ASD in the 21st Century

Wesley Spectrum Services
Night for Autism

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Director NIH Autism Center of Excellence

Pittsburgh, PA
November 2010
Autism Spectrum Disorder
DSM-V Coming 2012

- Continue to be behaviorally based
- Integration of broad impact?
- 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
Autism is a disorder of connectivity of cortical neurons.
Share mechanisms for connecting neurons together
With this, comes the beginning of biologic interventions like 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
1. Spontaneous Mutations: Increased rate of "de novo" copy number variations: submicroscopic deletions or duplications of DNA sequences. More common in simplex than multiplex families. Opened door to two genetic mechanisms: inherited gene mutations and spontaneous copy number mutations—instability in replication of DNA.

2. Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes) in adult mice.

**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
Discriminant Function Analysis: Domains Without Deficits

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

\(^1\)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 Analysis¹: Domains With Deficits

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

¹Based 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

<table>
<thead>
<tr>
<th>Intact or Enhanced</th>
<th>Cognitive Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Complex Sensory</td>
</tr>
<tr>
<td>Sensory Perception</td>
<td>Complex Motor</td>
</tr>
<tr>
<td>Elementary Motor</td>
<td>Complex Memory</td>
</tr>
<tr>
<td>Simple Memory</td>
<td>Complex Language</td>
</tr>
<tr>
<td>Formal Language</td>
<td>Concept-formation</td>
</tr>
<tr>
<td>Rule-learning</td>
<td>Face Recognition</td>
</tr>
<tr>
<td>Visuospatial</td>
<td></td>
</tr>
</tbody>
</table>
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)
What Are Infant Siblings Teaching Us About Autism in Infants?

- 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

- 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
- Less mouthing of objects - less vocalizations
- Truncal instability when sitting
Developmental Characteristics of Infant Sibs

- 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

- No social signs at 6 mos - 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
Lack of behavioral markers at 6 mos, earliest differences are subtle, involve a few behaviors or small differences

Socially normal at 6 mos

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
“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.
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 linear model centered at 12 months).
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
How the Brain Develops

- 15 1/2 wks
- 22 weeks
- 23 weeks
- ~25 weeks

- 27 weeks
- Full term brain
- Adult
How the Brain Develops

A  One month old
B  Six month old
C  24 month old
How the Brain Develops

A  One month old

B  Six month old

C  24 month old
Minicolumnar pathology in autism

Manuel F. Casanova, MD; Daniel P. Buxhoeveden, PhD; Andrew E. Switala; and Emil Roy, PhD
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

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

Control group

Group with autism

Functional connectivity (z)

ROI pairs

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 intervention
Share mechanisms for connecting neurons together
Mechanisms are basis of intervention

20-25 Genes Identified So Far
More As We Speak
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 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.

The AGP was initiated to pool resources, & clinical and scientific expertise. The clinicians & scientists participating in 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

Mapping autism risk loci using genetic linkage and chromosomal rearrangements
The Autism Genome Project Consortium

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 chromosomes 1q21-22 and 7q11.23 and neurexin, respectively, among other candidate loci. Neurexin teams with previously implicated neurotrophins 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

Paper due out before end of year.

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.
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.
Axonal Pathfinding and Targeting:
-- Cadherins
-- LRRs

Synaptic Targeting and Function:
-- Neurexins/Neuroligins

Dendritic Morphology/Function:
-- SHANKs

Adapted from www.morphonix.com
1. Genes whose products affect **axon 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.
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)
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.
Synaptic Targeting and Function:
-- Neurexins/Neuroligins

Axonal Pathfinding and Targeting:
-- Cadherins
-- LRRs

Dendritic Morphology/Function:
-- SHANKs

Adapted from www.morphonix.com
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)
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 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 ± SEM and were analyzed by ANOVA, followed by post hoc \( t \) test.
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
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

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
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)
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

Aversion to Faces? → Whole is more than sum of parts!

Greeble Intervention – Learning to Integrate the Elements
We wish to honor those individuals and families who have believed in research and been committed to participating again and again.