"Neurologic Basis of Autism"

Autism Course for PGY 2 Child and Adolescent Psychiatry Fellows

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Pittsburgh, PA
November 2008

1943-1980

- Described as a syndrome in 1943, 1944
- Thought to be psychogenic in etiology until 1970
- Originally described as a broad range of severity with emphasis on high functioning: 60/40 split
- By 1970, syndrome constricted to mild to moderate MR w/ echolalia & self-stim. behavior
- Originally distinguished from schizophrenia, then classified under childhood psychoses until 1980

Where We Were In 1980

- Autism introduced as a category in DSM/ICD
- No diagnostic instruments
- All cases thought to be caused by other disorders
- Focal brain dysfunction
- Single primary cognitive or sensory deficit
- Very rare disorder: 2/10,000
- Mental disorder

Pervasive Developmental Disorders (DSM)
*Autism Spectrum Disorders (Informal)

DSM-III (1980)
- Infantile autism
- Childhood onset pervasive development disorder
- Childhood onset PDD NOS

DSM-III-R (1987): Autistic Disorder
PDDNOS

DSM-IV (1994): Pervasive Developmental Disorders
- *Autistic Disorder
- *Asperger's Disorder
- *Pervasive Developmental Disorder NOS
- Childhood Disintegrative Disorder
- Rett's Disorder

Diagnostic Instruments

- Autism Diagnostic Interview-Revised
- Autism Diagnostic Observation Schedule
- Expert clinical opinion for confirmation
- Research reliability of administration & scoring of instruments- initial & ongoing
- Expert clinical opinion rules out cases but does not over-ride instruments to include cases

How Research Findings Changed The Disorder: Autism 1990

- Diagnostic methods resulted in recognition that 90-95% of cases idiopathic e.g. autism existed as a disorder in its own right & genetic in origin
- Dawning recognition of neural systems origin
- Increasing documentation of much higher prevalence 1-2/10,000 to 1/100 for ASD
- Recognition that cognitive & neurologic deficits involved higher order abilities in HFAs, not basic abilities, e.g. cerebral hemispheres and cortical systems in particular

Prevalence 1/166
2002-2006

Description	Baird et al[1]	Chakrabarti & Fombonne[2]	Brick Township, NJ[3]	Chakrabarti & Fombonne[4]
Autism	30.8/10,000	16.8/10,000	40.5/10,000	22.0/10,000
Other ASDs	27.1/10,000	45.8/10,000	26.9/10,000	36.7/10,000
Total for ASDs	57.9/10,000	62.6/10,000	67.4/10,000	58.7/10,000
Total for ASDs	1/170	1/170	1/150	1/170

- 1Baird et al, 2000
- 2Chakrabarti & Fombonne, 2001
- 3Bertrand et al, 2001
- 4Chakrabarti & Fombonne et al, 2001

Prevalence 1/150 or 1/100
February 2007

Description	Kadesjo, et al[1] 1999	Baird, et al[2] 2006	CDC[3] 2007
Autism	60/10,000	38.9/10,000	
Other ASDs	48/10,000	77.2/10,000	
Total for ASDs[4]	108/10,000	116.1/10,000	66/10,000
Total for ASDs	1/100	1/100	1/150

[1]Kadesjo et al, JADD, 29:4, 327-331

[2]Baird et al, The Lancet 368, 210-215 206

[3]ADDM Network, MMWR 02-09-07; 12-28

[4]This number was 20/10,000 in 1980

Estimates of Expressive Language Level at Age 9
151 Autism Participants

Lord et al Arch Gen Psych 2006; 63: 694-701

Description	Chicago	North Carolina
Complex sentences (ADOS Module 3)	40.9%	39.6%
Sentences but not fluent (ADOS Module 2)	35.3	28.9
Words but not sentences (ADOS Module 1; ADI-R = 1)	10.5	16.8
No or few consistent words (ADI-R=2)	14.3	14.4

Behavioral Neurology Appraisal

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

Synthesis: association cortex with sparing of primary sensori-motor cortices and white matter

Caveat: no focal signs- distributed neural systems disorder

Neurologic Approach to Deciphering Disease

Neurologists' approach to understanding disease is therefore to examine all impaired AND intact abilities to define common principles or characteristics of the underlying disease process.

Disease Processes

- 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

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

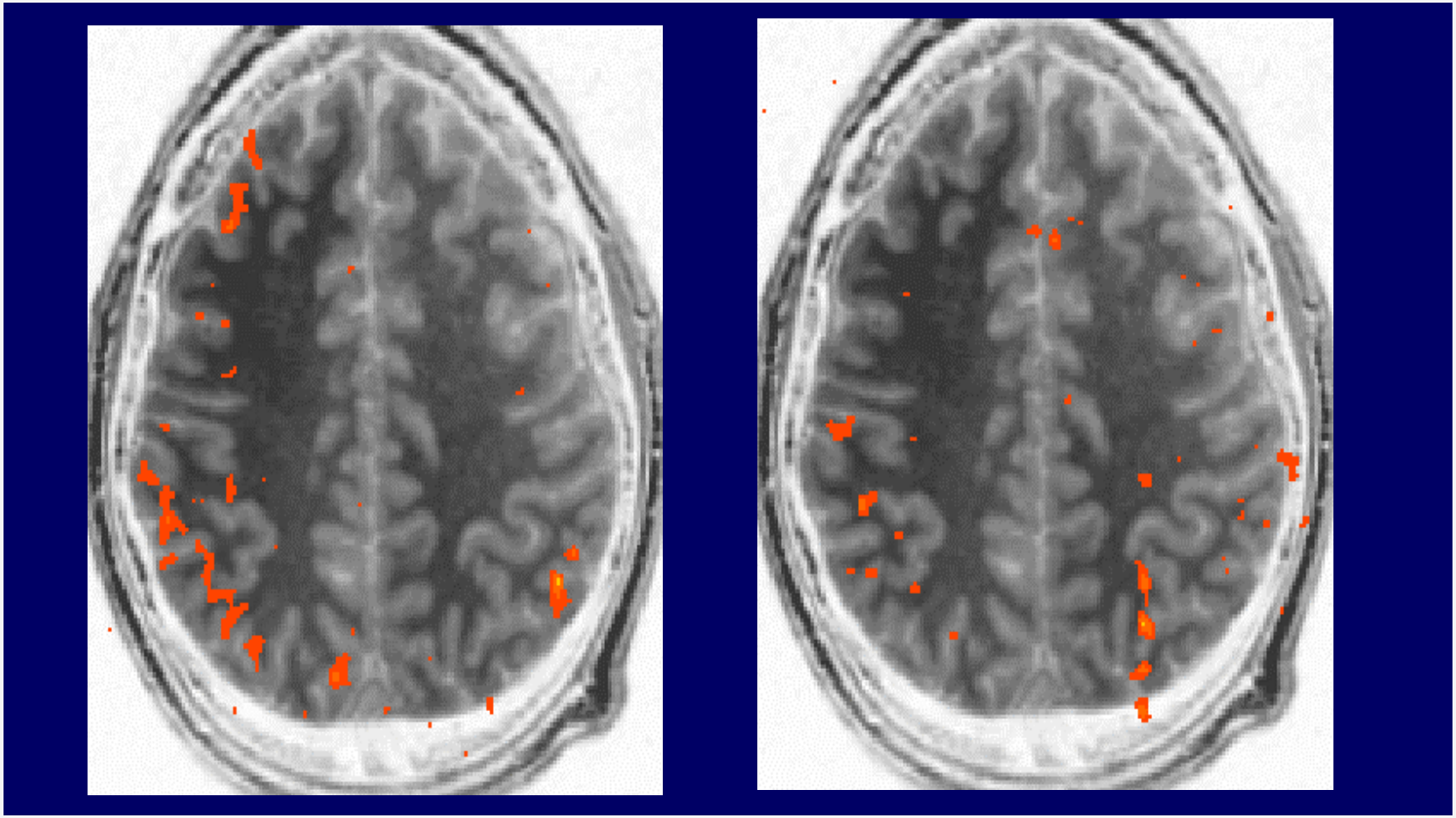
Cognitive Weaknesses

- 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)



Control Group

Autism Group

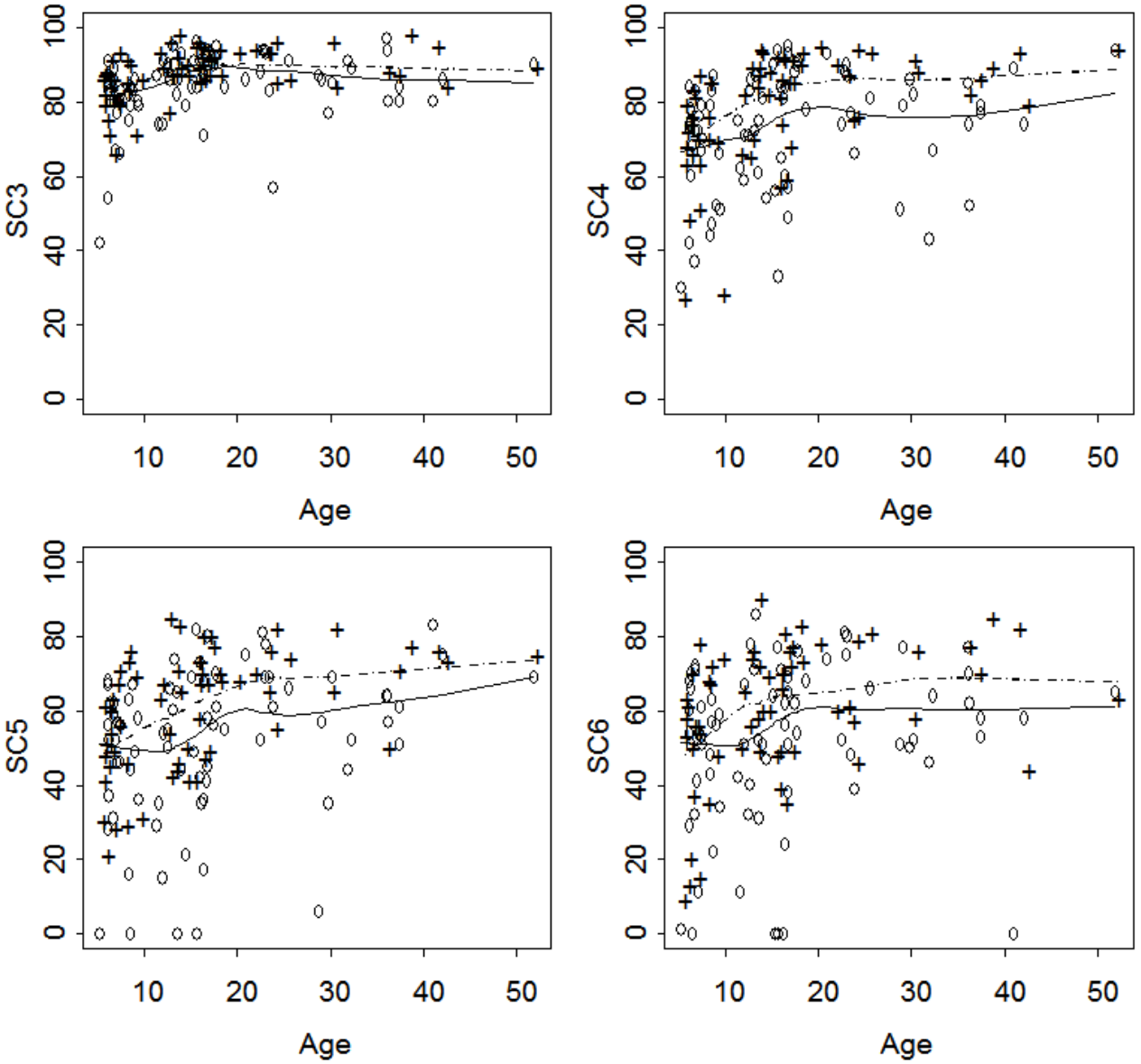
Converting Communication Failure to Success Pink Pill-Blue Pill

Jim was admitted for possible mania. He was agitated and had been sending money to television evangelists and became preoccupied with sin and going to hell. He carried and read from the Bible 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 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 lithium. 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 and he became disorganized but not manic. Socially-emotionally he was three.

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

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

The New Neurobiology of Autism

- Distributed or focal?
- Neocortical or subcortical?
- White matter or gray matter?
- Intra- and inter- hemispheric?

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

Implications of White Matter Dysfunction

- Why does WM damage from other causes not result in autism?
- Because autism is a disorder of neurons, not axons, myelin, or glia
- And because autism is a disorder of early brain development not of damage to already developed structures

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, Multi-Organs and Environment

- Theories have proposed that gi or immune dysfunction caused CNS dysfunction
- However, neurologic disorders are typically multi-organ disorders
- Scientific evidence is required before hypotheses become tentative fact. No evidence of environmental cause of vast majority of cases of autism. Compelling evidence of genetic role.

Genes and Multi-Organ Involvement

- 2.27 relative risk of autism diagnosis conferred by the CC genotype 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

Campbell et al. PNAS 2006, 45: 16834-16839

MET Story Continued

- mRNA levels reduced in autism postmortum brain
- In particular, comparing temporal (language) region from Autism and Asperger brain, the mRNA was reduced in the first but not the second, corresponding to the impaired language development in autism and its sparing in Asperger's disorder.
- This represents the first connection from gene to mRNA to brain structure to behavior in autism.

Campbell et al.

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, …

Cortical activation & synchronization during sentence comprehension in HFA subjects

Marcel Just
Vlad Cherkassky
Tim Keller
Nancy Minshew

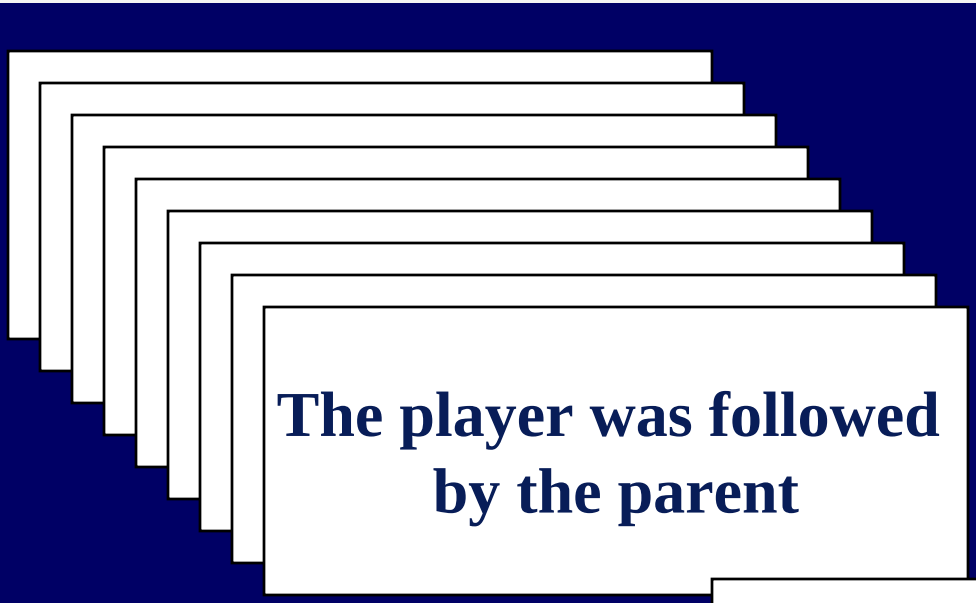
Center for Cognitive
Brain Imaging
Carnegie Mellon

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

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

Sentence reading task and comprehension probe



Center for Cognitive Brain Imaging

Who was following?

player **parent**

Brain activation during sentence comprehension in autism

In Brain, 2004

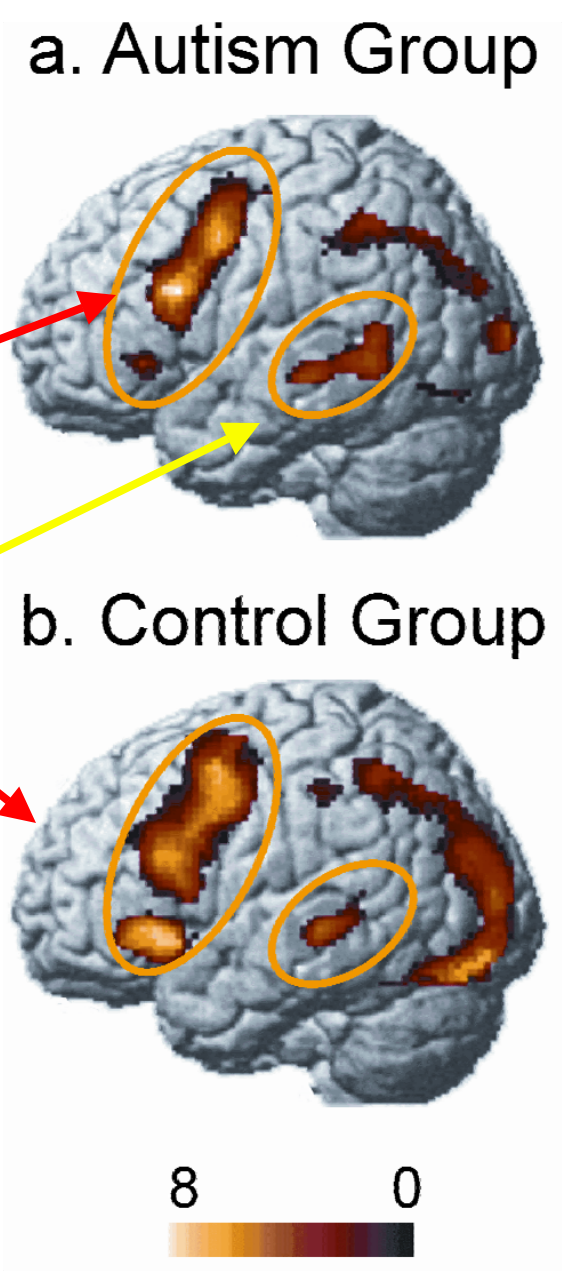
Autism group has less activation in **Broca's area**

- *(a sentence integration area)*

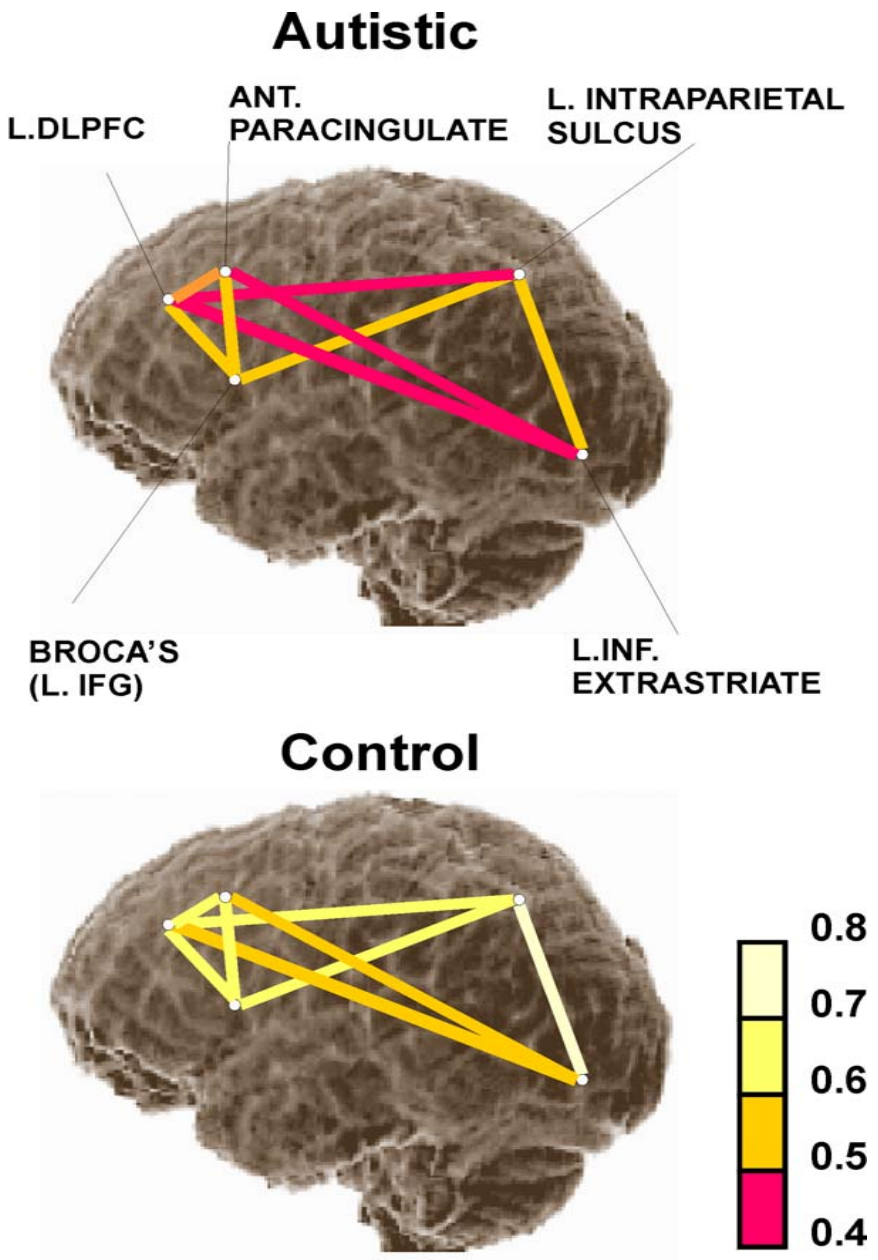
than the control group and more in **Wernicke's area**

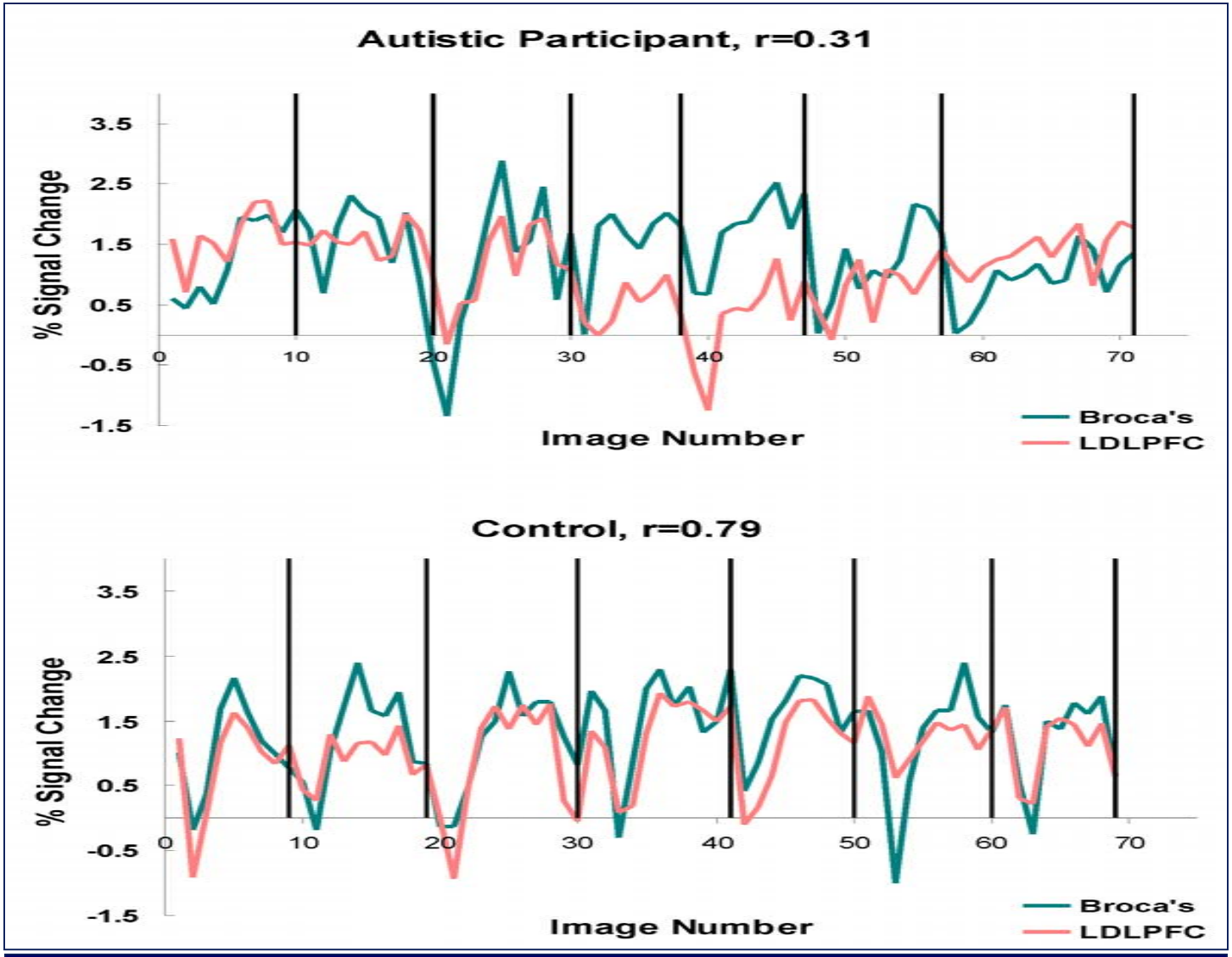
- *(a word processing area)*

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)

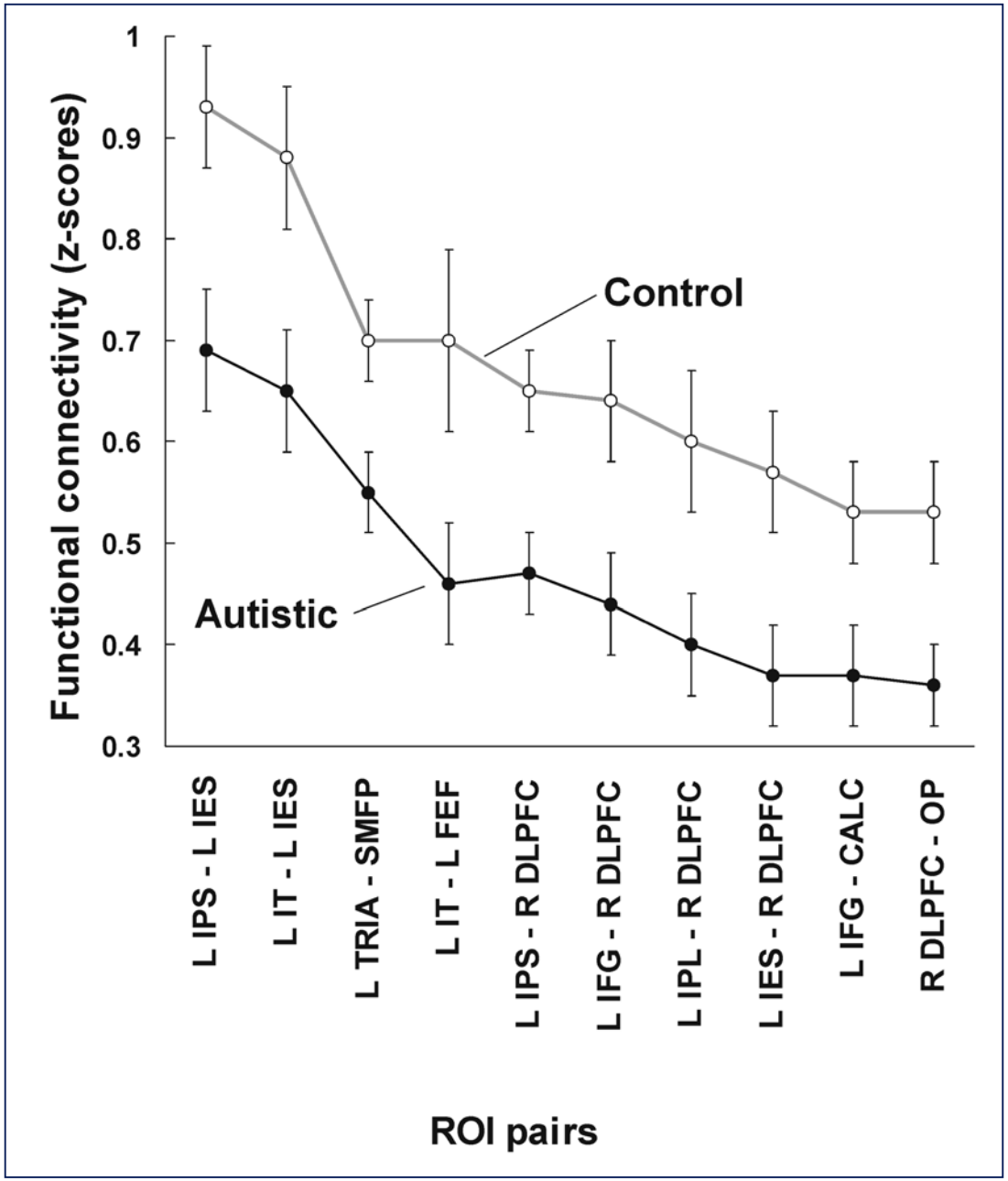




Functional Connectivity

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

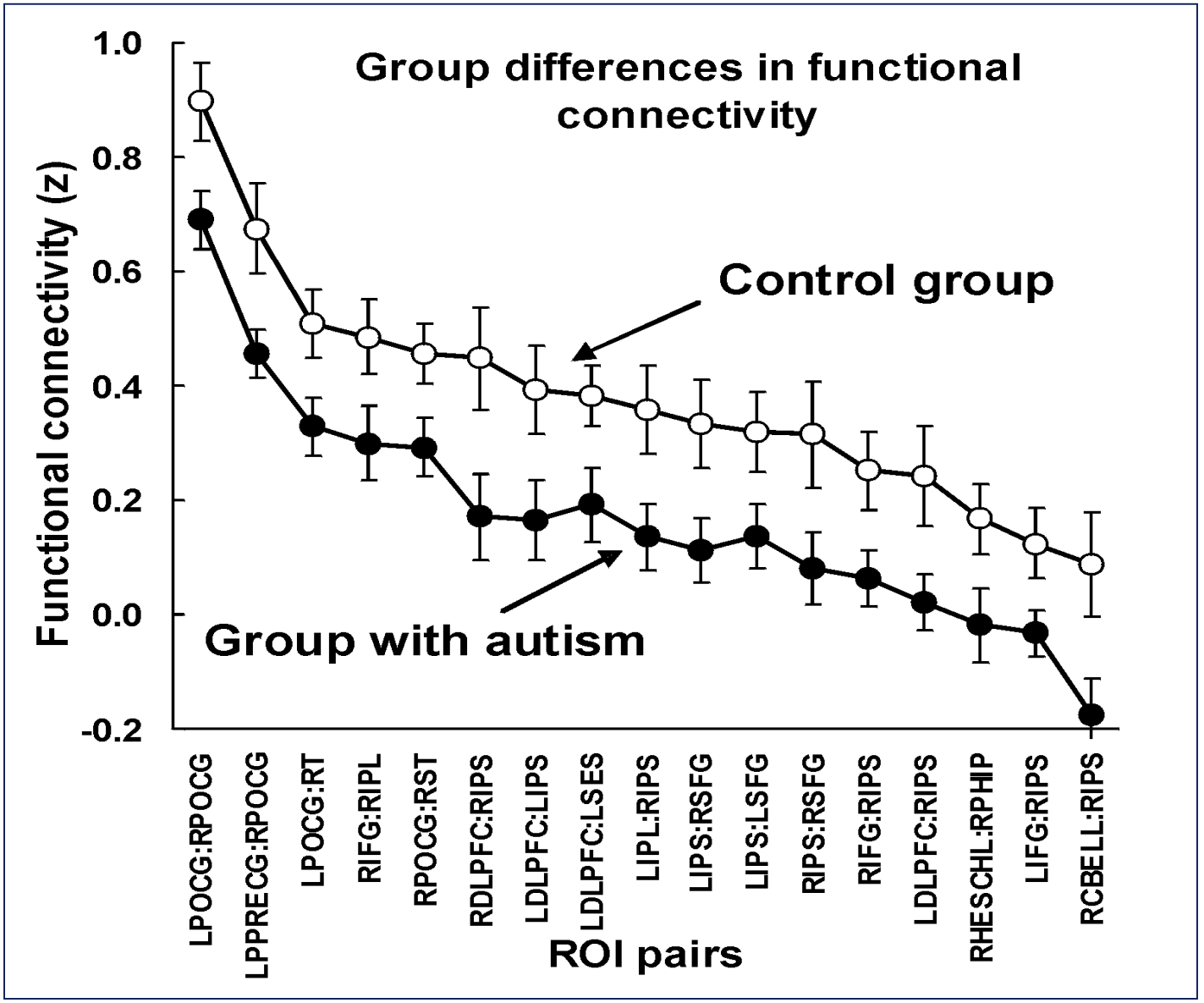
Reliable differences in functional connectivity: autism group has lower functional connectivity but same rank order



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
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

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

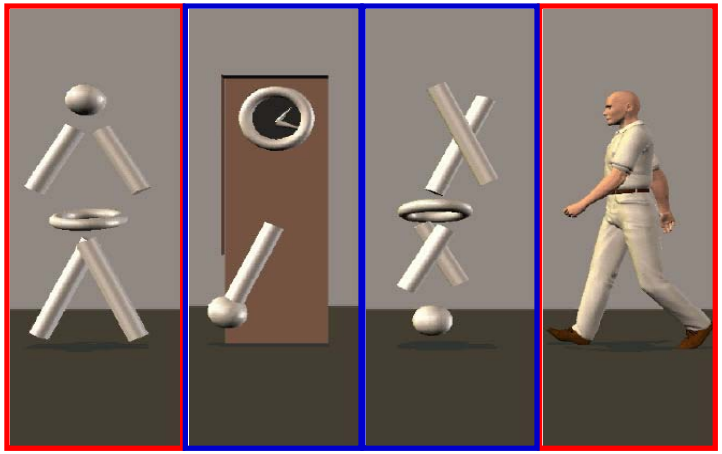
- Autism group used visually oriented processing of letters as visual-graphical codes
- Controls converted letter to verbal-phonological codes
- Autism group relied on lower level visuospatial analysis, and the large scale brain network has different organization from normals *(see factor analysis)*

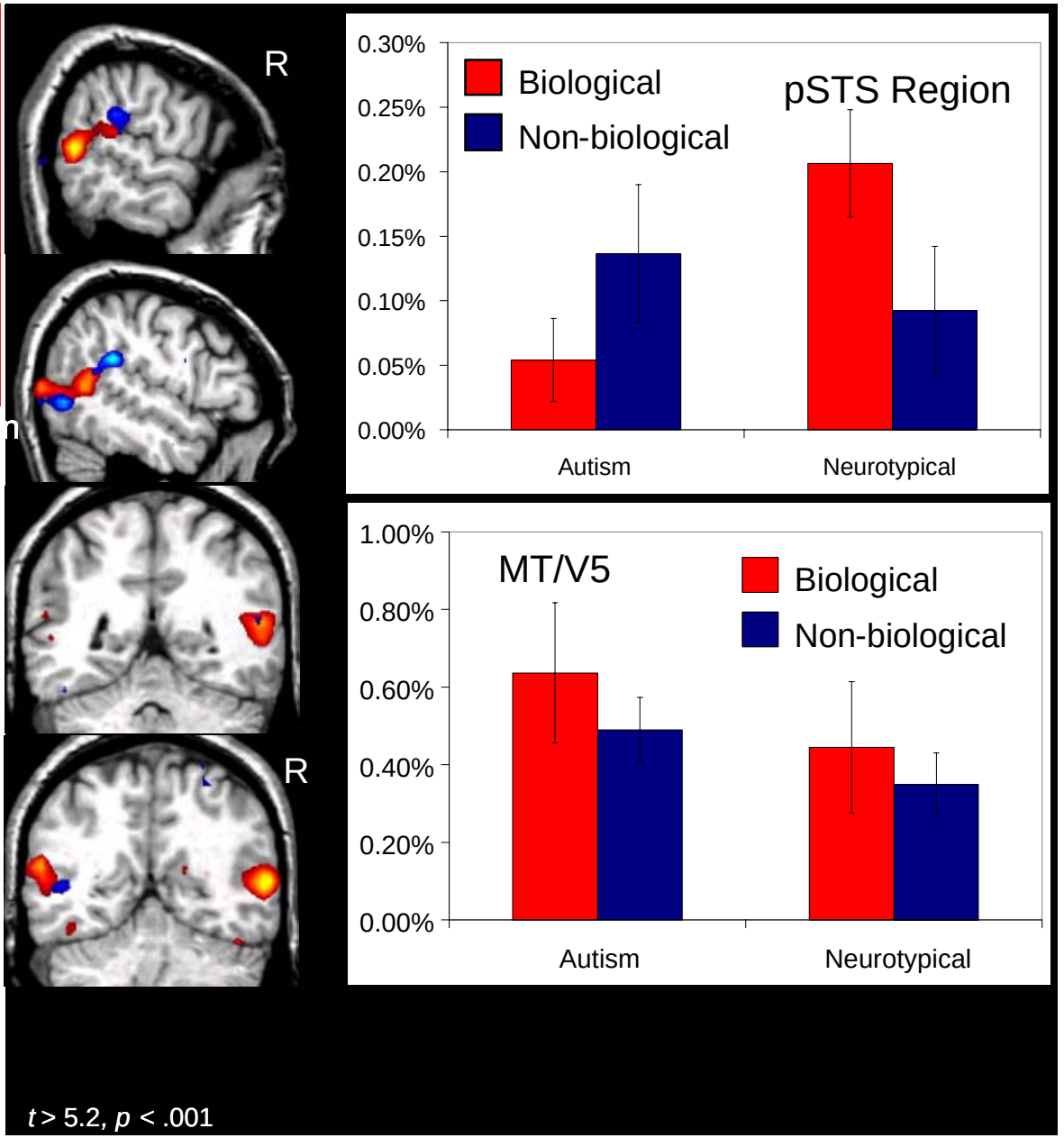
Common Features of fMRI Studies of Brain Connectivity in Autism

- General underconnectivity of cortices with frontal cortex
- Increased right posterior activation-compensatory
- Reduced inter-regional connectivity

Mirror Neuron System

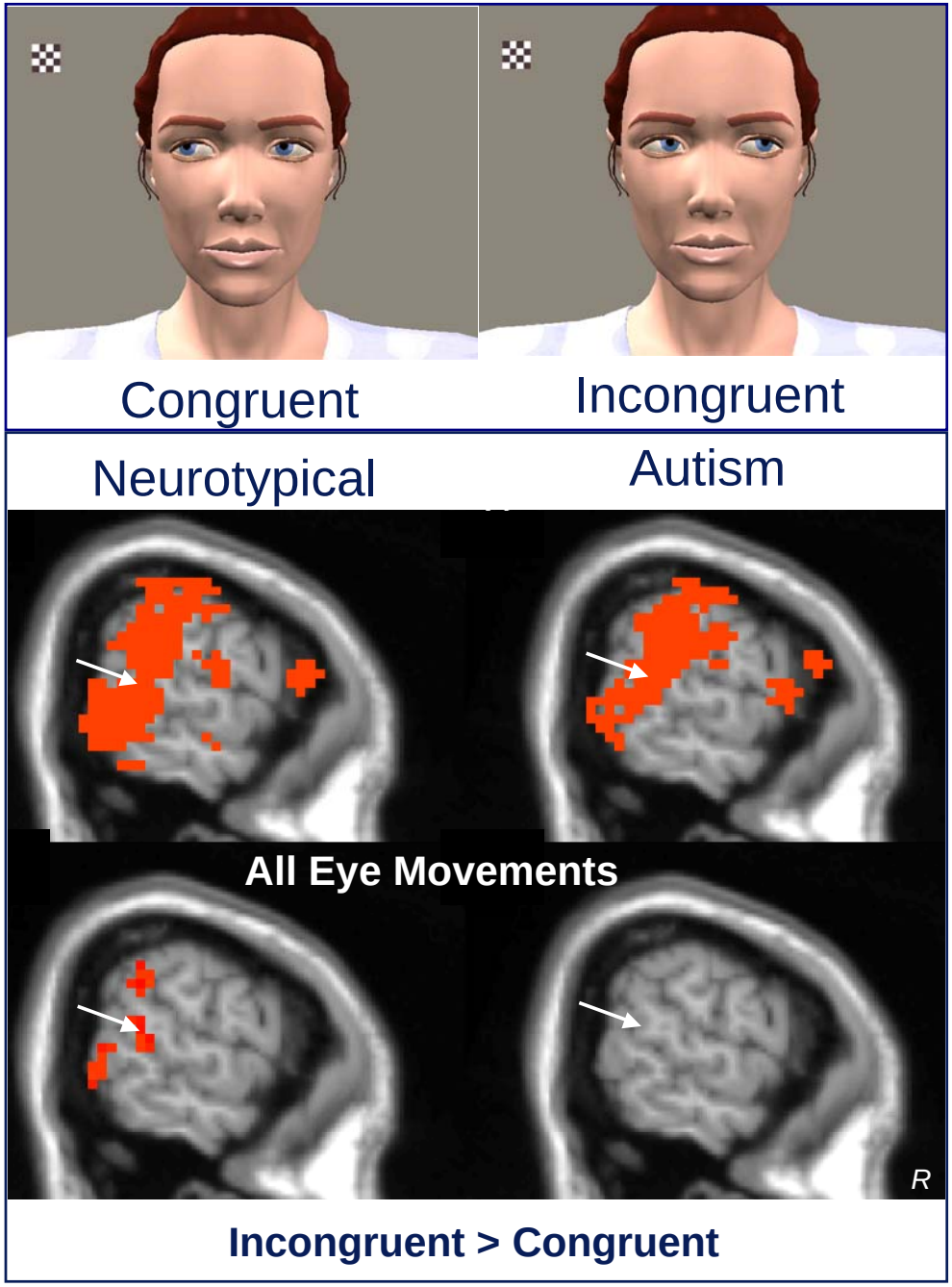
- MNS (pars opercularis in IFG) is active during observation, imitation, and performance of motor acts
- When acting in conjunction with the limbic system, it is thought to mediate the understanding of actions, emotions and internal experiences of others.

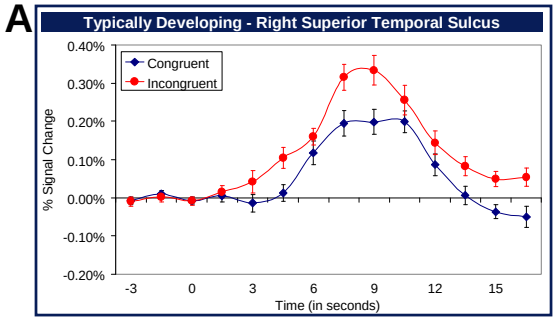


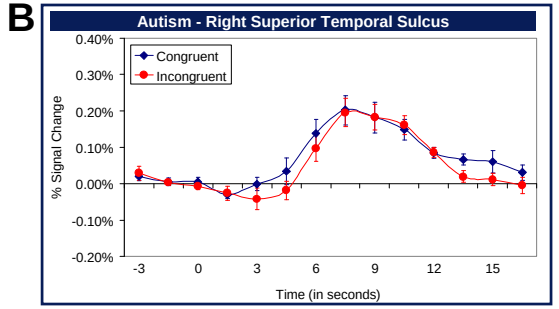


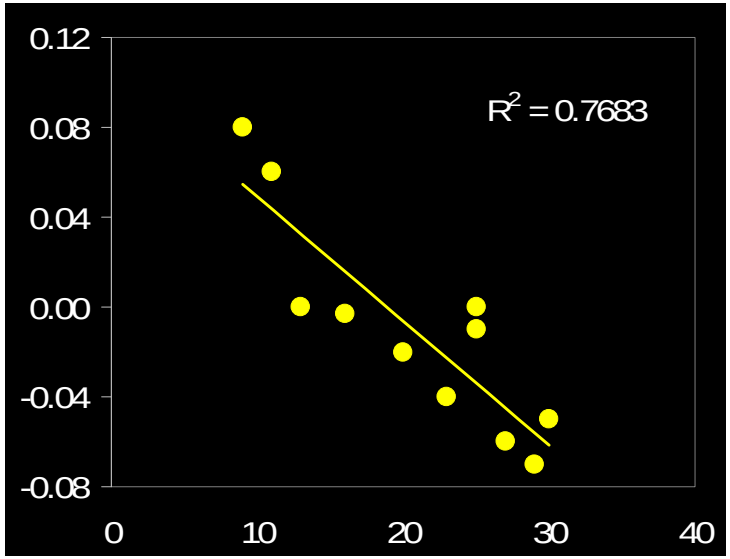
What are the brain systems involved in representing the actions and intentions of other people?

Pelphrey et al. (2003) *Journal of Neuroscience*
Carter & Pelphrey (2007) *Social Neuroscience*









Pelphrey et al. (2005) *Brain*

Concept Formation Impairments Present Globally
All rely on prototype formation mechanisms

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

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

Cognitively the problem is with prototype formation and

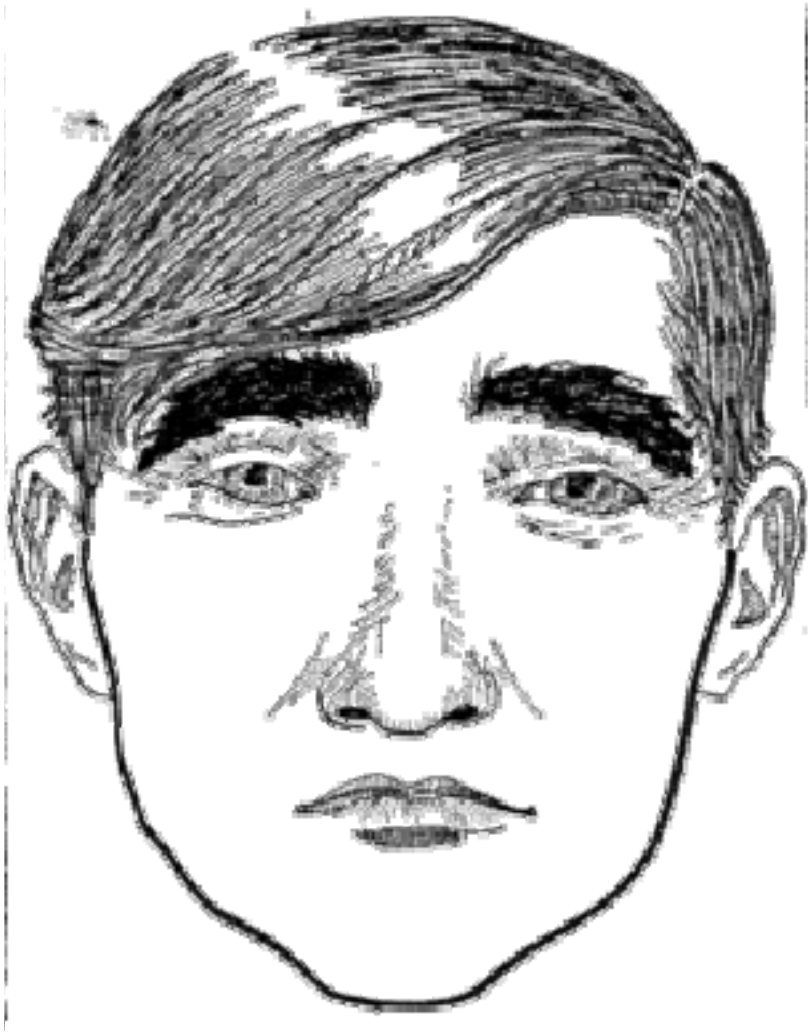
automatic processes

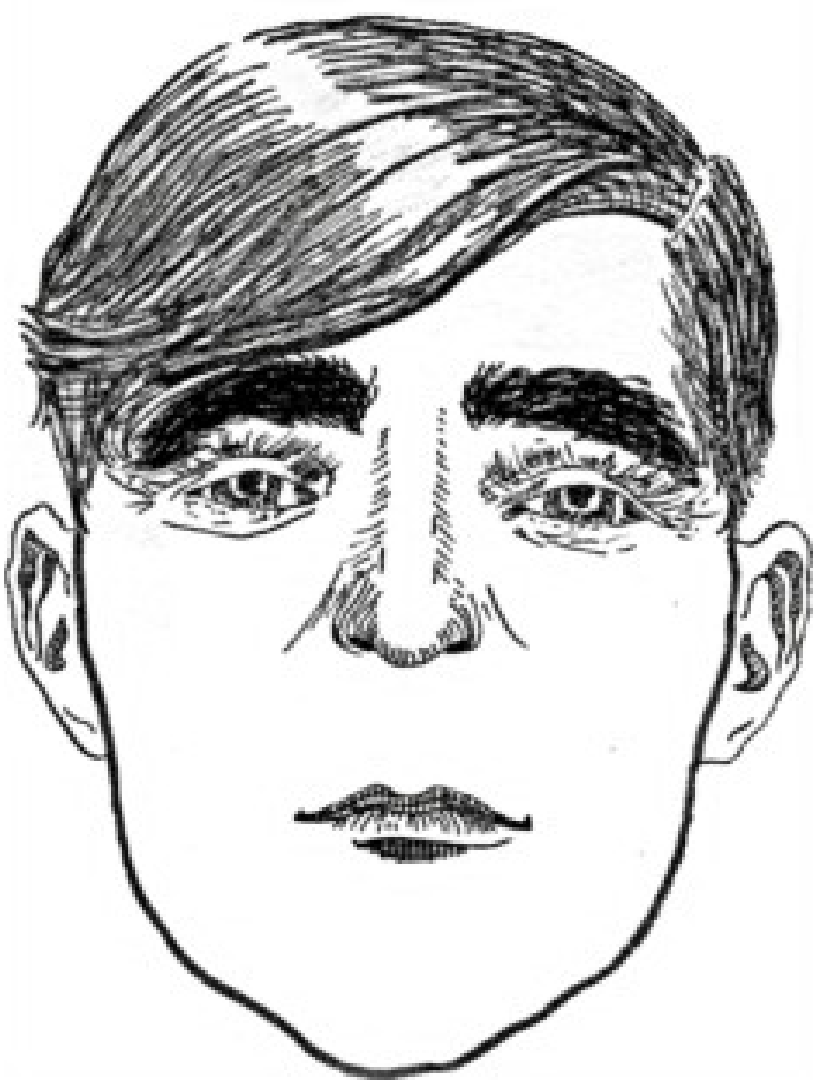
as opposed to conscious, verbally mediated reasoning.

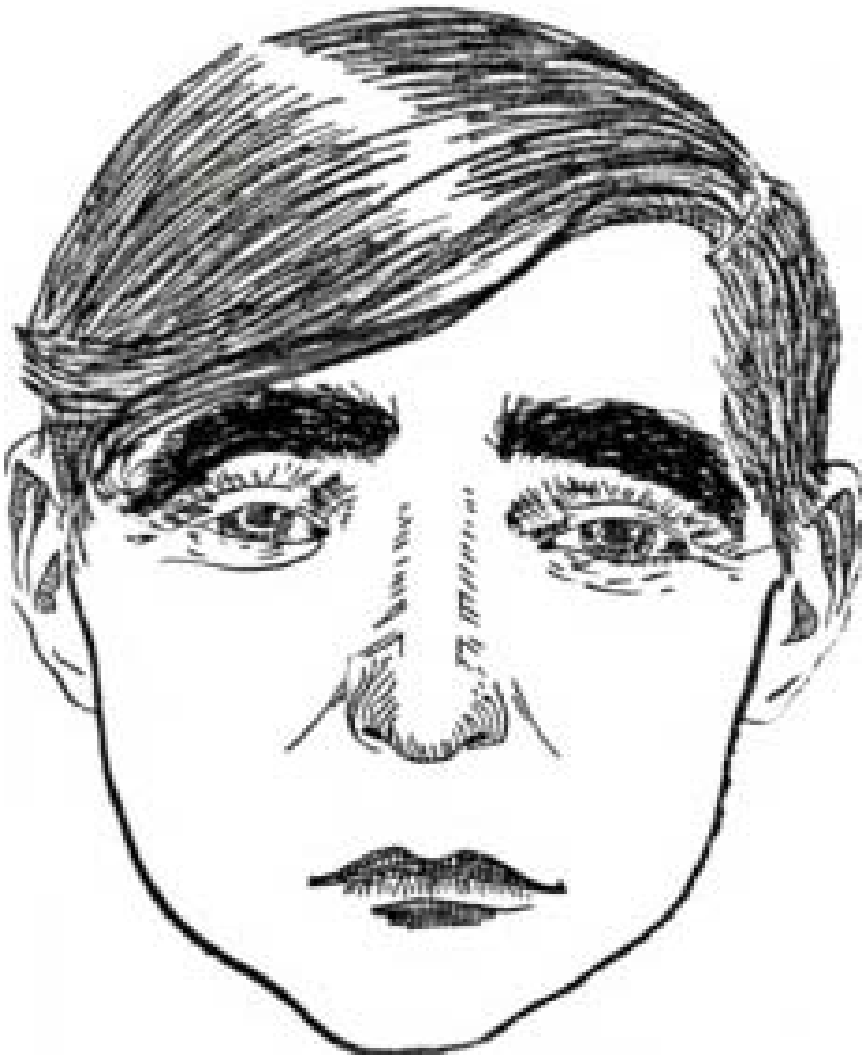
Pitt Infant and Toddler Development Center

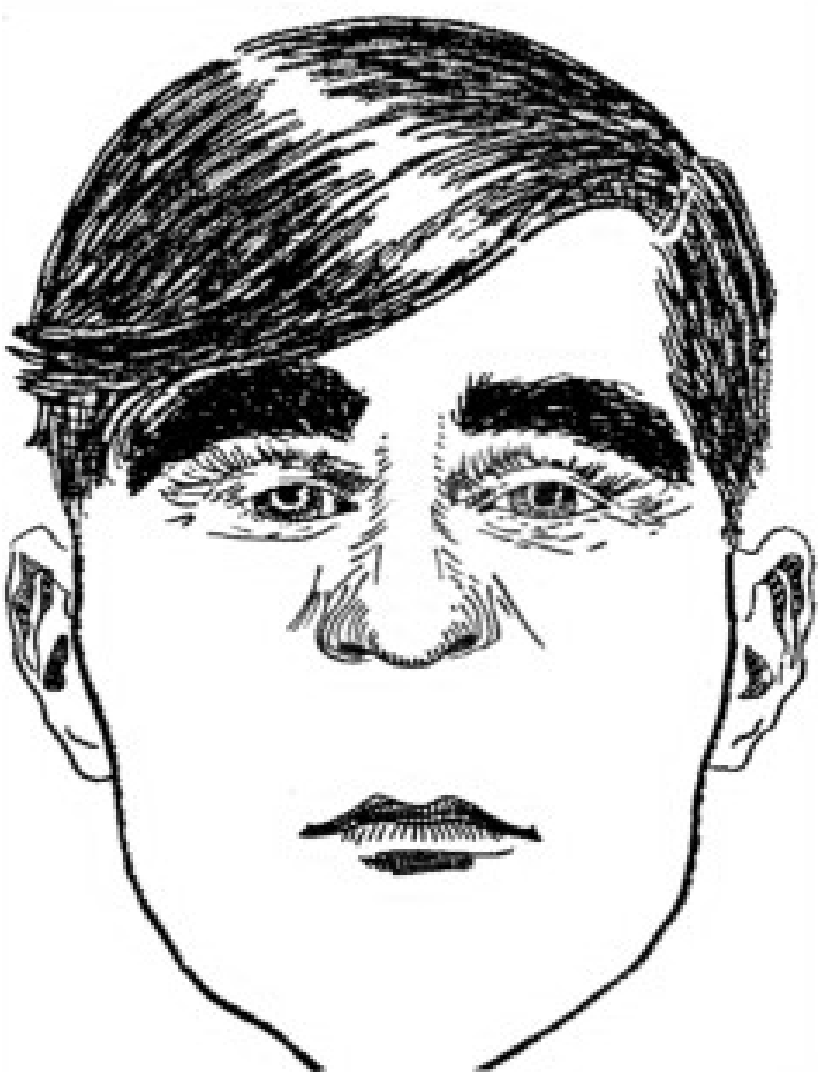
- Abilities that adults take for granted that normally develop in infancy and toddlerhood:
- For example:
  - ✓ Our abilities to recognize faces and emotional expressions
  - ✓ Our abilities to understand the difference between basic categories in the world– cats, dogs, lions …

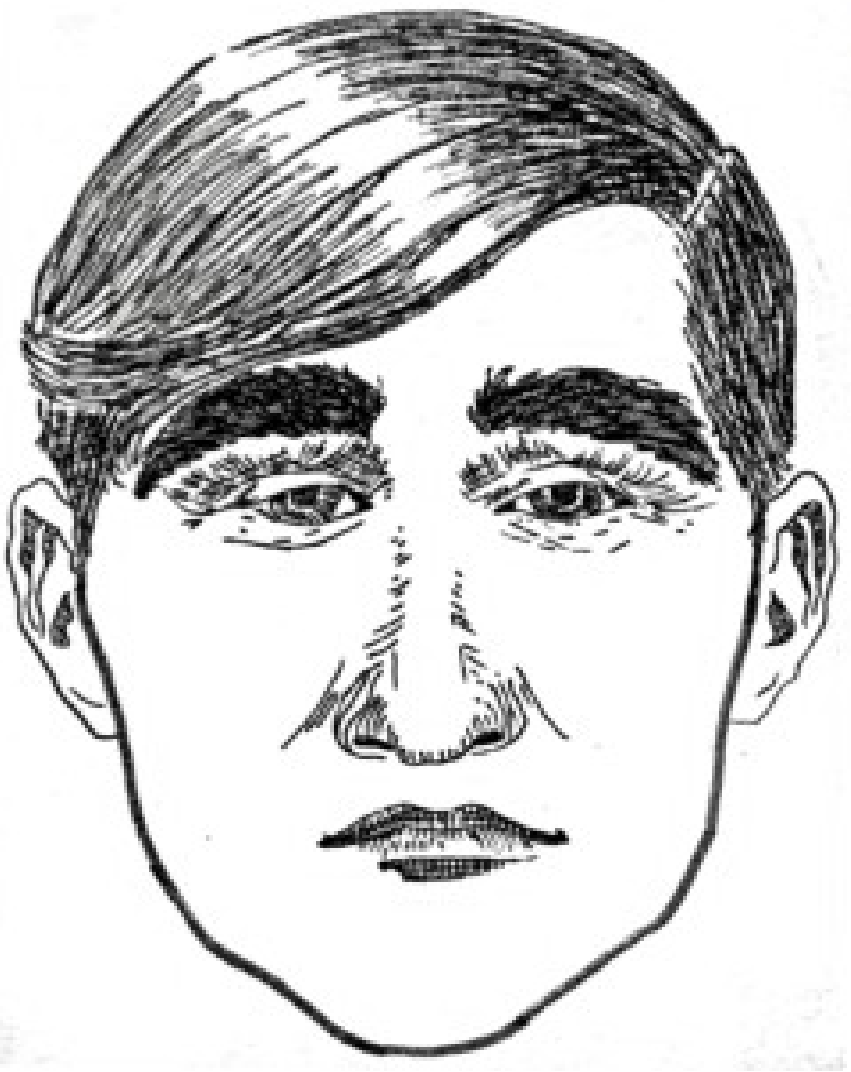
Which of these is the best example of a dog?











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











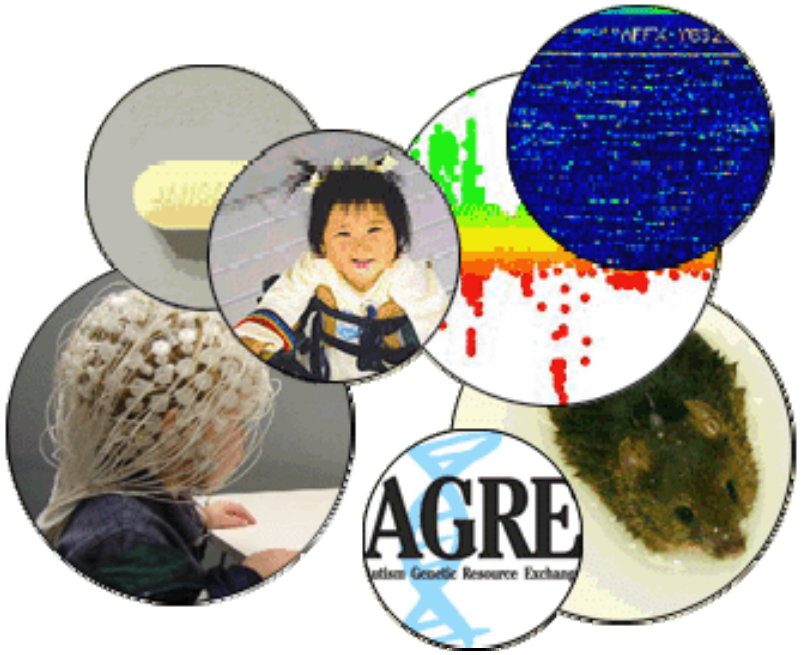

TYPICAL

SOMEWHAT TYPICAL

ATYPICAL

AUTISM SPEAKS™
It's time to listen.

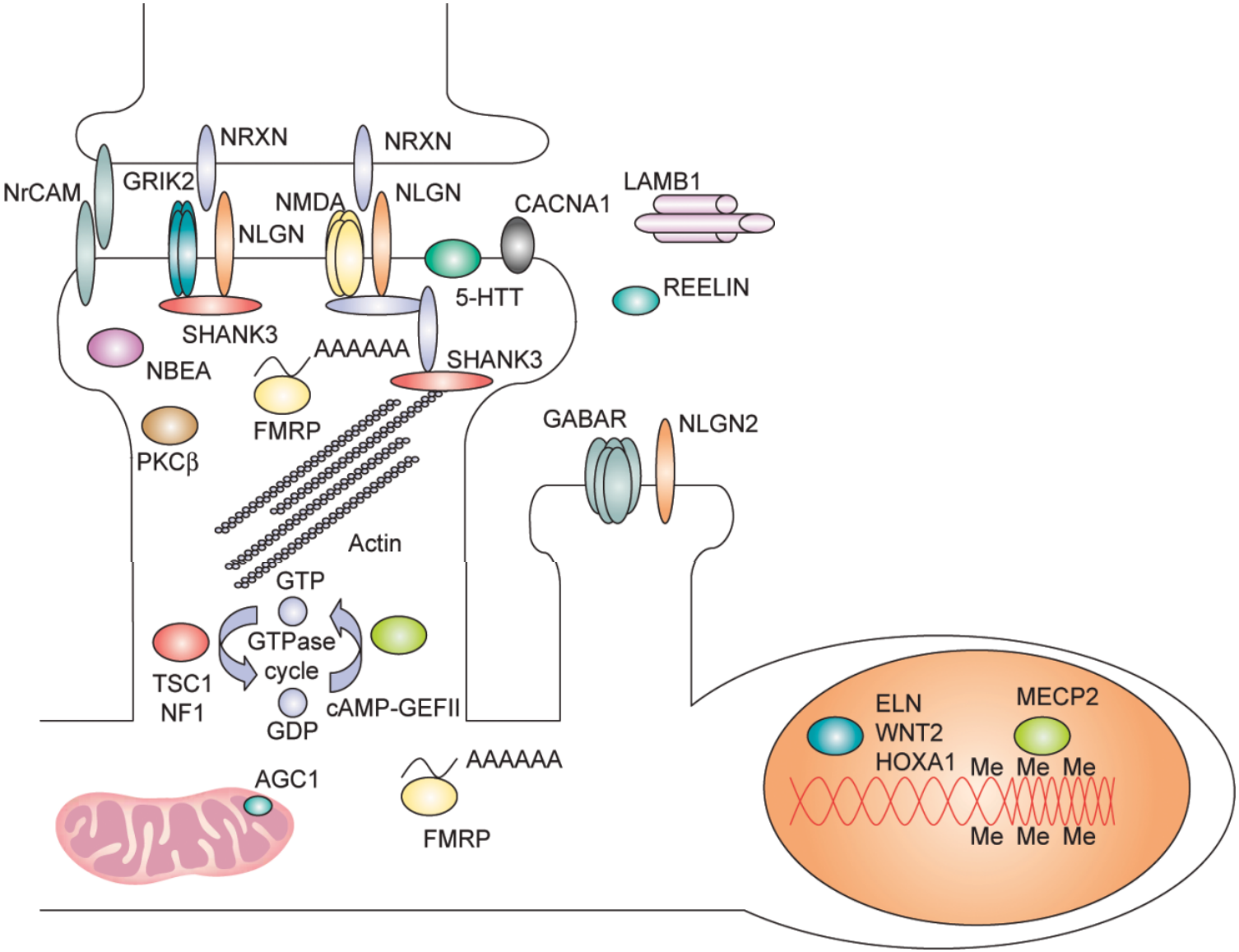
Top 10 Autism Research Events of 2007



Courtesy of:
http://www.autismspeaks.org/science/science_news/top_ten_autism_research_events_2007_main.php

The Top 10 of 2007

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


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

The Top 10 of 2007 *(cont'd)*

3. Autism Genome Project (AGP): largest genetics consortium, launched in 2004, largest study ever conducted to find the genes associated with risk of developing autism. 50 academic and research institutions from 19 countries, pooled resources and used DNA *microarray* to scan the human genome for genetic causes of autism; first analyses made public in 2007. Nature Genetics 2007. Chromo 2, 7, and 11 plus linkage signals only present in girls, identification of a specific candidate gene neurexin, associated with copy number variation

The Top 10 of 2007 *(cont'd)*

4. First drug approved by FDA to treat symptoms associated w/ autism; Risperdal
5. PTEN conditional knock out mice display enlarged brains and social behavioral deficits: PTEN interacts with several proteins in a signaling cascade that are tied to tuberous sclerosis and neurofibromatosis. 17% of individuals with autism & macrocephaly had PTEN gene. KO mice raises rescue possibilities.

The Top 10 of 2007 *(cont'd)*

6. Mouse models of genes associated with autism in humans: neuroligin-3 gene mouse model: mouse has deficits in social behaviors and an increased ability for spatial learning
7. Functional connectivity: neural deficits not in a single structure but in wiring that networks that connect different parts of brain.

The Top 10 of 2007 *(cont'd)*

8. Discovery of rare families with SHANK3 gene mutations added further evidence to synaptic dysfunction hypothesis. Codes for synapse formation & maintenance. It also interacts with neuroligins and neurolexins.
9. Lack of response to name at one year is one of earliest signs of autism; signs of autism can be identified at 14 mos in half of cases
10. Parental age (paternal or maternal or both) is related to but not necessarily the cause of increased risk of autism.

Transforming Findings

1. Autism as a disorder of complex information processing
2. Autism as a disorder of connectivity
3. Autism as a disorder of dysregulated growth of the cerebral hemispheres-gray and white matter but not corpus callosum
4. CNV in simplex; synapse-related genes in simplex & multiplex families
5. Selective gene expression will explain pattern of brain involvement and variability