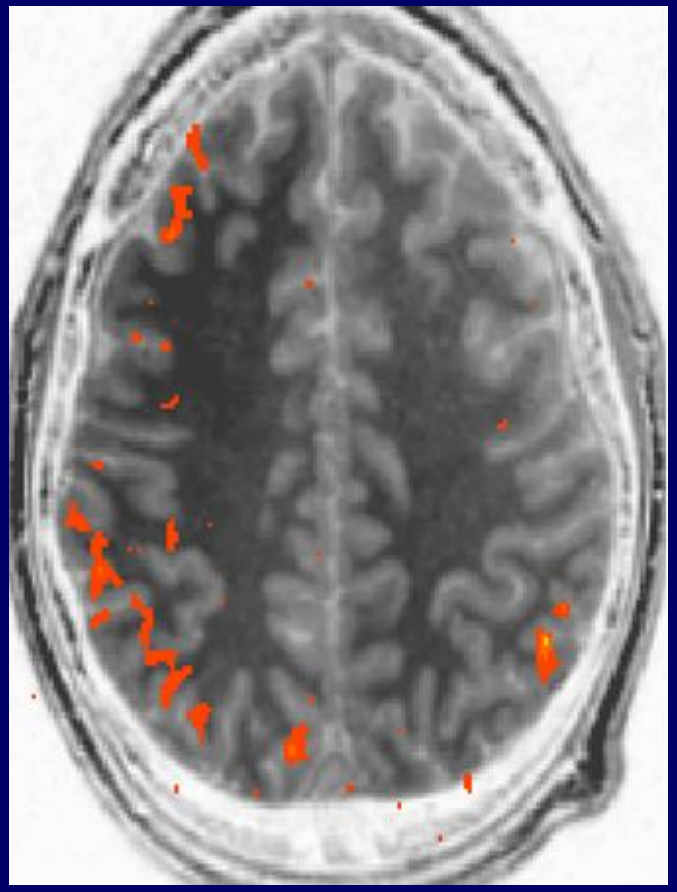
- Complex Sensory
- Complex Motor
- Complex Memory
- Complex Language
- Concept-formation
- Face Recognition

What Does The Profile Mean?

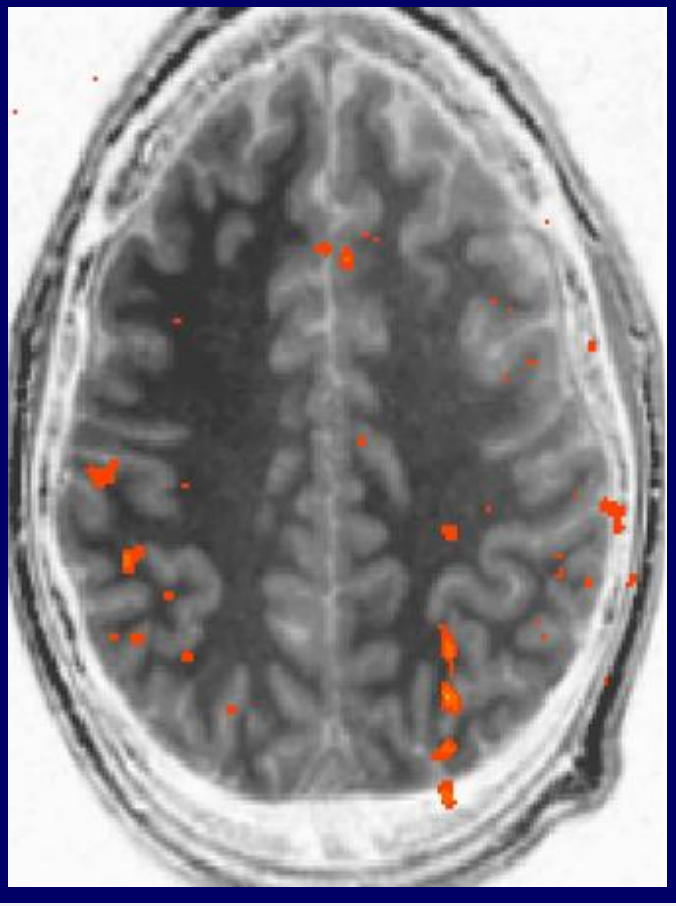
- Simpler abilities are intact or enhanced
- Information processing capacity is limited- & integrative processing & higher order cognitive abilities are disproportionately impaired

  Inference: higher order brain circuitry is under developed- they are reliant on lower order circuitry particularly visual circuitry to function.

fMRI Activation During a Spatial Working Memory Task (Courtesy John Sweeney)



Healthy Group



Autism Group

- Solid line for autistic subjects, broken line for control subjects. In the last three panels, difficulty emerges as platform motion is introduced and demand placed on multi-sensory integration; development delayed and failure to achieve adult levels.

BRAIN AFFECTED BROADLY in ASD

Cortical-Cortical Connections
Cortical-amygdala
Cortical-striate
Growth dysregulation at other critical ages

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

- 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

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

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.

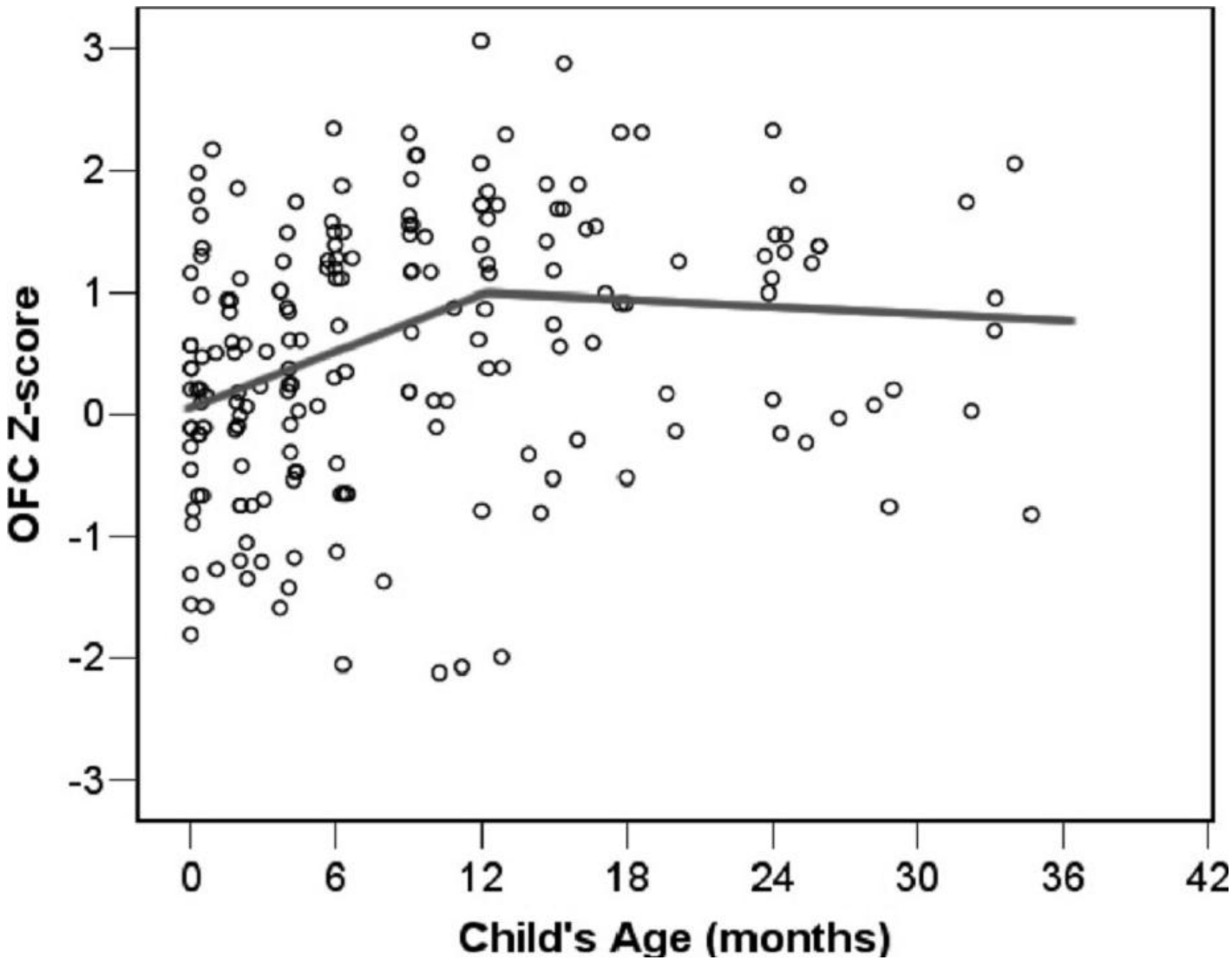


Figure 2. Occipital–frontal (OFC) *Z* score measurements (*N* 195) with mean estimated growth trajectory for 28 children with autism spectrum disorder (hierarchical linear model two-piece linearmodel centered at 12 months).

What is happening in the brain in infant sibs?

How do neurologists analyze this presentation and this broad profile of impairments and enhanced abilties?

Common Principles of Neurology

- Brain disturbances produce a constellation of cognitive & neurologic deficits, not a single deficit
- The constellation & mode of presentation reflect the underlying brain mechanism and its location
- Vascular, infectious, traumatic, autoimmune, developmental-maturational-degenerative

Developmental Neurobiologic Processes

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

A Disorder of Brain Connectivity: al Profile Results From

Underconnectivity of cortical networks

Excessive local connections

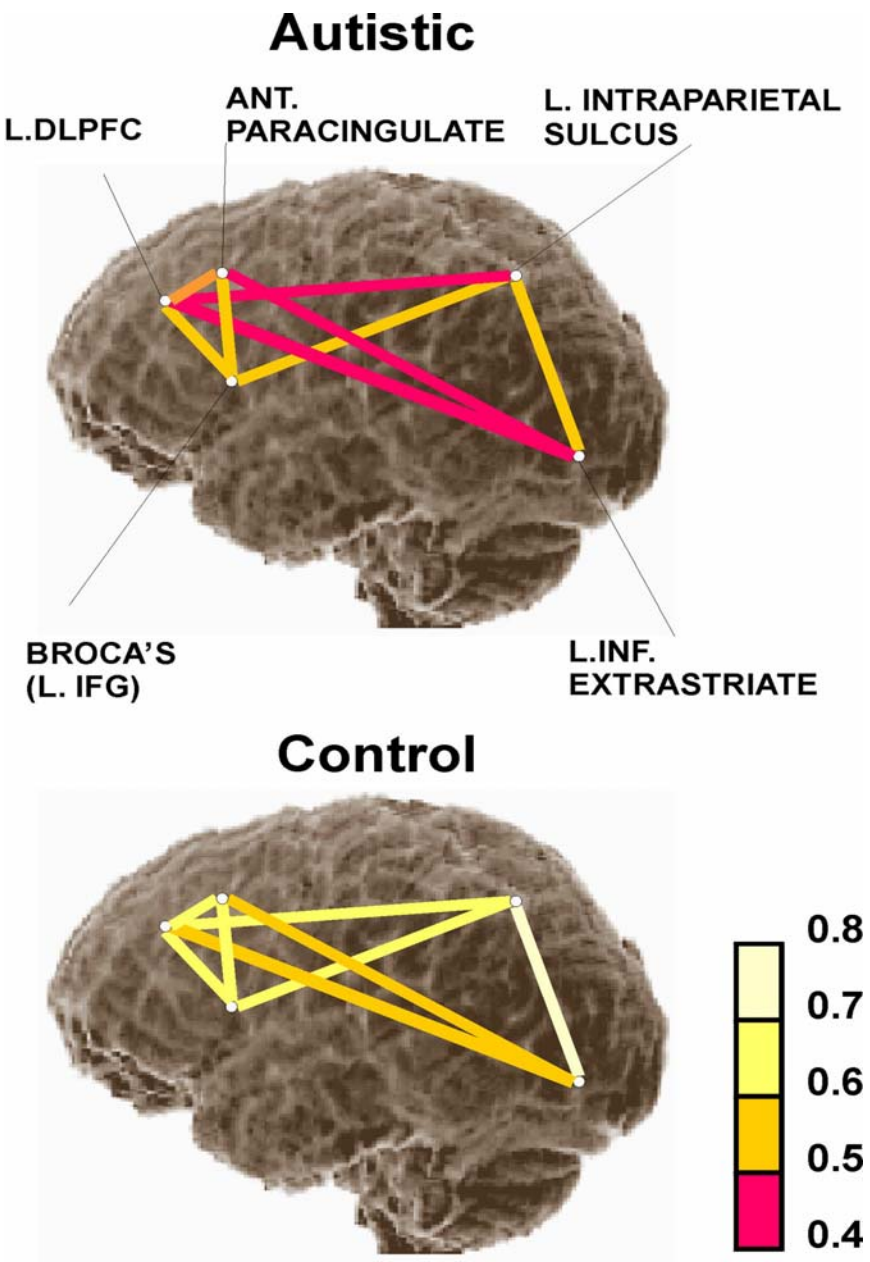
Cortical activation & synchronization during sentence comprehension in HFA subjects

Marcel Just
Vlad Cherkassky
Tim Keller
Nancy Minshew

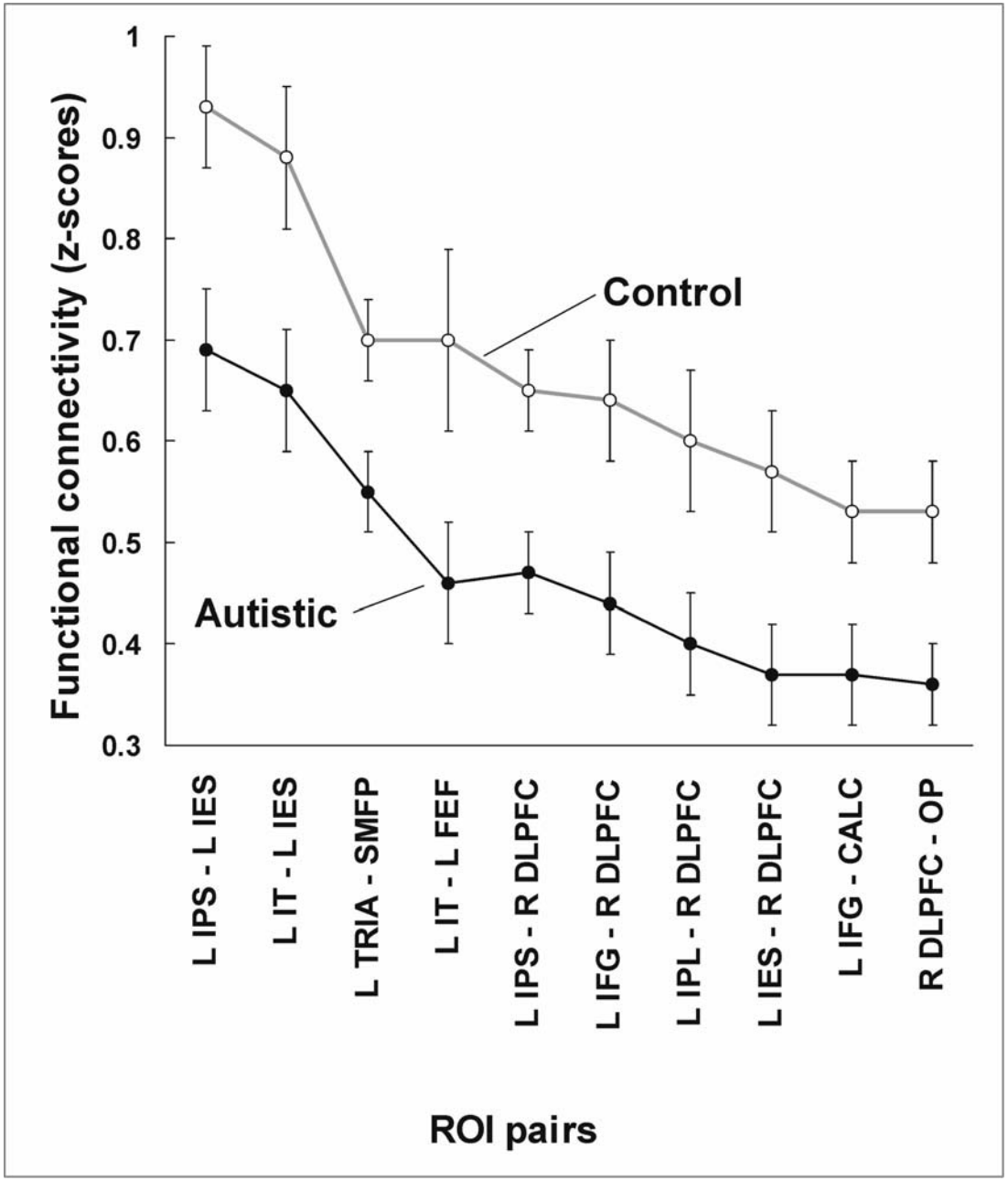
Center for Cognitive Brain Imaging
Carnegie Mellon

Just et al. 2004, Brain 127: 1811-1821

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



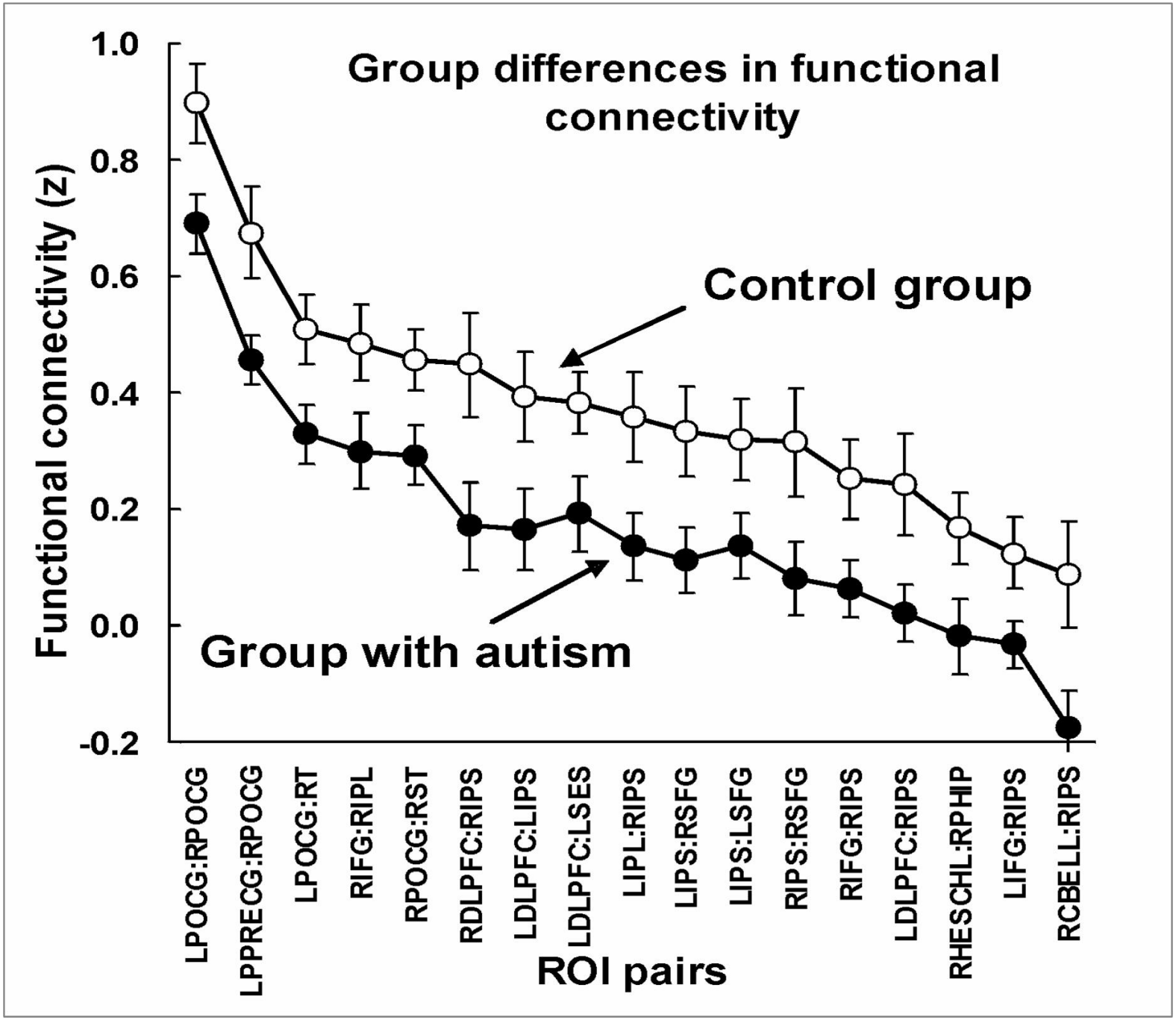
Reliable differences in functional connectivity: autism group has lower functional connectivity but same rank order



Functional Underconnectivity: fMRI of the Tower of London

Marcel Just
Nancy Minshew
Tim Keller
Vlad Cherkassky
Rajesh Kana

Just et al., 2006 [Epub ahead of print], Cereb Cortex


Group differences in functional connectivity
Functional connectivity (z)
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
Control group
Group with autism
LPOCG:RPOCG
LPPRECG:RPOCG
LPOCG:RT
RIFG:RIPL
RPOCG:RST
RDLPFC:RIPS
LDLPFC:LIPS
LDLPFC:LSES
LIPL:RIPS
LIPS:RSFG
LIPS:LSFG
RIPS:RSFG
RIFG:RIPS
LDLPFC:RIPS
RHESCHL:RPHIP
LIFG:RIPS
RCBELL:RIPS
ROI pairs

How Does the Brain Classify Words?

- Encoding by the brain is distributed- involves multiple brain regions- leads to flexibility
- Each word encoded according to five attributes:
  - Eating
  - Shelter
  - Manipulation
  - Number of characters in the word
- First studies completed in adults; studies in children will guide early intervention- Carol Gray has discovered this already

20-25 Genes Identified So Far
More As We Speak

Share mechanisms for connecting neurons together

Mechanisms are basis of intervention

The Autism Genome Project (AGP)

- Large-scale, collaborative genetics research project
- To identify genetic factors underlying autism
- Involves researchers from over 50 centres in the USA, Europe, and Canada
- AGP members published more than 200 peer-reviewed manuscripts on autism since 2003

www.autismgenome.org

Autism Genome Project

Autism is a **complex genetic disorder**. The identification of autism risk factors requires **large samples** of well-characterized individuals, & strong scientific cooperation between clinical & laboratory researchers.

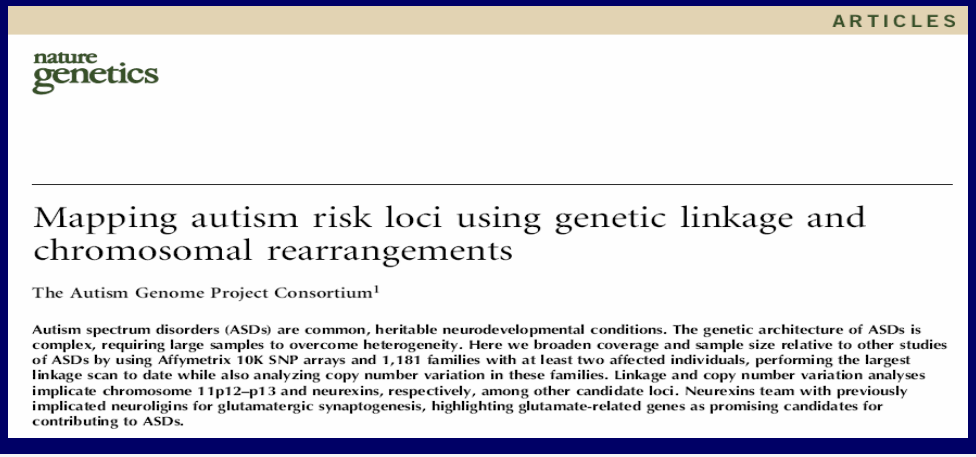
AGP was initiated to **pool resources**, & clinical & scientific expertise. The clinicians & scientists of the AGP embody the phenotypic, statistical, molecular, & functional expertise needed to define the **genetic architecture of autism.**

AGP Phase I:

Assembled world's largest autism gene bank & completed world's most comprehensive genome scan

AGP Phase I – Affymetrix 10K SNP Array

- Linkage scan – over 1400 families
- Copy Number Variations (CNVs) low resolution
- Nat Genet. 2007 Mar;39(3):319-28



ARTICLES

nature genetics

Mapping autism risk loci using genetic linkage and chromosomal rearrangements

The Autism Genome Project Consortium[1]

Autism spectrum disorders (ASDs) are common, heritable neurodevelopmental conditions. The genetic architecture of ASDs is complex, requiring large samples to overcome heterogeneity. Here we broaden coverage and sample size relative to other studies of ASDs by using Affymetrix 10K SNP arrays and 1,181 families with at least two affected individuals, performing the largest linkage scan to date while also analyzing copy number variation in these families. Linkage and copy number variation analyses implicate chromosome 11p12–p13 and neurexins, respectively, among other candidate loci. Neurexins team with previously implicated neuroligins for glutamatergic synaptogenesis, highlighting glutamate-related genes as promising candidates for contributing to ASDs.

AGP Phase II Study Design

AGP Phase II – Illumina 1M

- Genome-Wide Association Scan (GWAS)
- 3,000 families (1,500 complete)
- Mito-analysis

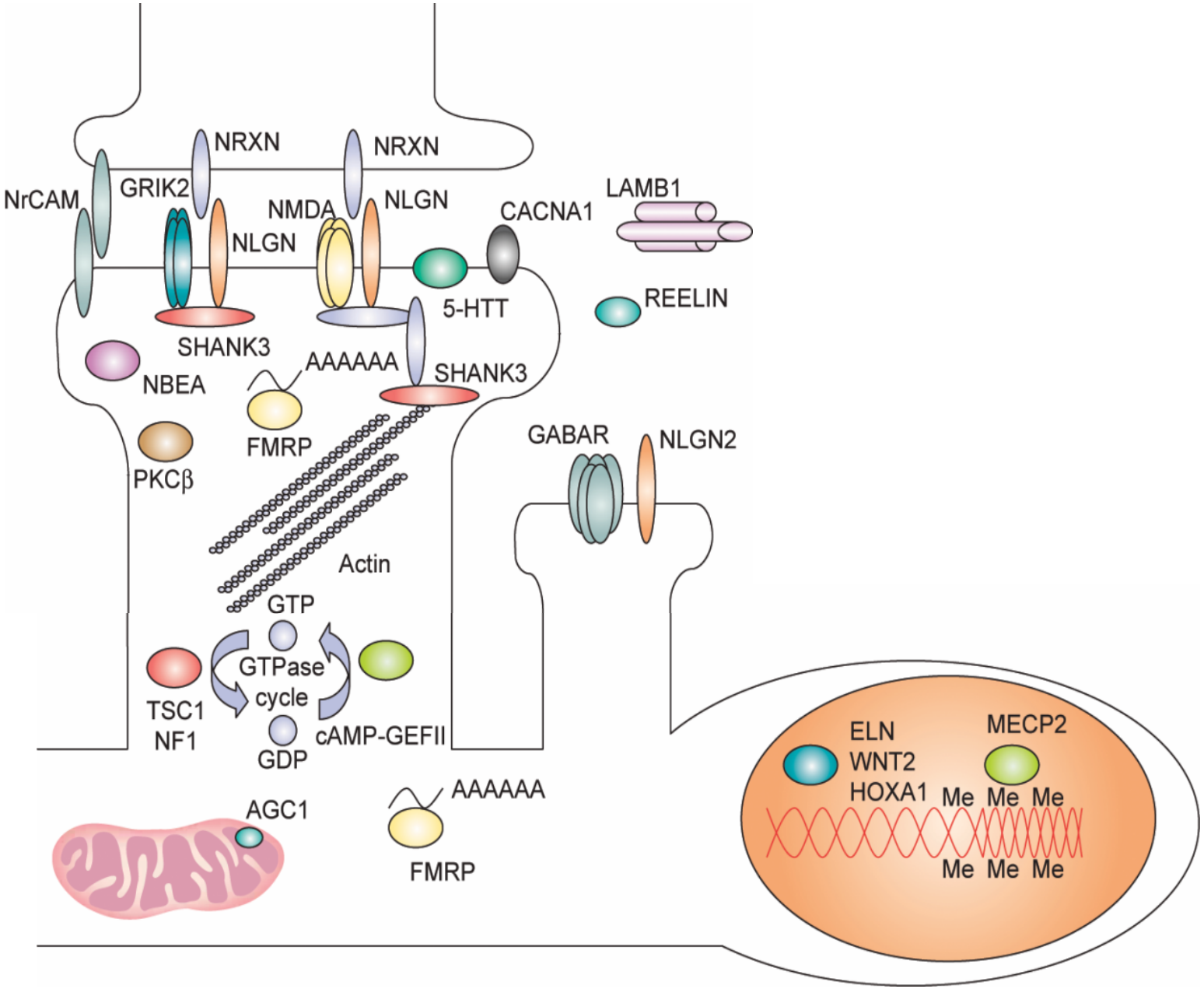
→ **High-resolution CNV scan**

Subsequent goals: analysis of **trait-based subsets** of autism for genotype-phenotype relationships, fine-mapping of linkage regions identified in AGP Phase I; and more in-depth evaluation of **candidate genes**.

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.

But tend to have one thing in common: are involved in determining **where and how brain cells (neurons) are connected and talk to each other**.


NRXN
NRXN
NrCAM
GRIK2
NMDA
NLGN
NLGN
CACNA1
LAMB1
5-HTT
REELIN
SHANK3
SHANK3
AAAAAA
NBEA
FMRP
PKCβ
GABAR
NLGN2
Actin
GTP
GTPase
cycle
TSC1
NF1
GDP
cAMP-GEFII
AGC1
AAAAAA
FMRP
ELN
WNT2
HOXA1
MECP2
Me Me Me
Me Me Me

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.

A Molecular Pathophysiology Emerges

With this comes the beginning of biologic interventions

A Molecular Pathophysiology Emerges

- Definition of molecular mechanisms-how and why things go differently at the molecular level empowers a new world of interventions

- mTor inhibitors prevent development of seizures in tuberous sclerosis; these clinical trials continue: will this drug prevent development of mental retardation and ASD in TS? (rapamycin)

More Accurate Understanding of Brain & Cognitive Basis Brings New Interventions

- Cognitive Enhancement Therapy for adults
- Griebles: building integration skills in the mind & connections in the brain of 10-15 year olds
- Iconz: all ages, broader ability; building functional capacity and thinking in daily life
- Coming soon: new approach to early intervention & approaches to emotion regulation

Cognitive Enhancement Therapy

- A cognitive rehabilitation intervention for remediating neurocognitive and social-cognitive deficits developed by Hogarty and colleagues (2004, 2006).
- Neurocognitive Training
  - Computer-based training in attention, memory, and problem-solving.
  - 1 hour/week
  - 60 hours total
- Social-Cognitive Group Therapy
  - Training in perspective-taking, gistfulness, non-verbal communication, emotion perception, and much, much more.
  - 1.5 hours/week
  - 45 sessions
- More information and CET Training Manual (Hogarty & Greenwald, 2006) at www.CognitiveEnhancementTherapy.com

Goals of CET

I. *Foster Higher Thinking By Becoming*:

Gistful	vs.	Concrete
An Active Thinker	vs.	Passive Receiver of Information
Cognitively Flexible	vs.	Following Rigid Rules
More Spontaneous	vs.	Rehearsed
More of an Initiator	vs.	Doing Nothing

Goals of CET con't.

II. Help to develop:

- Social Wisdom (norms and rules of behavior)
- Context Appraisal (what is going on)
- Perspective Taking (how others feel, think and respond)
- Foresightfulness (If I do this ..., then ...)
- Empathy and Support (being reciprocal)
- Social Comfort

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)

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.