Discovering the Mind & the Brain in ASD

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Biological Basis of Autism
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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 1/150
February 2007

Kadesjo, et.al.[1] 1999	Baird et al[2], 2006	CDC[3] 2007
60/10,000	38.9/10,000	
48/10,000	77.2/10,000	
108/10,000	116.1/10,000	66/10,000
1/100	1/100	1/150

327-331; [2]Baird et al, The Lancet 368; 210-215 2006
07; 12-28 [4]This number was 20/10,000 in 1980

Common Principles of Neurology

- Brain disorders produce distinctive constellations of cognitive [thinking & behavioral] & neurologic [brain abilities] disturbances, not single deficits

- Multiple organ involvement is the rule in neurologic disorders not due to acquired brain damage- because they are caused by faulty genes and these genes are present in every cell in the body

Neurologic Approach to Deciphering Disease

Neurologists' approach to understanding disease is to examine all impaired AND intact abilities to define shared features that will identify the underlying disease process and its location in the brain.

Disease Processes

- Infectious disease
- Vascular disease
- Tumor or mass
- Toxins (signatures like CO sometimes)
- Developmental processes

Developmental Processes

- Organogenesis (basic form of the nervous system)
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination

Clinical Appraisal of Autism: Where & What

- Complex behavior abnormalities
- Cognitive impairments w/ MR in 50-60%
- Seizures in 30%
- Absence of blindness, deafness, long tract signs

Cognitive: higher order abilities impaired; simple intact

Brain: association cortex generally disturbed with sparing of primary sensori-motor cortices and white matter

Caveat: no focal signs- distributed neural systems disorder

What Question to Ask?
Big Picture, Little Picture

Research studies have always shown an uneven cognitive profile:

- What do their cognitive strengths have in common?
- What do their cognitive weaknesses have in common?
- Answers to these questions provide insight into the underlying cognitive processes and neural mechanisms

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

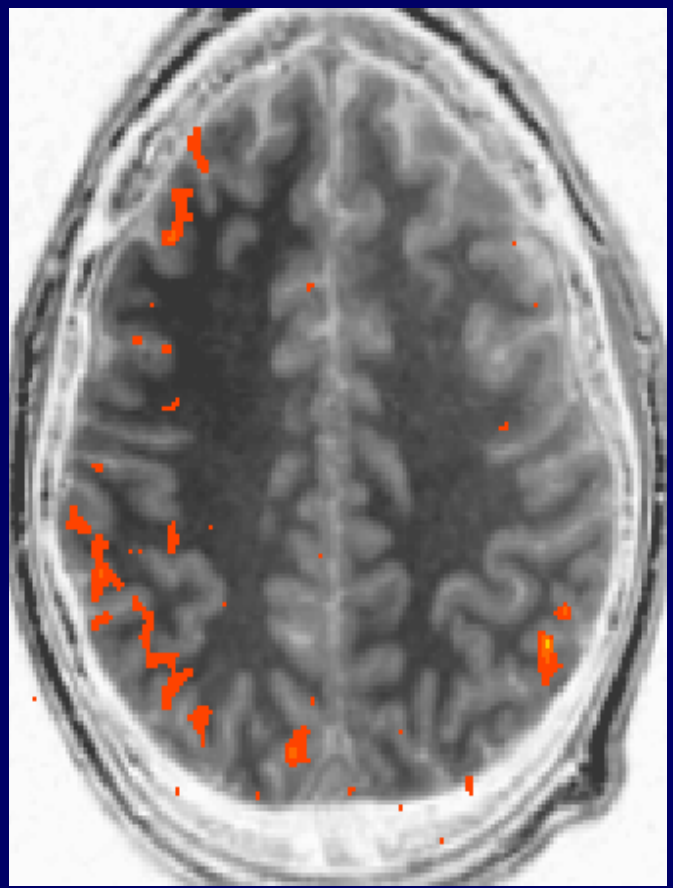
- Complex Sensory
- Complex Motor
- Complex Memory
- Complex Language
- Concept-formation
- Face Recognition

What Does The Profile Mean About Neurologic Function & Neural Circuitry?

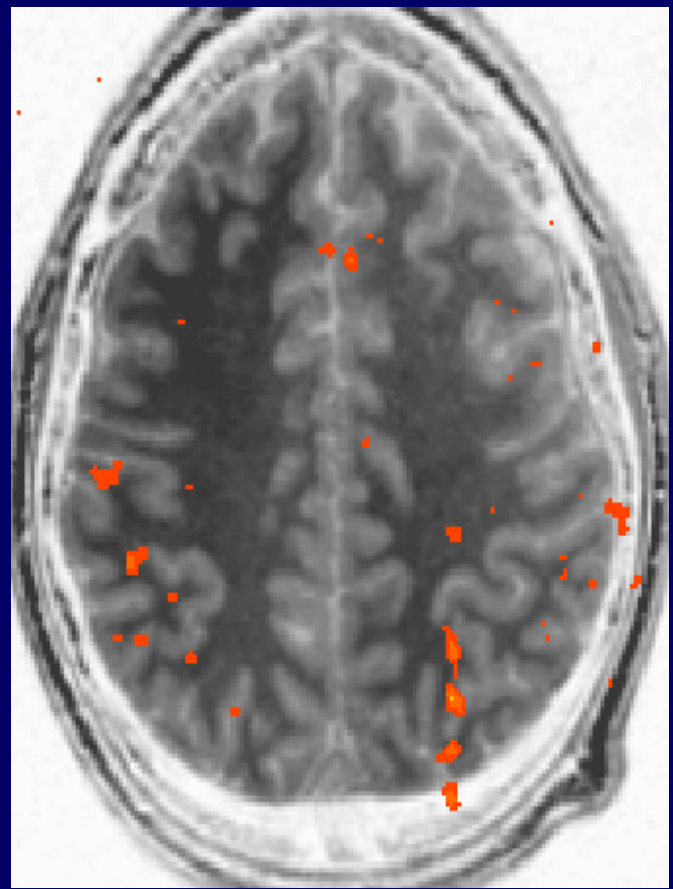
- Simpler processing & abilities are intact/enhanced
- Information processing capacity is limited- integrative processing & higher order cognitive abilities are disproportionately impacted

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)



Healthy Group



Autism Group

Behavioral Example of Cognitive Profile: Using the Profile to Intervene

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 PERSUADE him to try lithium but he refused. His reason was that he took lithium on June 4, 1978 and he got a stomachache. He went to the clinic and a scene ensued. Staff yelled at him. No amount of REASONING 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 three years old. He was not reciprocal in conversation. He talked, the doctors talked.

Effect of dual task on memory span and tracking performance

	Digit recall			*Tracking performance*			*Mu score*
People with autism (n = 16)	*single*		*dual*	*single*		*dual*	
Mean	86.19	>	48.13	52.75	>	37.81	66.87
SD	7.55		16.77	10.47		8.22	10.74
Controls (n = 16)							
Mean	87.25	=	86.88	54.06	=	55.25	84.75
SD	4.81		7.58	14.61		7.39	11.52

Digit recall is expressed as a percentage of correct sequences.

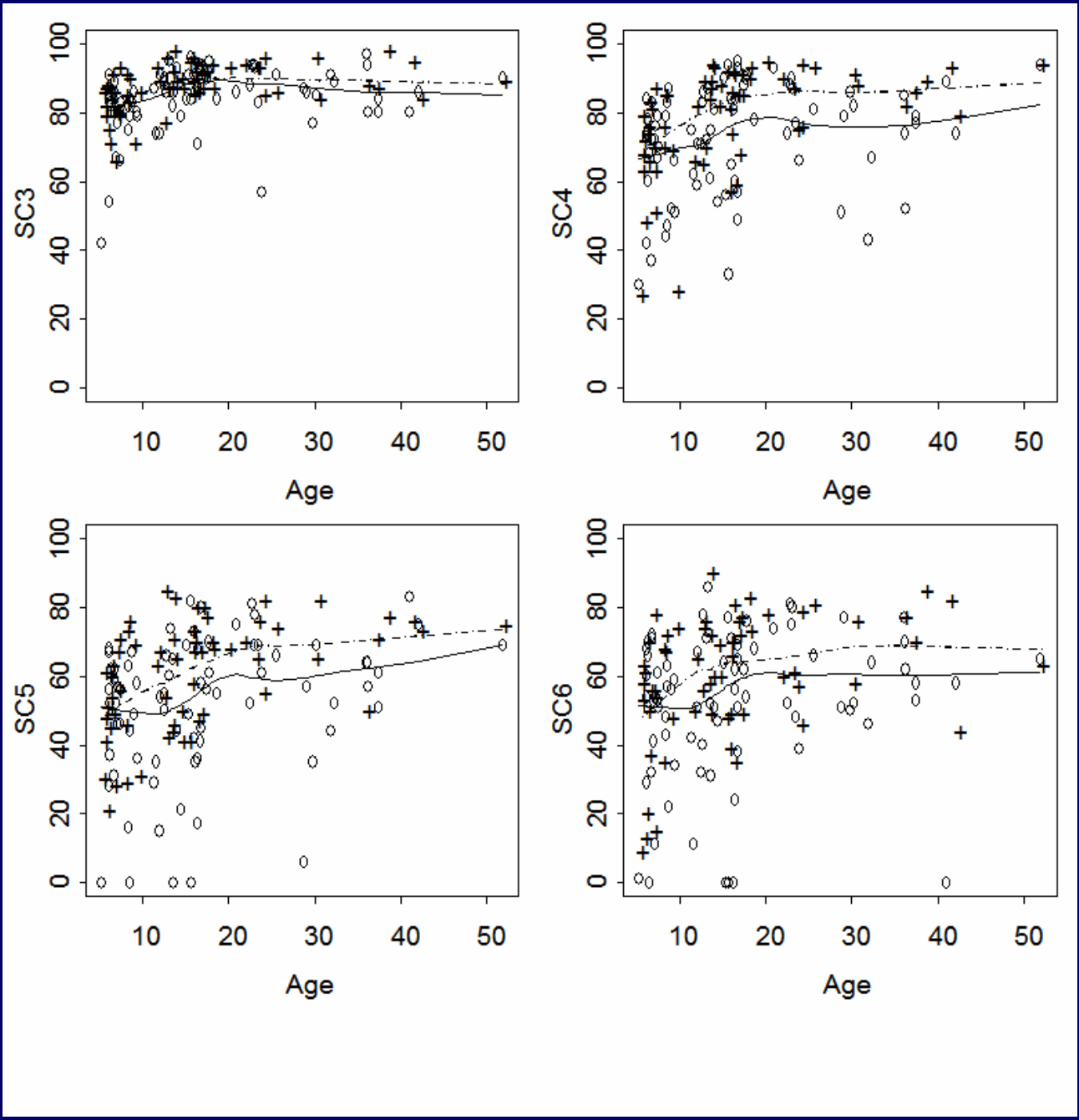
Dual task performance deficit in autism;

(but matched performance in single task conditions)

Garcia-Villamisar & Della Sala, 2002 Cognitive Neuropsychiatry

Minshew et al. (2004) Underdevelopment of the postural control system in autism. Neurology; 63:2056-2061.

- 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.
- 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).


SC3
SC4
SC5
SC6
Age
0
20
40
60
80
100
10
20
30
40
50

Additional Implication of Profile: Triad to Brain-Wide

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 brain-wide disturbance in information processing.

Williams et al. 2006, 12: 279-298

Unique Characteristic of Within Domain Disturbances

Within each domain, there was a pattern of intact and impaired abilities. The dissociation was characteristic and was exemplified by the abstraction-EF domain. The result has a marked impact on behavior, and also on adaptive function. Along with social ineptness, the hallmark of autism in verbal individuals is their reliance on rules despite failure and generally slow processing speed.

Abstract Reasoning: Concept Identification & Concept Formation

- 90 verbal individuals with autism >12 yrs
- 107 control volunteers
- Concept identification
  - Attribute identification
  - Rule-learning
- Concept formation
  - Self-initiated strategy
- Cognitive flexibility
- Extent to which these were dissociable skills

Dissociation Between Concept Identification & Concept Formation in Autism

- *Intact* concept identification :
  - Attribute identification
  - Rule learning
- *Inflexible* in applying rules in changing contexts
- I*mpaired* concept and strategy formation
- These two classes of abilities are dissociable in autism: do not develop simultaneously as they do in normal children

Minshew, Meyer & Goldstein, 2002, Neuropsychology 327-334.

Behavioral Example of Cognitive Profile: Rules Override Concepts

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 learned to stay out of his way. 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.”

Local Global Processing: Next Arena of Information Processing & Connectivity Research in Autism

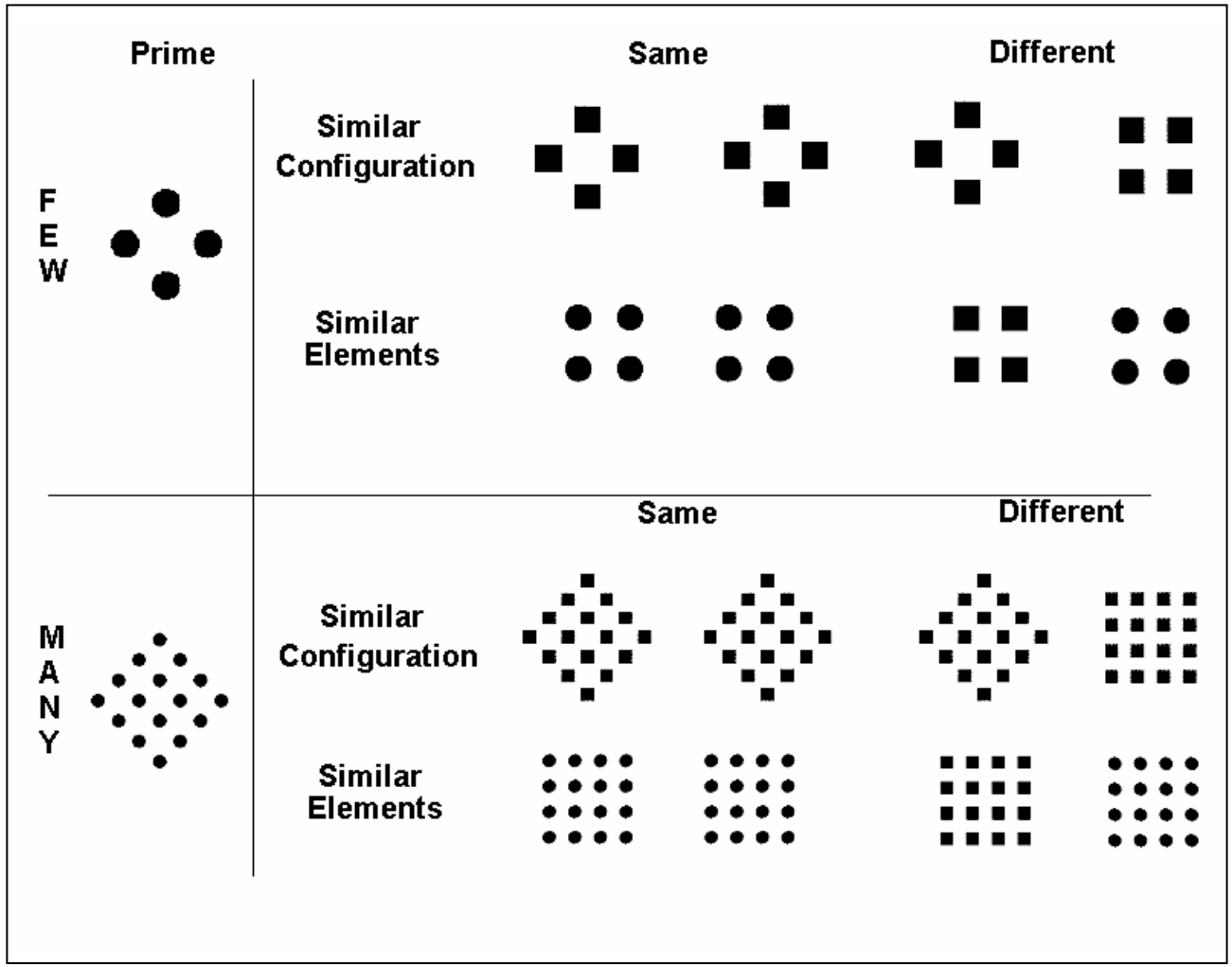
A bias toward seeing the local details (local processing) over seeing whole (global processing) has long been debated as part of the basis for behavior in autism from preoccupation with object parts, remarkable notation of details, resistance to change, to a few interests with an obsession over a large number of details. Specialized methods are used to evaluate these perceptual biases.

Local Processing in Autism: Clinical Tests

- Superior Embedded Figure Test performance
- Block design
- Visual Search
- Complex Visual Figure construction

Initial reports: MR autistic children exhibited superior performance= local processing bias & led to WCC

Recent reports: HFA performed equal to or more poorly than peers on local processing tests but use local approach on complex figures


Prime
Same
Different
FEW
Similar Configuration
Similar Elements
Same
Different
MANY
Similar Configuration
Similar Elements

Implications of Global-Local Processing For Neural Connectivity Disturbances

- Existing data suggests enhanced local connectivity in mildly retarded autistic children & its absence in normal IQ individuals with autism
- Ho: Enhanced local processing reflects abnormally enhanced local connectivity in LFA
- Ho: Impaired global processing in HFA reflects reduced cognitive strategies & reduced frontal connections
- General cognitive slowly probably also reflecting reduced use of strategies

Head Growth in Autism

Lainhart et al. Am J Med Genet 2006, 140A:2257-2274

- 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

Synthesis of Brain Volume Studies

- Major role for white matter but without accompanying long tract signs and thus the difference between acquired and devel. 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

Minicolumn Abnormalities in Autism: Evidence of Cortical Involvement

- First substantive abnormalities of cerebral cortex
- Radially oriented arrays of pyramidal neurons, interneurons, axons and dendrites
- Smallest radial unit of information processing; then macrocolumns and receptive fields?
- Bilateral abnormalities in areas 3, 4, 9, 17, 21, 22
- Increased #, narrower, reduced neuropil space (inhibitory neurons), neurons small

Casanova et al. Acta Neuropathol 2006; 112:287-303

Additional Evidence of Cortical Involvement

- Proton MRS study of 3-4 yr olds with autism, DD, TD: reduced choline compound concentrations and transverse relaxation, suggestion decreased cellularity or density in ASD but not DD or TD
- T2 relaxation in same children prolonged in GM but not WM in ASD but in both GM and WM in DD. Selective involvement of GM interpreted as abnormal developmental process in ASD

Friedman et al. Arch Gen Psych 2006; 63:786—794;
Petropoulous et al. Neurology 2006; 67:632-636

Additional Evidence of Cortical Involvement

- 26 males 6-17 years IQ>70 w/ autism & 26 controls
- Proton MRs revealed significantly lower levels of cortical gray matter NAA and glutamate-glutamine that were widespread in cerebral lobes and cerebellum
- Conclusion: widespread reduction in gray matter neuronal integrity and dysfunction of cortical and cerebellar glutamatergic neurons

DeVito et al Biol Psychiatry 2007; 61:465-473

Genes and Multi-Organ Involvement

- 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

Genes to Behavior: the MET Story

- mRNA expression levels correlated with DNA alterations in temporal lobe
- Levels correlated with presence or absence of early developmental language delay
- Imaging study has shown that history of language delay is associated with alterations in volume of temporal lobe

Neural Basis of Clinical Symptoms

- 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

Center for Cognitive Brain Imaging
Carnegie Mellon

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

Sentence reading task and comprehension probe

Center for Cognitive Brain Imaging

The player was followed by the parent

Who was following?

player parent

Brain activation during sentence comprehension in autism In Brain, 2004

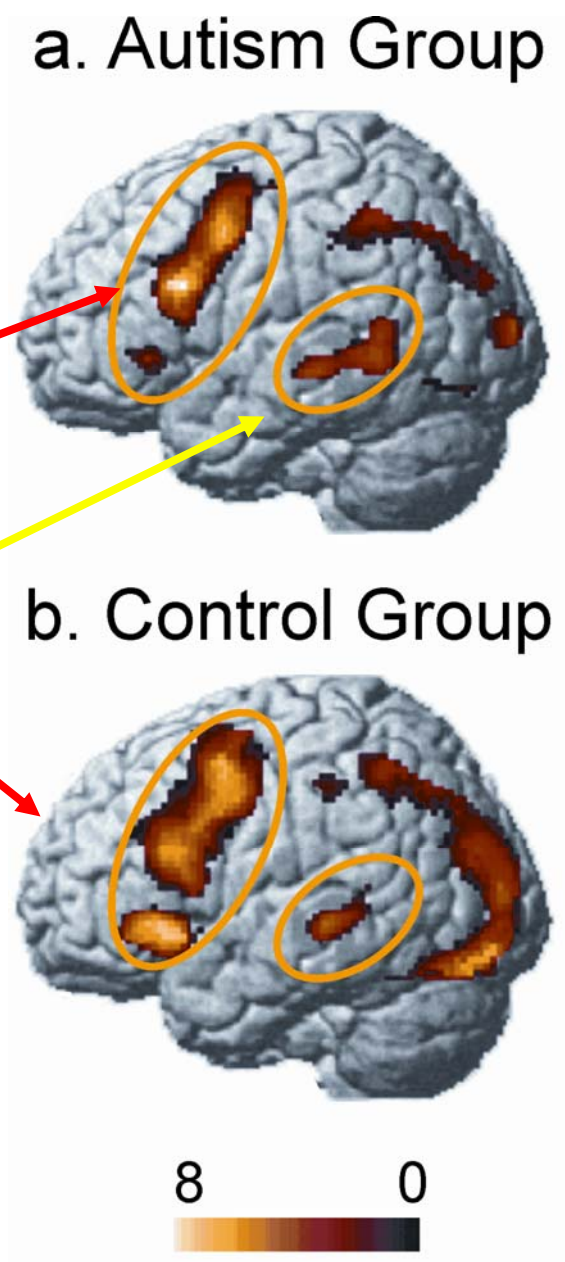
Autism group has less activation in **Broca's area**

- *(a sentence integration area)*

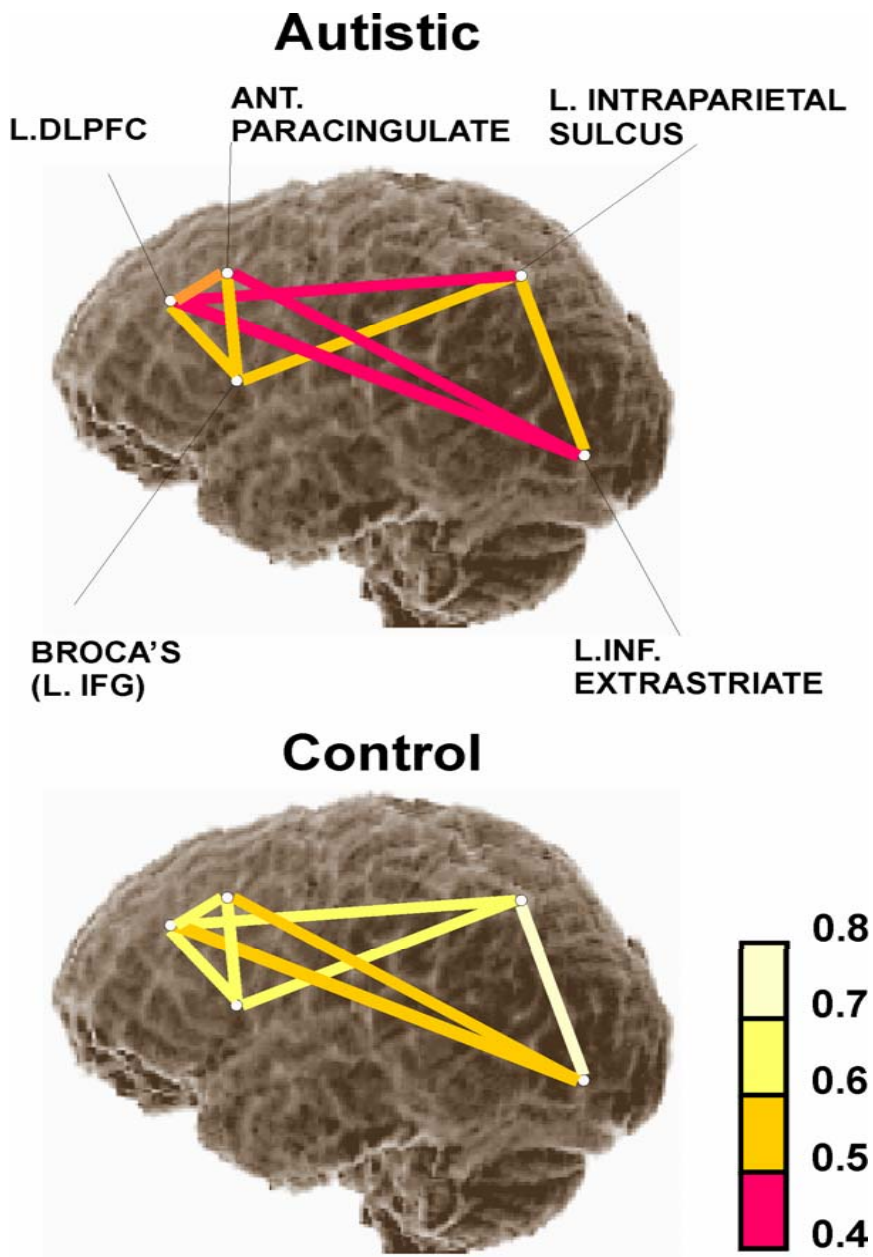
than the control group and more in **Wernicke's area**

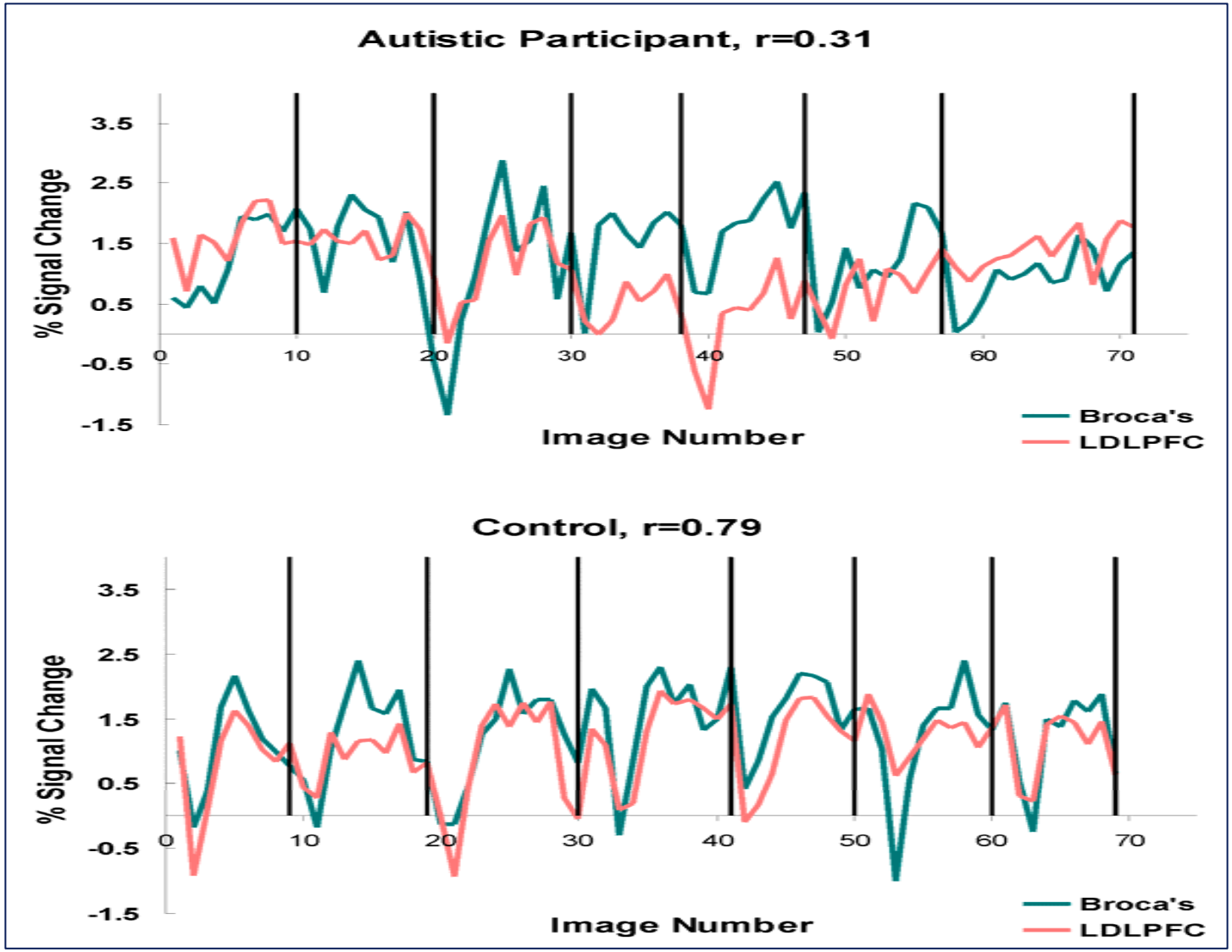
- *(a word processing area)*

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)

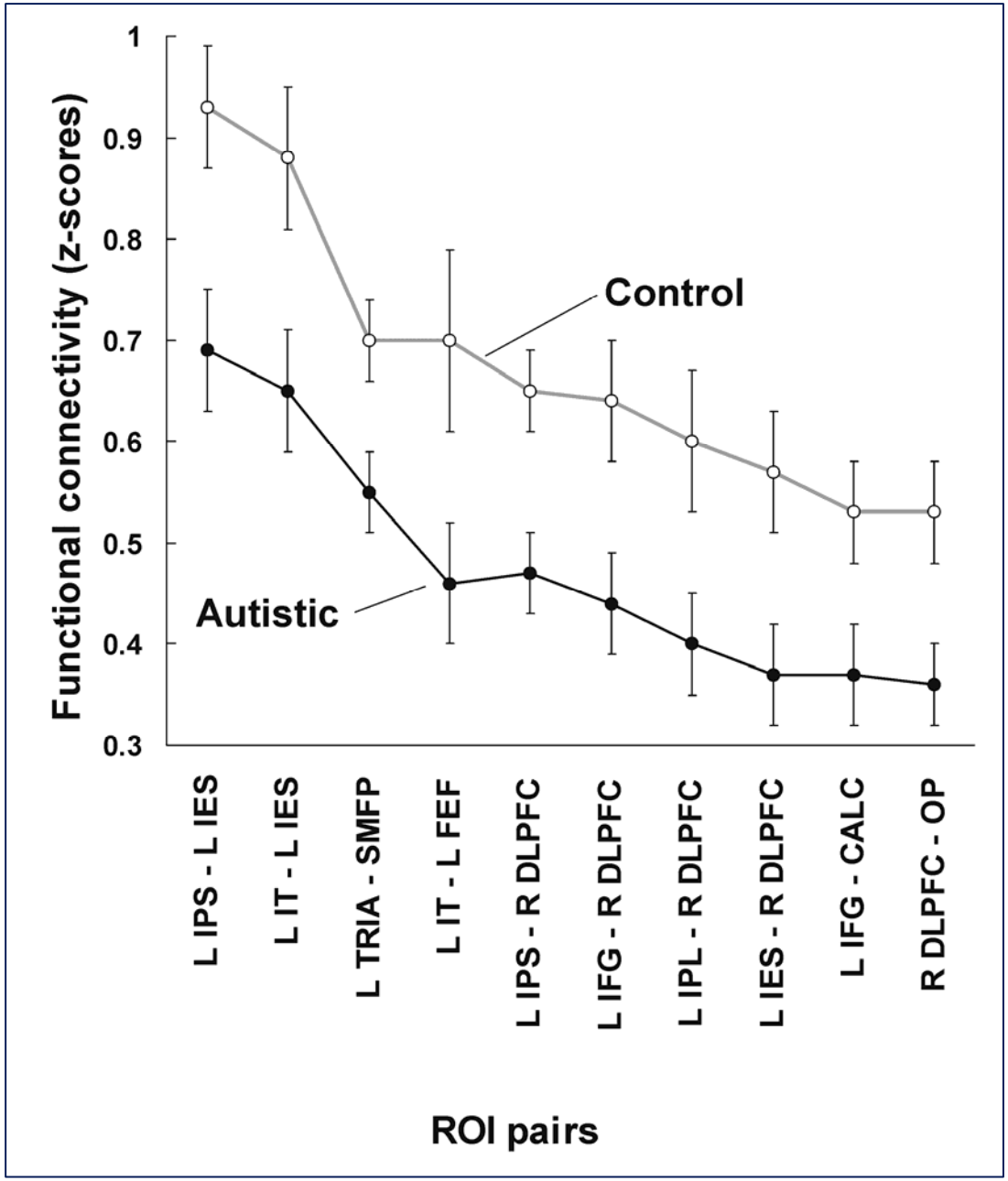




Functional Connectivity

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

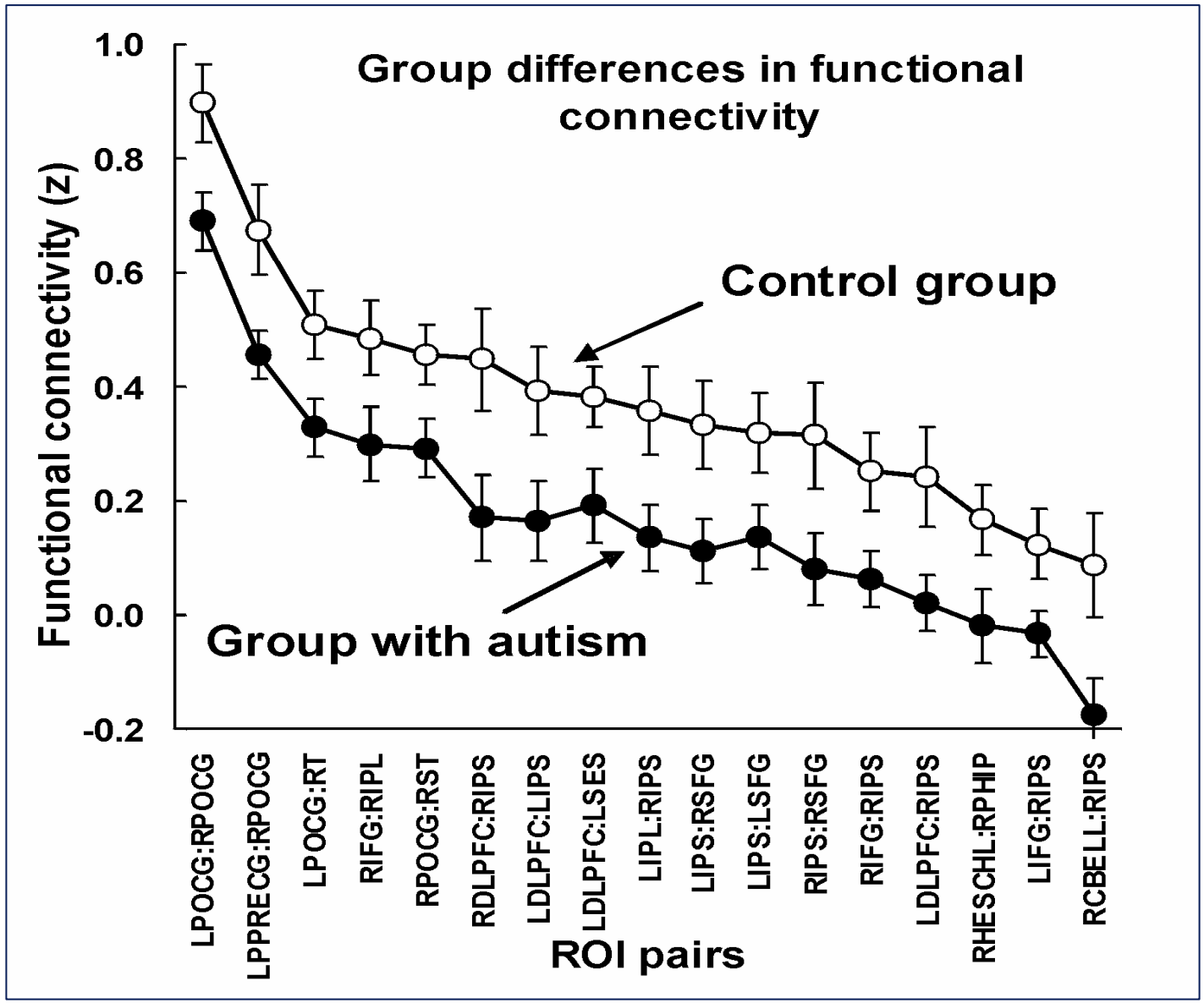
Reliable differences in functional connectivity: autism group has lower functional connectivity but same rank order



Functional Underconnectivity: fMRI of the Tower of London

Marcel Just
Nancy Minshew
Tim Keller
Vlad 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)
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
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

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.

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

N-Back Results: Alternate Cognitive & Neural Strategies in Autism

- 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, and the large scale brain network has different organization from normals *(see factor analysis)*

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

The Functional Neural Basis of Autism

- Information processing capacity is reduced-dual task, speed of processing and any task relying on strategy
- Functional under-connectivity of neural systems is a general feature of the brain in autism; under developed frontal connectivity is common to all affected systems
- Circuitry underlying basic abilities is intact, and there is increased reliance on these circuits to perform tasks that typical individuals perform using integrative circuitry and higher order abilities
- Both a cortical gray & white matter disorder

How the mind organizes information, Or not, in the case of autism

Cognitively the problem is with prototype formation and

automatic processes

as opposed to conscious, verbally mediated reasoning.

Concept Formation Impairments Global: All Rely On Prototype Formation & Frontal Connections

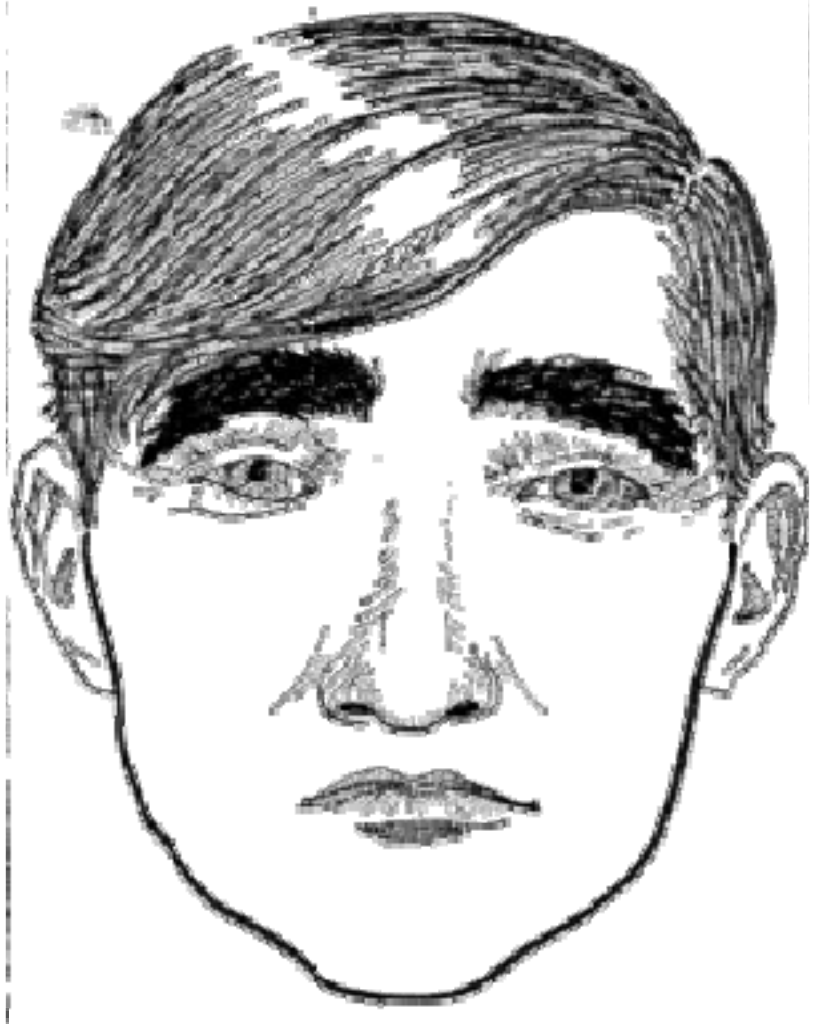
- Motor concept learning
- Memory dependent on strategies
- Story creation or theme identification
- Face recognition
- Face affect recognition
- Strategy formation, problem solving

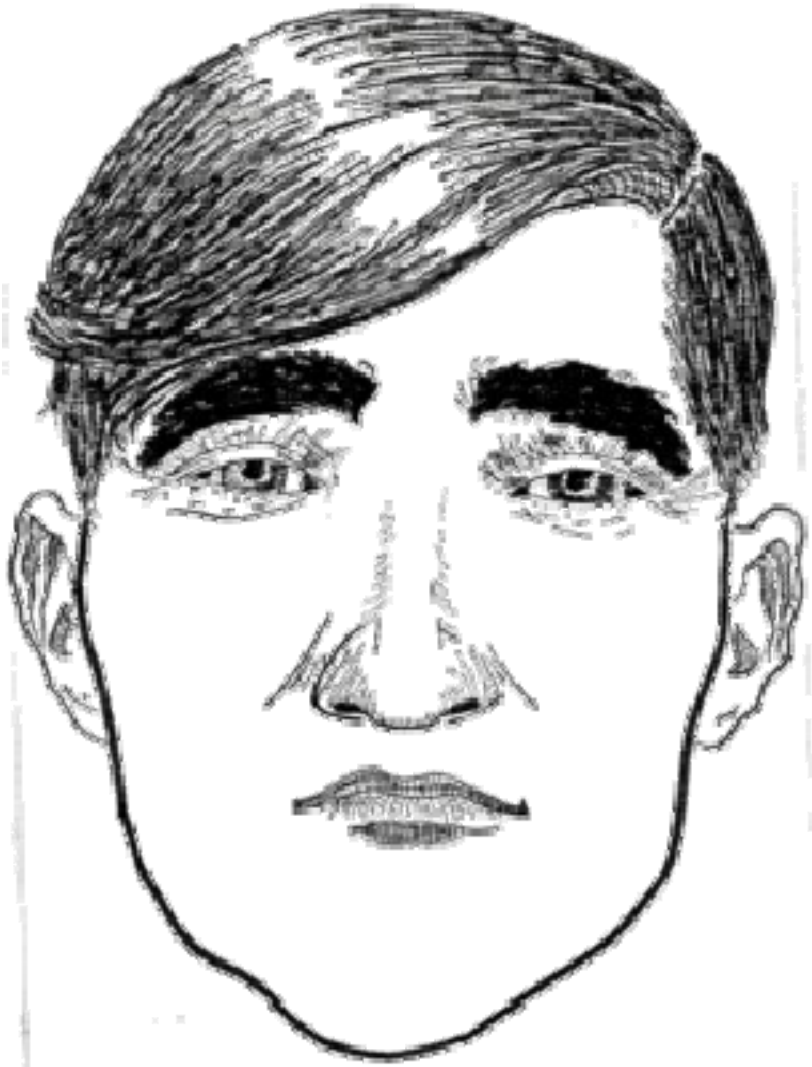
Pitt Infant and Toddler Development Center

- 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 …

Infants are born with automatic mechanisms that allow them to form Prototypical Representations of Information

Which of these is the best example of a dog?





Which of the following two faces looks more familiar to you?

1

2

Cognitive Research in 5-50 year old HFAs

- The way individuals with autism come to learn about both the world and people is different from individuals who do not have autism.
- There are core differences in the way they learn categorical information and acquire “expertise”

Gasgeb, Strauss, & Minshew. Child Dev 2006; 77: 1717-1729

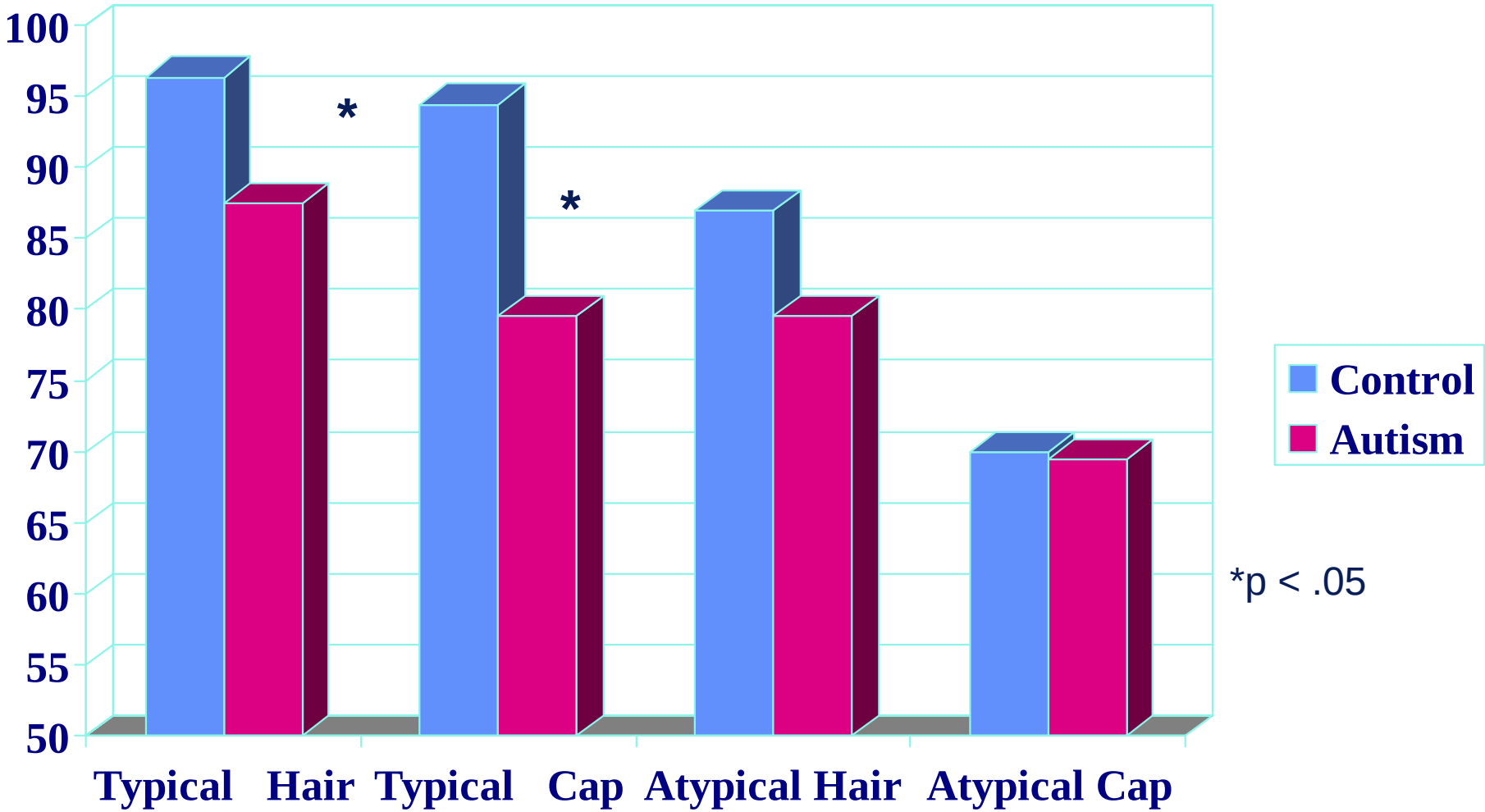
TYPICAL SOMEWHAT TYPICAL ATYPICAL

Difficult discrimination for 1/3 of people with autism

Dr. Nancy Minshew	Dr. Geraldine Dawson
Pittsburgh	Seattle

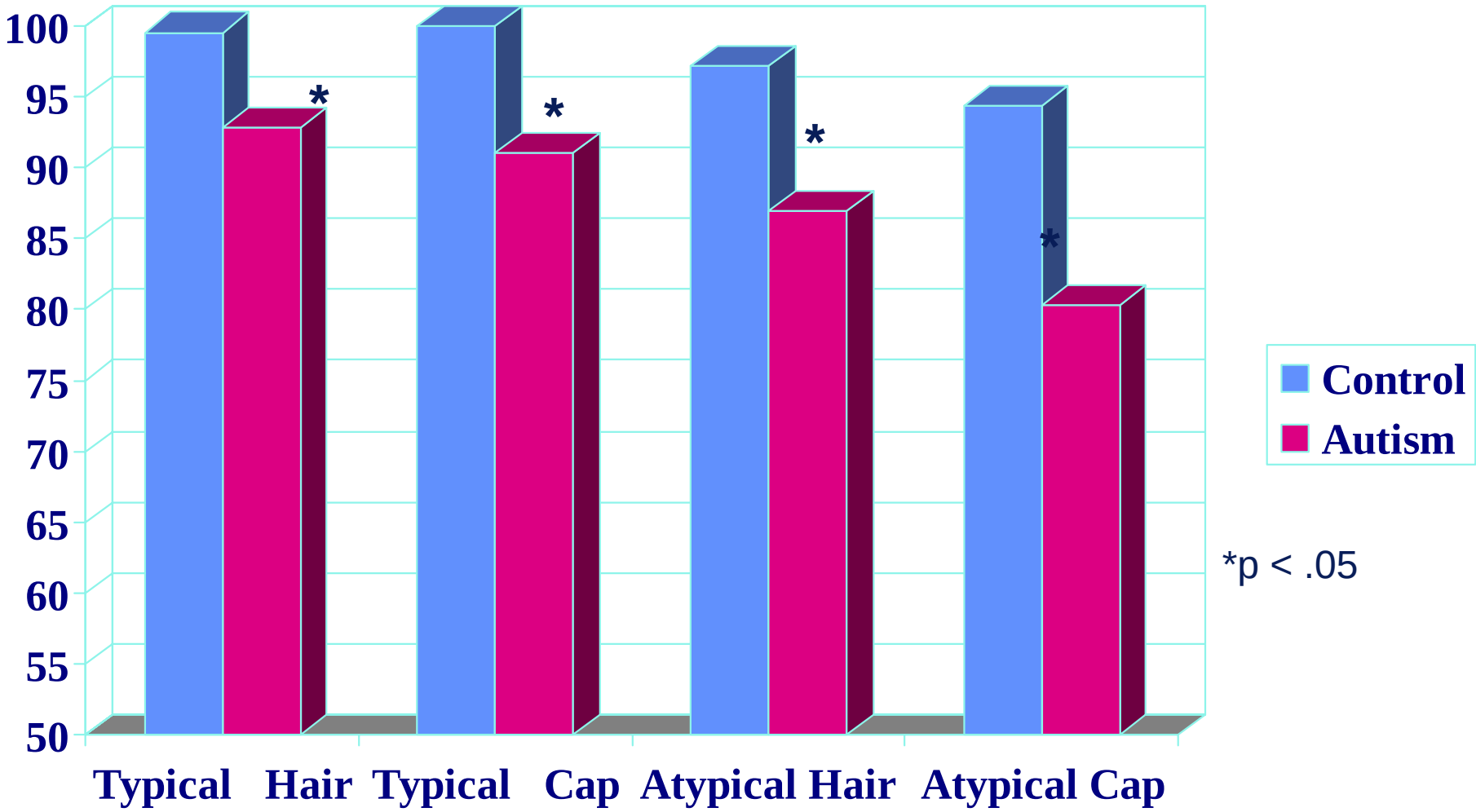
Most Difficult Faces for Participants with Autism To Classify By Gender

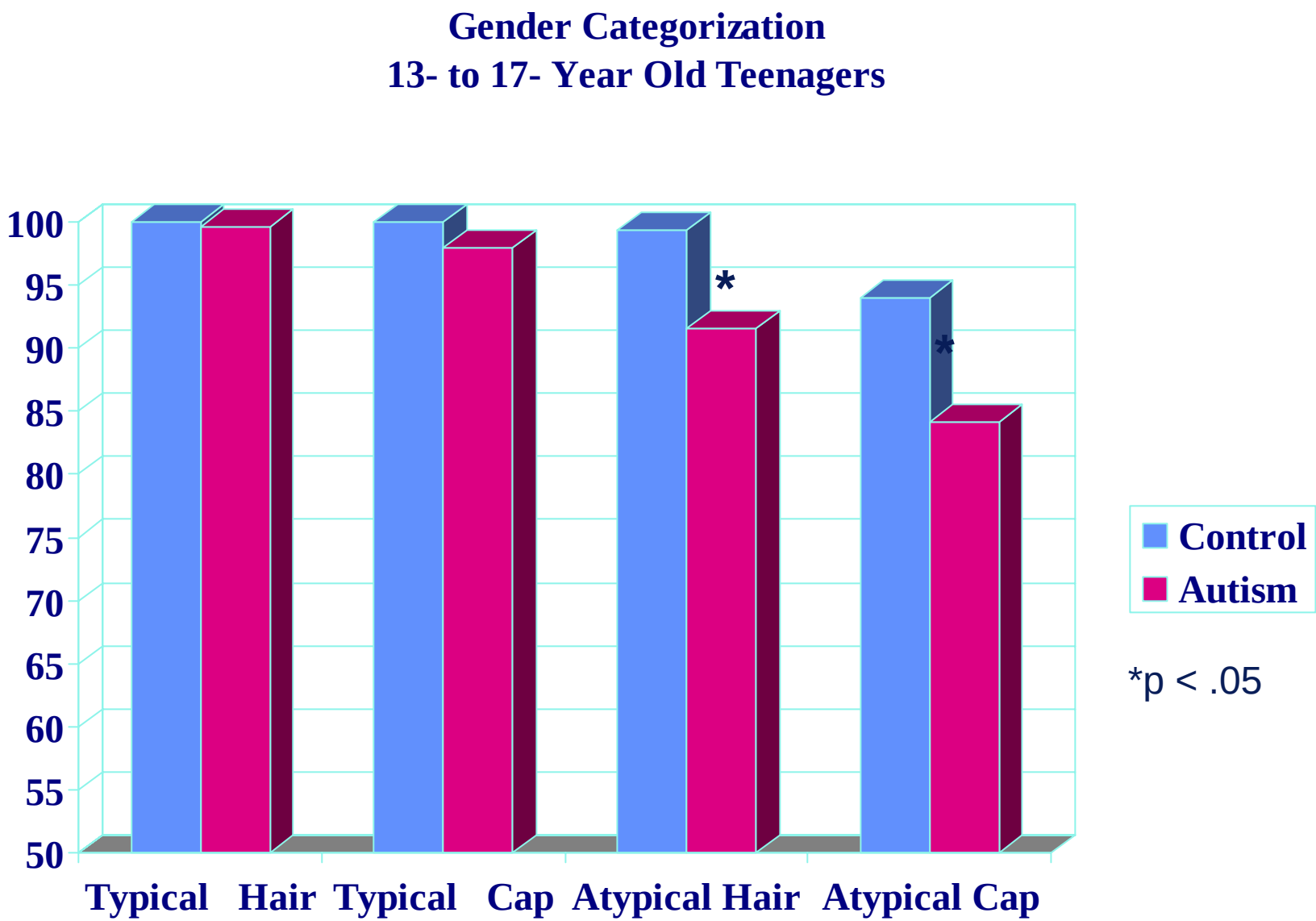
Gender Categorization
5- to 7- Year- Old Children

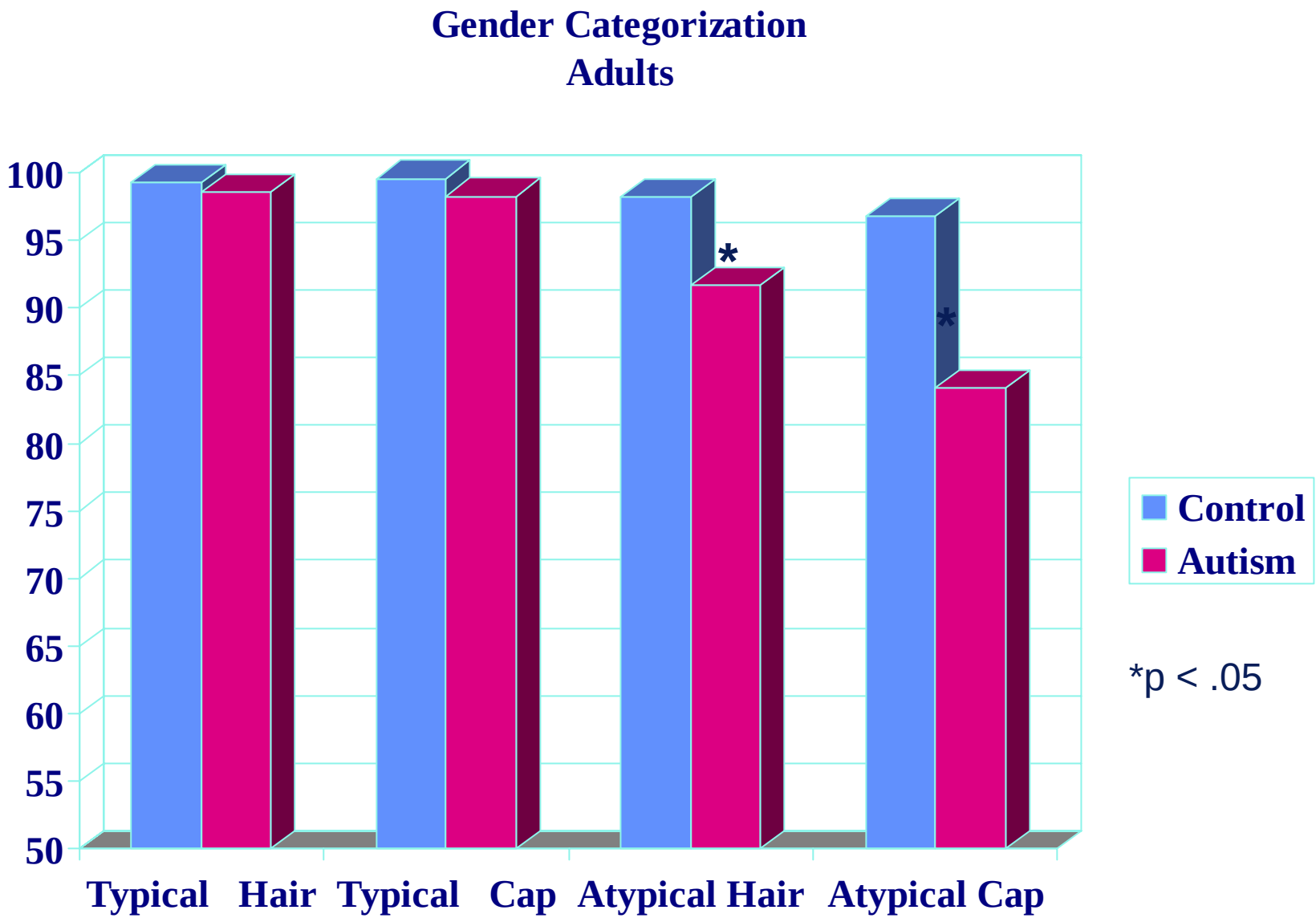


Strauss, M.S. et al., Child Development (under revision)

Gender Categorization
8- to 12- Year Old Children




Gender Categorization
13- to 17- Year Old Teenagers
100
95
90
85
80
75
70
65
60
55
50
*
*
Typical Hair
Typical Cap
Atypical Hair
Atypical Cap
Control
Autism
*p < .05


Gender Categorization
Adults
100
95
90
85
80
75
70
65
60
55
50
*
*
Typical Hair
Typical Cap
Atypical Hair
Atypical Cap
Control
Autism
*p < .05

Why are less typical faces so difficult?

- Require comparison to prior stored knowledge (e.g., prototypes)
- Require subtle spatial/configural processing
- Require flexible weighting of features and perhaps formation of a holistic representation
  - (Note the importance of varying both age and difficulty of task)