The Neurologic Basis of Behavior in ASD: Implications for Learning & Intervention

Orange County, CA
September 26, 2008

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Verbal individuals 5-45 years with autism, Asperger disorder, NOS, or PDD, IQ 80-120, speaking in sentences, some medication restrictions

No costs for tests; participant payment; airfare & hotel paid; report on test results

Through 2012

Autismrecruiter@upmc.edu
Pervasive Developmental Disorders (DSM)  
*Autism Spectrum Disorders (Informal)

DSM-IV (1994): Pervasive Developmental Disorders
-  *Autistic Disorder
-  *Asperger’s Disorder
-  *Pervasive Developmental Disorder NOS
-  Childhood Disintegrative Disorder
-  Rett’s Disorder
# Prevalence 1/166
## 2002-2006

<table>
<thead>
<tr>
<th>Description</th>
<th>Baird(^1)</th>
<th>Chakrabarti &amp; Fombonne(^2)</th>
<th>Brick Township, NJ(^3)</th>
<th>Chakrabarti &amp; Fombonne(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>30.8/10,000</td>
<td>16.8/10,000</td>
<td>40.5/10,000</td>
<td>22.0/10,000</td>
</tr>
<tr>
<td>Other ASDs</td>
<td>27.1/10,000</td>
<td>45.8/10,000</td>
<td>26.9/10,000</td>
<td>36.7/10,000</td>
</tr>
<tr>
<td>Total for ASDs</td>
<td>57.9/10,000</td>
<td>62.6/10,000</td>
<td>67.4/10,000</td>
<td>58.7/10,000</td>
</tr>
<tr>
<td>Total for ASDs</td>
<td>1/170</td>
<td>1/170</td>
<td>1/150</td>
<td>1/170</td>
</tr>
</tbody>
</table>

\(^1\) Baird et al, 2000  
\(^2\) Chakrabarti & Fombonne, 2001  
\(^3\) Bertrand et al, 2001  
\(^4\) Chakrabarti & Fombonne et al, 2001
Prevalence 1/150  
February 2007

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>60/10,000</td>
<td>38.9/10,000</td>
<td></td>
</tr>
<tr>
<td>Other ASDs</td>
<td>48/10,000</td>
<td>77.2/10,000</td>
<td></td>
</tr>
<tr>
<td>Total for ASDs</td>
<td>108/10,000</td>
<td>116.1/10,000</td>
<td>66/10,000</td>
</tr>
<tr>
<td>Total for ASDs</td>
<td>1/100</td>
<td>1/100</td>
<td>1/150</td>
</tr>
</tbody>
</table>

\(^1\)Kadesjo et. al. JADD Vol. 29 No. 4 327-331  
\(^2\)Baird et al, The Lancet 368; 210-215 2006  
\(^3\)ADDM Network, MMWR Feb 9, 2007; 12-28  
\(^4\)This number was 20/10,000 in 1980
The Changing Face of Autism

- The full spectrum within autism
- Kanner originally described a full range of severity all the way from the ‘form fruste to those who were profoundly affected
- All shared the same qualitative features
- By the 70’s, the top high of autism lost and the lowest also lost in practice
**Broadening of Severity Spectrum Brought Recognition of Other ASDs**

- As severity spectrum of autism re-expanded, it became clear that there were variations from autism but still the same quality of deficits.
- Asperger’s Disorder: no delayed development of language and no mental retardation.
- PDDNOS: symptoms not as severe for IQ as autism or not present in the communication and repetitive behavior domains as in autism.
General level of function, FS IQ, VIQ, Vineland
Language comprehension level, communication
Flexibility-rigidity
Impulsivity, overactivity, inattentive
Redirectability, motivation
Social-emotional age, social tolerance
Sensory issues
Problem solving: identifies problems, planning, identifies failure, changes strategies, asks for help
INTERVENTION CHECKLIST:
Person Factors Cont’d

- Temperament
- Mood lability
- Aggression
- Seizures
- Tolerance of change (flexibility), rituals
- Obsessions, preoccupations, special interests
INTERVENTION CHECKLIST:
Environment Factors (All)

- Environmental structure/order/chaos
- Environmental noise, visuals, smells
- Autism skills of teachers; attitude of teacher
- Expectations of child=child abilities?
- Peer or adult bullying
- Transitions, lunchroom, playground, hallways, bus
- Changes in schedule, teachers, rooms, peers, etc
Quick Diagnosis of ASD in Verbal Individuals

- Strange or odd, reflecting social impairment
- Monotone voice, little to no facial expression
- Upset by change, rituals for doing things in set ways; little scripts; evolves into obsessions
- Obsessions w/ focus on facts or collections; memory for detail superb
- Clumsy, awkward
Most severe: essentially mute, no comprehension, no prosody, no adaptive behavior, attends to details. Direct care staff knows who has autism vs non-autism MR because deficits disproportionate for IQ

Intermediate severity: echolalia, few scripted stereotyped sentences; socially isolated; approach for needs only; self-stimulatory behavior; no imaginative play- odd play; difficulty with change; sensory issues
Brain disorders produce distinctive constellations of cognitive [thinking abilities] & neurologic [brain abilities] deficits, NOT a single deficit

Multiple organ involvement is the rule in brain disorders not caused by brain damage- because they are caused by faulty genes and these genes are present in every cell in the body; they are selectively expressed in the brain and in the body
2.27 relative risk of autism diagnosis conferred by the CC genotype at MET receptor tyrosine kinase. MET signaling is involved in neocortical and cerebellar development, immune function, and gastrointestinal repair, consistent with the multi-organ symptoms reported in autism.

Need not invoke GI or immune disease as causing brain dysfunction; same gene may cause all.

Campbell et al. PNAS 2006, 45: 16834-16839
Neurologists’ approach to understanding brain dysfunction is therefore to examine all impaired AND intact abilities to identify common characteristics that define the underlying disease process or mechanism and its location in the brain.
Disease Processes or Mechanisms

- Infectious disease
- Vascular disease
- Tumor or mass
- Toxins
- Developmental processes
Developmental Processes

- Organogenesis (basic form of the nervous system)
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination
Most research has focused on a single domain as the cause of the syndrome often predicting focal brain deficits. We hypothesized a multiple primary deficit model and a distributed neural network or neocortical neural systems disorder. Interventions often do the same.
What do their cognitive strengths have in common?

What do their cognitive weaknesses have in common?

Answers to these questions provide insight into their thinking and the circuitry differences in the brain in autism.
## Discriminant Function Analysis: Domains Without Deficits

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa&lt;sup&gt;1&lt;/sup&gt;</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&lt;sup&gt;2&lt;/sup&gt;</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>

<sup>1</sup>Kappa below .40 indicates poor agreement beyond chance

<sup>2</sup>Significant Kappa reflects superior performance by autistic subjects

<sup>3</sup>Based on 33 individually age, IQ, gender matched pairs of subjects
### Discriminant Function Analysis¹: Domains With Deficits

<table>
<thead>
<tr>
<th>Domain</th>
<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)
<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>Elementary Sensory</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 processing</td>
<td></td>
</tr>
</tbody>
</table>
What Does This Mean About COGNITION?

- Information acquisition intact
- Simpler processing & abilities are intact/enhanced
- Selective impairment in complex information processing across domains e.g. tasks that require an increase in the number of cognitive processes or brain regions for task performance
Complex Information Processing Model

✓ Not a General Information Processing Disorder or both simple and complex abilities would be impacted

✓ Not a Simple Information Processing Disorder or individuals with ASD would have dyslexia, dyscalculia, and visuospatial problems (see SLI)

✓ Despite the title, this model also infers intact or enhanced basic skills. This is a two-part model, as distinguished from schizophrenia.
Jim was admitted for possible mania. He was agitated and had been sending money to television evangelists and became preoccupied with sin and being good, which he talked about constantly. The psychiatrists attempted daily to convince him to try lithium but he refused. His reason was that he took lithium on June 4, 1978 and he got a stomach ache. He went to the clinic and a scene ensued. Staff yelled at him. No amount of appeal worked to change his mind, until he was told and SHOWN there were now two forms of lithium - one was pink and one was blue. He took the bad blue before, but this time he would take the good pink. He immediately agreed to the medication. The deterioration in his behavior was the result of losing his job for asking a woman a question about her clothing, which was interpreted as sexual harassment. All structure was gone from his life. Socially-emotionally he was 3. He had been diagnosed since early childhood as having schizophrenia despite the absence of hallucinations.
Detroit Learning Aptitude Test: Another Lesson in the Impact of Processing Demands

![Bar graph showing scores for letter sequences, word sequences, and oral directions for Autism and Control groups. The graph indicates significantly different scores marked by an asterisk.]
### Dual task performance deficit in autism; *(but matched performance in single task conditions)*
Garcia-Villamisar & Della Sala, 2002 Cognitive Neuropsychiatry

#### Effect of dual task on memory span and tracking performance

<table>
<thead>
<tr>
<th>People with autism (n = 16)</th>
<th>Digit recall</th>
<th>Tracking performance</th>
<th>Mu score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>single</td>
<td>dual</td>
<td>single</td>
</tr>
<tr>
<td>Mean</td>
<td>86.19</td>
<td>&gt; 48.13</td>
<td>52.75</td>
</tr>
<tr>
<td>SD</td>
<td>7.55</td>
<td>16.77</td>
<td>10.47</td>
</tr>
<tr>
<td>Controls (n = 16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>87.25</td>
<td>= 86.88</td>
<td>54.06</td>
</tr>
<tr>
<td>SD</td>
<td>4.81</td>
<td>7.58</td>
<td>14.61</td>
</tr>
</tbody>
</table>

Digit recall is expressed as a percentage of correct sequences.
Simpler processing & abilities are intact/enhanced

Information processing capacity is limited-integrative processing & higher order cognitive abilities are disproportionately impacted

Inference: higher order circuitry is under developed-they are reliant on lower order circuitry & basic cognitive abilities to function.
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
<table>
<thead>
<tr>
<th>Abstract Reasoning: Concept Identification &amp; Concept Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 verbal individuals with autism &gt;12 yrs</td>
</tr>
<tr>
<td>107 control volunteers</td>
</tr>
<tr>
<td>Concept identification</td>
</tr>
<tr>
<td>Attribute identification</td>
</tr>
<tr>
<td>Rule-learning</td>
</tr>
<tr>
<td>Concept formation</td>
</tr>
<tr>
<td>Self-initiated strategy</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
</tr>
<tr>
<td>Extent to which these were dissociable skills</td>
</tr>
</tbody>
</table>
Results in Non-Retarded Autistic Individuals

- Concept identification intact:
  - Attribute identification
  - Rule learning

- Inflexible in applying rules in changing contexts

- Concept and strategy formation impaired

- Dissociable skills in autism but not in typical devt
This Dissociation in Abstraction Abilities Explains Developmental & Severity Features

- Rote training of concepts, first attributes then rules
- Difficulty generalizing outside original learning setting
- Rule-bound and difficulty considering context
- Difficulty in novel situations or any situation requiring spontaneous problem solving or strategy formation
- Do not acquire the concept formation abilities that allow flexible use of or development of new strategies in novel situations.
- No adaptive function or generalization of learned interventions to real life (changing/novel) circumstances.
- Multi-dimensional, on-line integration of information
Bill is a young adult with autism who decided to take figure skating lessons. His mother drove to the rink several times a week. After a while, she decided to skate while he had his lesson. Bill performed his routine, but people had to stay out of his way as he was not mindful of their space: he went where his program required him to go regardless of others. One day his mother forgot to note where Bill was and he ran her over, knocking her unconscious. The emergency team was called and she was given first aide and taken to the hospital. The next day she asked Bill why he did not come to her assistance, since he was an Eagle Scout with a first aide badge. He replied “It expired.”
Can’t rely on them to identify problems or ask for help- the first requires concept formation and the latter is a strategy and then requires social contact- which will also get people upset at their failure

Need a review of systems approach & a reporter

They will need external organizer & prioritization

May not be able to handle as much as others

Avoidance- the bathroom, their room; Denial-it’s fine; Flip out: or E for “everything” or “nothing”.

Related Executive Function Impairments: Adaptive Behavior
Measures for autistic subjects (circles) and control subjects (crosses) and locally smoothed curves (solid line for autistic subjects, broken line for control subjects). R-square for fits: 0.198 (SC3), 0.164 (SC4), 0.175 (SC5), and 0.170 (SC6).

In the last three panels, SC4-SC6, the difficulty emerges as platform motion is introduced. These panels demonstrate delayed development and a failure of the autism group to achieve adult levels.
Autism is defined on the basis of abnormalities in social, communication and imaginative play, and restricted interests-repetitive behavior.

The neuropsychologic and postural findings define deficits considerably beyond this triad, suggesting a more widespread but selective disturbance in information processing by the brain.

Williams et al. 2006, 12: 279-298
Social Emotional Immaturity: Disturbance in Affective Contact Not Included in DSM

- Capacity to experience, comprehend, and regulate emotions at a basic and cognitive level is severely impaired and unrecognized despite frequent abnormal imaging abnormalities of the amygdala, an emotion structure of the brain.
- Most verbal ASD adults are socially-emotionally 12-18 months to 4-5 years of age. Failure to recognize this in treatment worsens behavior.
- Group mean 60-70%
- Onset accelerated growth at 12 months w/ 15-20% macrocephaly by 4-5 years
- Growth decelerates and plateaus so that brain volume “normalizes” in childhood, though subset remain macrocephalic throughout life
- Important to recognize that HC>HT is not universal in autism and HC=HT and HC<HT growth trajectories compatible with autism
Increased Brain Volume in Autism: What does it Mean?

- Group TBV paralleled group HC findings; increase related to intracerebral white matter, and cortical gray matter depending on parcellation.
- Herbert et al. parcellated white matter into inner and outer radiate white matter: increased volume of outer intra-hemispheric short and medium range cortico-cortical connections; no increase in inter-hemispheric or cortical-subcortical connections.

Herbert et al. Brain 2003; 126: 1182-92
Major role for white matter but without accompanying long tract signs and thus the difference between acquired and develop. disorders

Disturbance in connectivity

Increased white matter volume was associated with dysfunction not increased function

Inter-hemispheric white matter e.g. corpus callosum was not involved in the same process

Minshew & Williams, Arch Neurol in press
Visual Perception: Part-Whole Processing

- Observation supports enhanced perception of detail
- Tests like Embedded Figures & unsegmented block design add empiric support, but not universal
- Some studies do not support local precedence
- Some studies do not support lack of global precedence
- Micro-analytic technique (advanced research approach) separates out confusing factors and looks just at local vs global processing
A bias toward seeing the whole (global processing) over seeing the details (local processing) has long been debated as part of the basis for behavior in autism from resistance to change to obsessions with the details a few interests over concepts and a broad range of interests. Specialized methods are used to evaluate these perceptual biases.

Neuropsychologia 2007 45: 4:685-695
Embedded Figures

Here is a simple form which we have labeled "X":

This simple form, named "X", is hidden within the more complex figure below:

Courtesy of: http://lucarinfo.com/inspire/embeddedfigure2.jpg
Optical Illusions

(a)

(b)

In verbal individuals with autism in this study, all had local processing bias but only some had global precedence.

This variability needs to be compared to performance on cognitive tests including face recognition and to behavioral flexibility/rigidity and memory for details to begin to explain the variability typical of the autism spectrum.
Automatic Processing & Categorization Mechanisms

Cognitively the problem is with prototype formation and *automatic processes* as opposed to conscious verbally mediated reasoning.
Abilities that adults take for granted that normally develop in infancy and toddlerhood:

For example:

- Our abilities to recognize faces and emotional expressions
- Our abilities to understand the difference between basic categories in the world—cats, dogs, lions …
Which of these is the best example of a dog?
Which of the following two faces looks more familiar to you?
Gender Categorization
5- to 7- Year- Old Children

Strauss, M.S. et al., Child Development (under revision)

Typical Hair  Typical Atypical Hair  Typical Cap  Atypical Cap

Control  Autism

*p < .05

Strauss, M.S. et al., Child Development (in press)
Gender Categorization
8- to 12- Year Old Children

- *p < .05

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control</th>
<th>Autism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Hair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical Hair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical Cap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical Cap</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* indicates significant difference at p < .05.
Gender Categorization
13- to 17- Year Old Teenagers

*\( p < .05 \)
Gender Categorization
Adults

- Typical Hair
- Typical Cap
- Atypical Hair
- Atypical Cap

* *p < .05

Strauss, et al., *Child Development*, in press
Difficult discrimination for 1/3 of people with autism

Dr. Nancy Minshew
Pittsburgh

Dr. Geraldine Dawson
Seattle
Attractiveness Ratings

Correlation of ratings by Controls vs. Autistics: $r = -.06$
Conclusions

- Individuals with autism have difficulty with categorizing atypical exemplars of categories.
- While categorization improves with development, adults with autism never reach the “expertise” abilities of controls.
- These deficits are seen with both faces (e.g., gender discrimination) and object categorization.
- The inability to form prototypical representations of categories also impacts facial recognition skills so that distinctive faces are not remembered better than typical faces.
- A lack of facial prototypes can also be seen in their not perceiving “average” or prototypical faces as attractive.
fMRI studies have been the window on the mind and the path to understanding of complex behavior and higher order cognition

Extensive studies- social cognition system, emotion system, mirror neuron system, gaze processing, motion processing, face processing, …
Language Profile in HFA

- Superior to age-, IQ-, gender-matched controls on word & non-word decoding, spelling, vocabulary, fluency

- Inferior to controls on comprehension of sentences, idioms, metaphors, stories
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
The player was followed by the parent

Who was following? player parent
Brain activation during sentence comprehension in autism in Brain, 2004

Autism group has less activation in **Broca’s area**
- *(a sentence integration area)*
than the control group and more in **Wernicke’s area**
- *(a word processing area)*
Results are consistent with poorer comprehension of complex sentences, coupled with good word reading (spelling bee champs)
Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)
Functional Connectivity

The activation in two cortical areas can be less synchronized (upper panel) or more synchronized (lower panel) for different people.
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 Cherkassy
Rajesh Kana

Just et al., 2006 [Epub ahead of print], Cereb Cortex
Mechanisms Underlying fMRI Abnormalities

- imbalance between inhibitory & excitatory mechanisms in cerebral cortex may impact cortical specialization
- glutamate cell reduction may reduce inhibition
Compensatory Mechanism

fMRI studies have also revealed that individuals with autism are performing tasks using different cognitive abilities and different areas of the brain than typical individuals use for task performance. Inferences cannot be made about brain-behavior relationships from cognitive task performances.
Mental Imagery in Autism: Thinking Pictures All the Time—Bypass Language

Rajesh Kana
Nancy Minshew
Tim Keller
Vlad Cherkassky
Marcel Just

Kana et al. 2006, Brain, 129(9):2484-2493
fMRI of N-back Letter Task in Autism

Hideya Koshino
Patricia Carpenter
Nancy Minshew
Vlad Cherkassky
Tim Keller
Marcel Just

NeuroImage 2005; 24:810-821
Autism group used more nonverbal visually oriented processing and retained letters as visual-graphical codes

Controls converted letter to verbal-phonological codes

Autism group relied on lower level visuospatial analysis, had less activation in anterior regions and more in posterior regions associated with visual processing, more activation in right than left hemisphere
Mirror Neuron System

- MNS (pars opercularis in IFG) is active during observation, imitation, and understanding of the intentions of others
- Thought to provide a mechanism for understanding the actions & intentions of others
- When acting in conjunction with the limbic system it is thought to mediate the understanding of emotions and the internal experiences of others.
Second Hit: Failure of Frontal Lobe to Mature

- Oculomotor studies have demonstrate a delay and incomplete maturation of the frontal lobe in the second decade of life in HFA
- This accounts for the apparent worsening of function in the second decade as the skills needed to cope with more challenging problems fail to emerge
- It also explains the poorer than expected outcomes and poorer adaptive behavior in adults
• High functioning individuals 5-45 years with autism, Asperger disorder, PDDNOS, IQ 80-120, speak in sentences, some med exclusions
• Through July 2012; no cost; participant payment; we pay airfare & hotel
• autismrecruiter@upmc.edu
• Toll Free 866-647-3436
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-in instability in replication of DNA.

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

Four Stages in Development of Friendship

Courtesy of Tony Atwood
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.

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

Level 1: Approximately 3 to 6 years

1. Recognition of sharing and turn taking.
2. Friend has toys and child wants to play with.
3. One way assistance (he helps me).
4. Proximity.
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.

Level 1: Approximately 3 to 6 years

5. Why is ______ your friend?
6. “He sits next to me.”
7. Momentary friends
8. Conflict resolved by force and a referee.
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.

Level 2: Approximately 6 to 9 Years

Courtesy of Tony Atwood
1. Reciprocity and being fair.
2. Mutual assistance.
3. Like the same activities.
4. Why is ______ your friend?
5. “She comes to my party and I go to hers.”
7. Offender needs to retract the action (an eye for an eye).
8. Role play activities, rehearsal, feedback and rewards.
10. Resources.

Level 2: Approximately 6 to 9 years
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.

Level 3: Approximately 9 to 13 Years

Courtesy of Tony Atwood
1. Aware of other’s opinion of them and how their words and actions affect the feelings of others (white lies).
3. Cooperation more than competition.
4. Share thoughts rather than toys.
5. Personality characteristics, audacious, humor.
6. Helps in times of emotional distress.
7. Help the child feel good about themselves (compliments).
8. Greater selectivity and durability.
Level 3: Approximately 9 to 13 years

8. Gender split (boy and girl activities).
9. Trust, loyalty and keeping promises.
10. Why is _______ your friend?
11. “I can trust her with my secrets.”
12. Conflict resolved by discussion that can strengthen the relationship
13. Conflict forgiven.
Level 4: Adolescence to Adult

1. Peer group acceptance more important than the opinion of parents.
2. Greater depth and breadth of self disclosure.
3. Desire to be understood by friends?
4. Friends character compatible with their own.