Autism: Perspectives on Genetics, Neurology and Behavior

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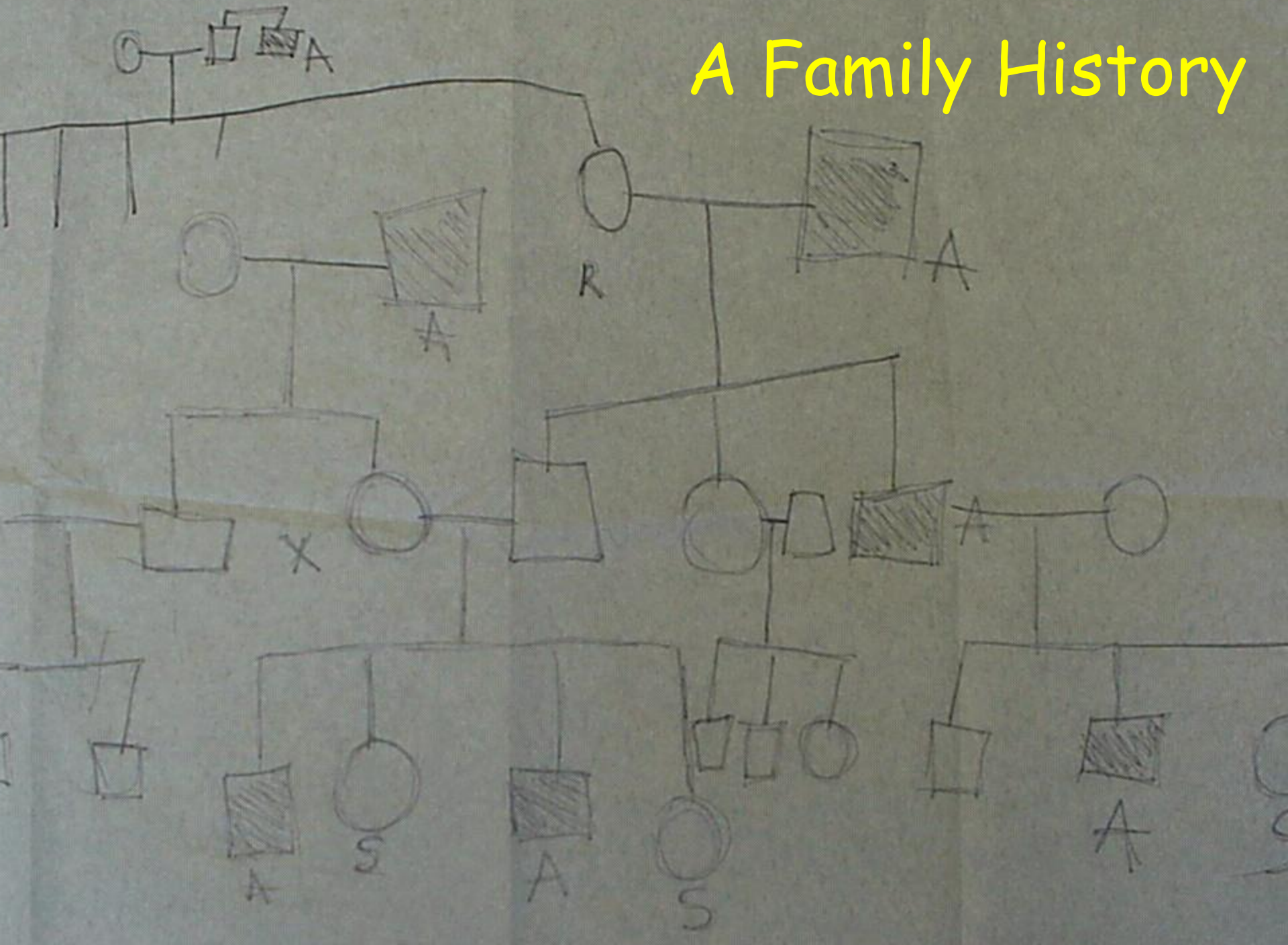
So – what is Autism all about?

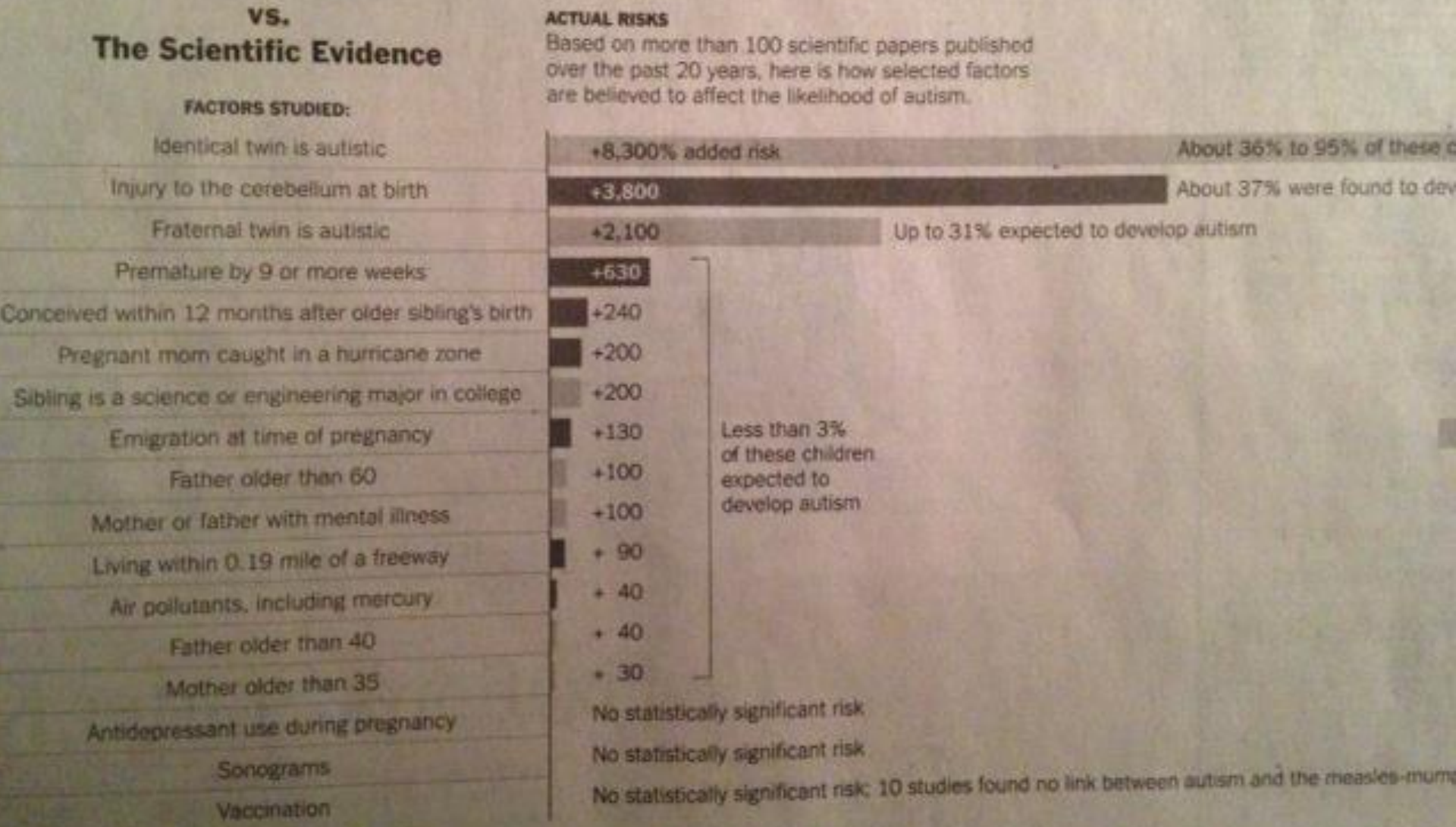
Autism can be viewed as a genetically determined neurodevelopmental disorder

A Family History



Risk of Autism

Press Attention
vs.
The Scientific Evidence



Genetics

- With identical twins, there is a 36-95% chance the other child will also have ASD
- With non-identical twins, there is a 0-31% likelihood
- Parents who have a child with ASD have a 2%–18% chance of having a second child who also has ASD
- About 10% of children with ASD are also identified as having other genetic and chromosomal disorders

Common Genetic Conditions associated with Autism

- Fragile X
- Rett's Syndrome
- Tuberous Sclerosis
- Neurofibromatosis
- Down Syndrome
- 22q11 deletions (Di George Syndrome)
- Other micro-array anomalies
- Mitochondrial Disorders

Genetics: Microarray

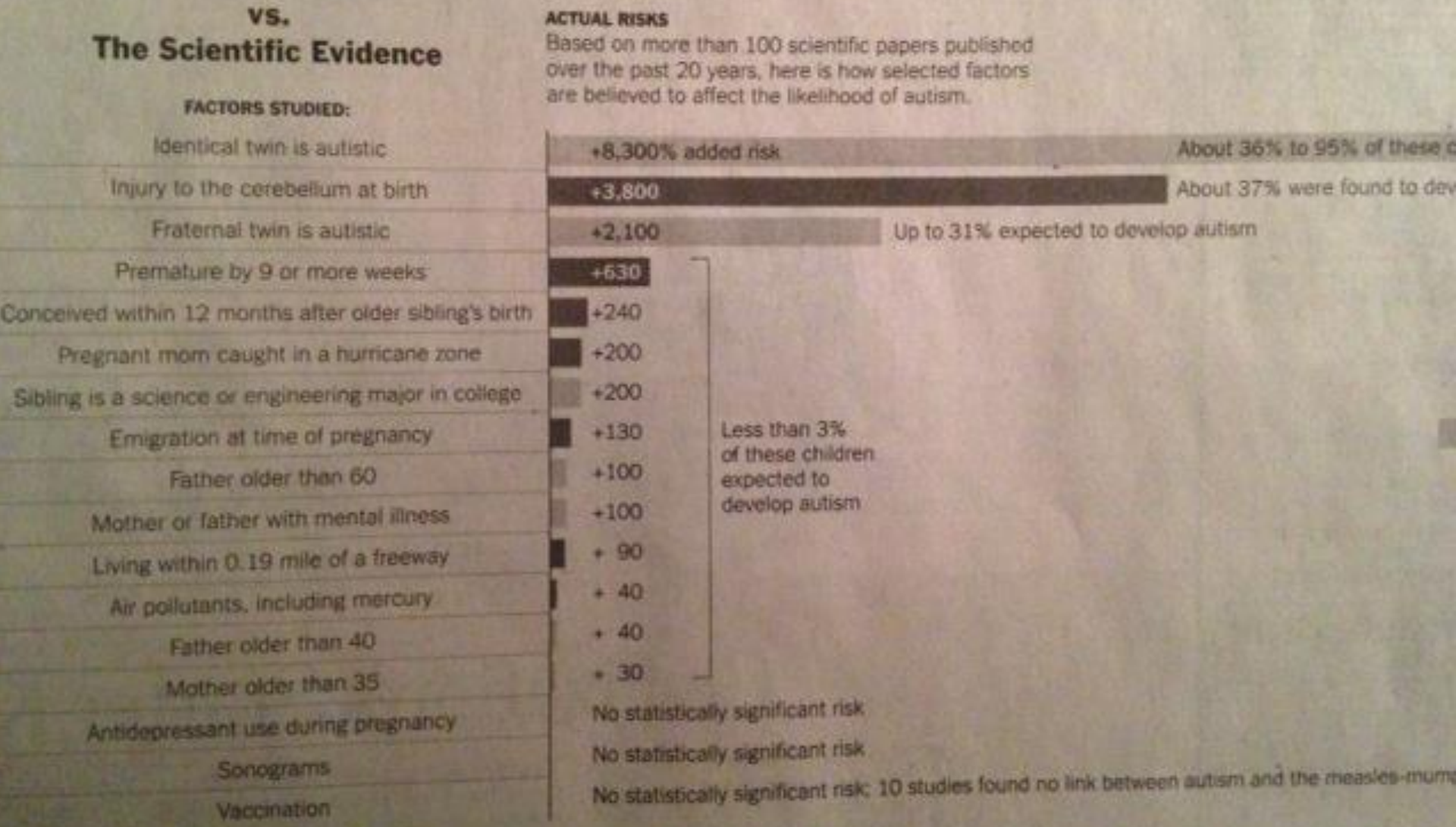
- New genetic anomalies are being identified with the Microarray technology and we are trying to sort out what all this means

Genetics

- Fragile X syndrome is the most common identified genetic condition associated with Autism
- Recurrence rate in families
  - 20% increased prevalence of ASD and related disorders in families
- Twin Studies
  - 75-90% concordance in monozygotic twins
  - 5-10% concordance in same-sex dizygotic twins

Risk of Autism

Press Attention
vs.
The Scientific Evidence



Other Etiological Considerations

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Prematurity and Autism

- A population-based study of adults born at very low gestational age compared with term-born adults described a significant increased risk for Autism:
  - relative risk of 7.3 among those born at 28 to 30 weeks gestation
  - relative risk of nearly 10 in those born at 23 to 27 weeks gestational age

(Moster, Markestad, et al, 2008)

Autism in ex-preterm infants

- 91 ex-preterm infants < or = 1500 g at birth were studied using the
  - MCHAT
  - Vineland Adaptive Behavior Scale
  - Child Behavior Checklist

- 26% had a positive result on the autism screening correlating highly with
  - internalizing behavioral problems on the *Child Behavior Checklist* and
  - socialization and communication deficits on the *Vineland Scales.*

Limperopoulos et al, Pediatrics. 2008 McGill University, Montreal, Quebec, Canada.

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Prematurity & ASD: Cerebellar Hemorrhage

- Children with isolated cerebellar injury versus preterm age-matched controls demonstrated significantly greater motor disabilities, language delays, and cognitive deficits

- **37% of infants with cerebellar injury tested positive for early signs of autism using the M-CHAT**

(Limperopoulos, Bassan, Gaureau et al, 2007).

Perinatal Risk Factors for Autism Spectrum Disorders

- Overall, between 12-13% of ASD among children in multiple U.S. communities was related to being born too early, too small, and/or by Cesarean delivery.
- In other words, if it were possible to eliminate the many different reasons children are born too early, too small, and/or delivered by Cesarean, the number of children with ASD would be reduced by 12-13%.

Ann Epidemiol. 2014 Apr;24(4):260-6.

Perinatal Air Pollution & ASD

- Perinatal exposures to the highest versus lowest quintile of diesel, lead, manganese, mercury, methylene chloride, and an overall measure of metals were significantly associated with ASD, with odds ratios ranging from 1.5 (for overall metals measure) to 2.0 (for diesel and mercury).

Environmental Health Perspectives 121:978-985 2013

Particulate Matter Air Pollution & ASD

- Higher maternal exposure to PM2.5 during pregnancy, particularly the third trimester, was associated with greater odds of a child having ASD.

Environ Health Perspect; volume 123 | number 3 | March 2015 •

Agricultural Pesticides and Autism

- Children of mothers living within 500 m of field sites with the highest amount of organochlorine pesticide compared to those with mothers not living near field sites had an odds ratio for ASD of 6.1

Roberts et al Environ Health Perspect. 2007 Oct;115(10):1482-9.

Gene-Environment Interaction

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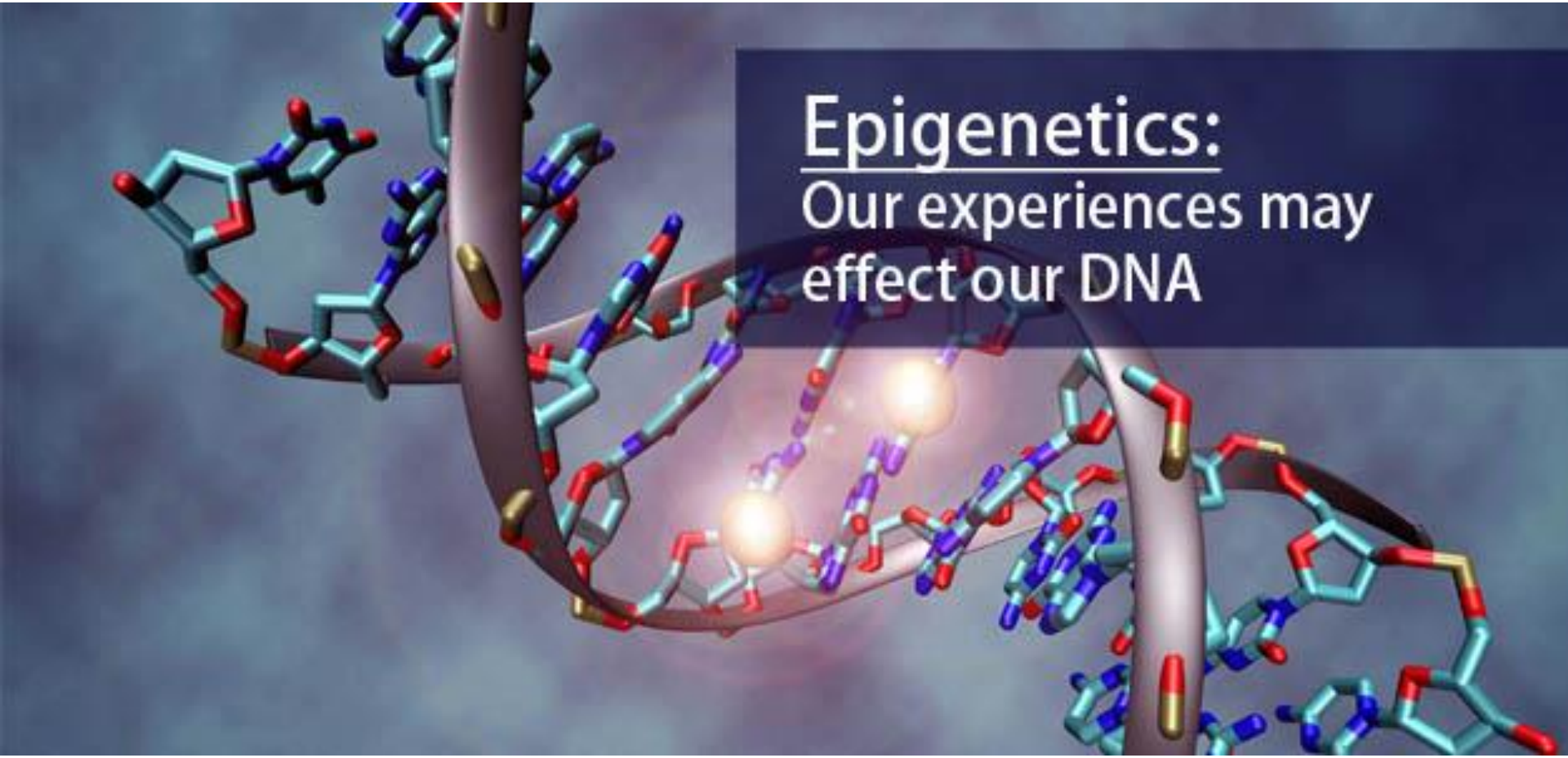
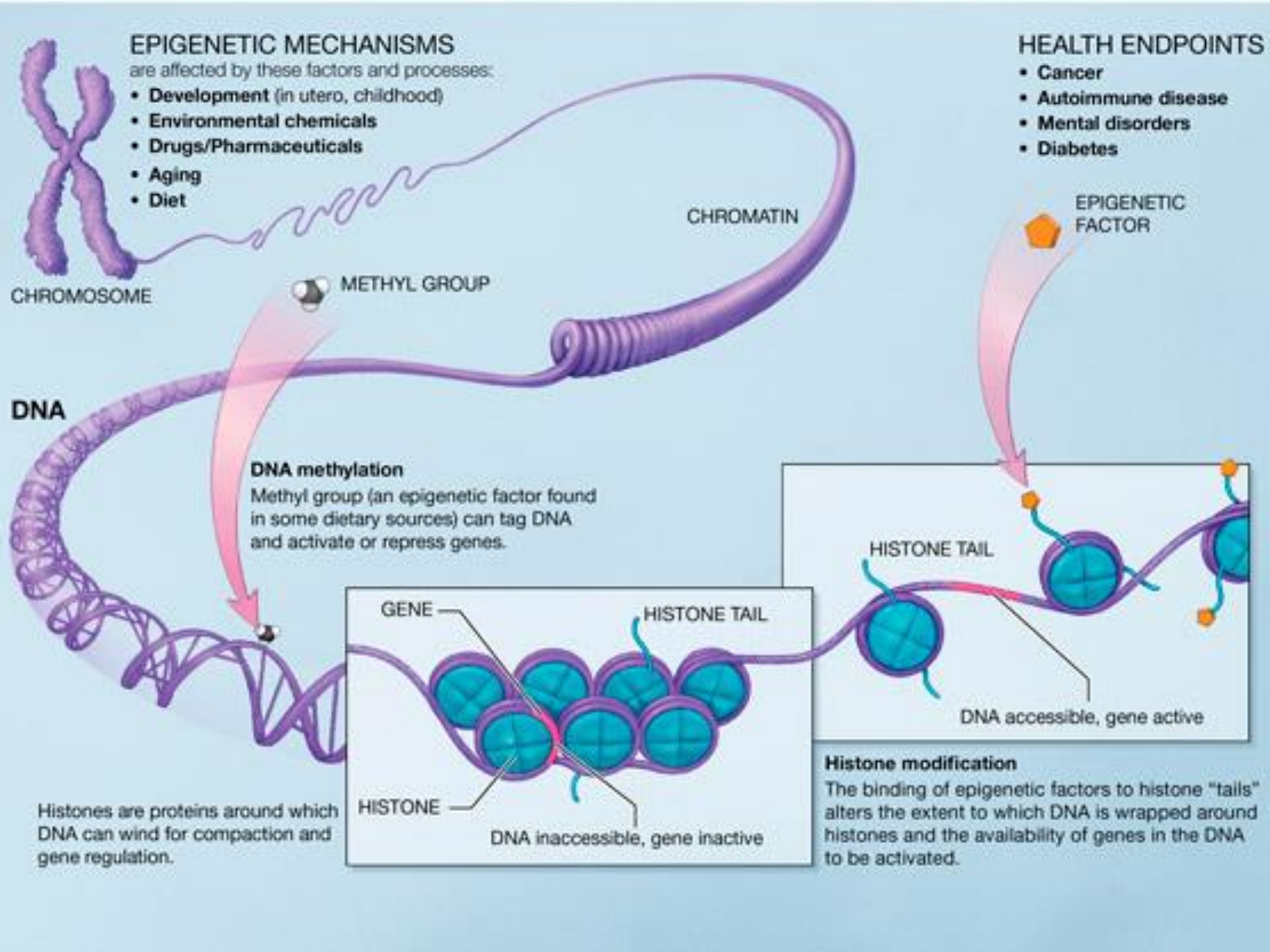
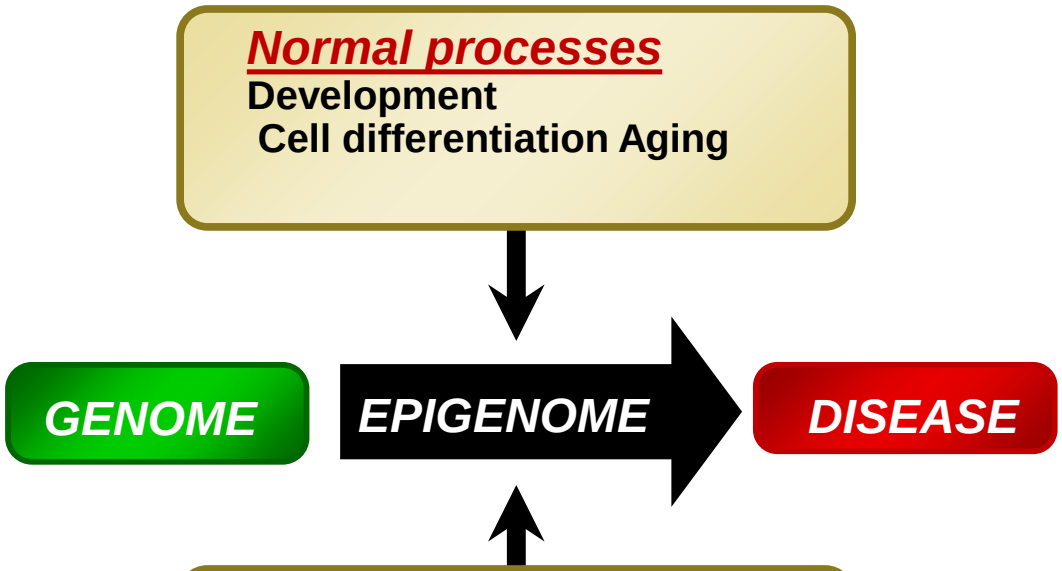

Epigenetics:
Our experiences may
effect our DNA


EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Epigenetic Changes and Human Diseases



Adverse health outcomes

- Cancer
- Cardiopulmonary disease
- Autoimmune disease
- Obesity
- Diabetes
- Neurodevelopmental disorders
- Schizophrenia
- Addiction
- Depression

Slide Curtesy of Linda Birnbaum NIEHS 2012

Neurology of Autism

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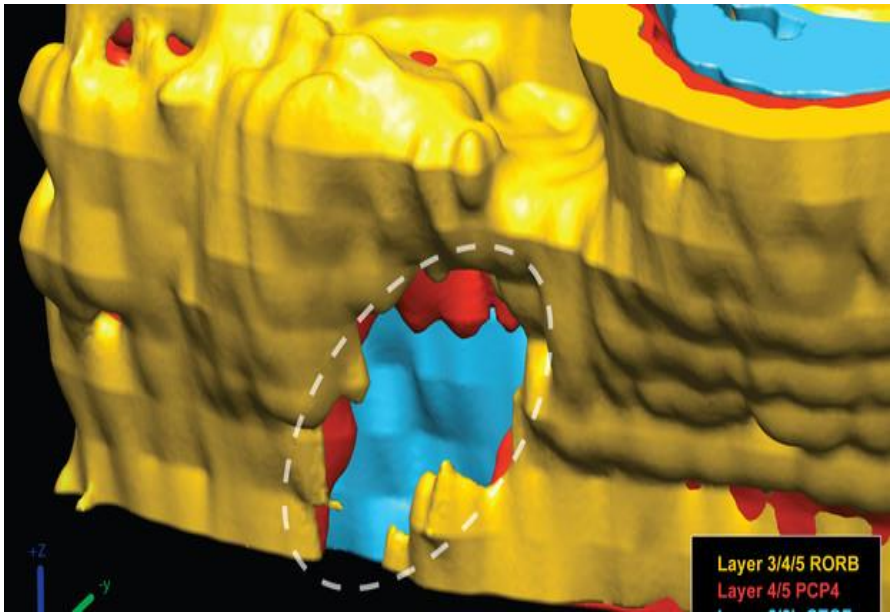
Patches of Disorganization in the Neocortex of Children with ASD

- Molecular analysis of postmortem samples of brain tissue obtained from 11 children with autism showed that the prefrontal and temporal cortexes had patches of neuronal disorganization
- There was a high variability across samples



Stoner R., et al. N Engl J Med 2014; 370:1209-1219

Patches of Disorganization in the Neocortex of Children with ASD

- "We found a novel aspect of cortical development which points directly and clearly to autism beginning during early pregnancy"
- By the second trimester, fetal brain cells are making complex connections
- Assembly patterns and connections perform unique roles in processing information.

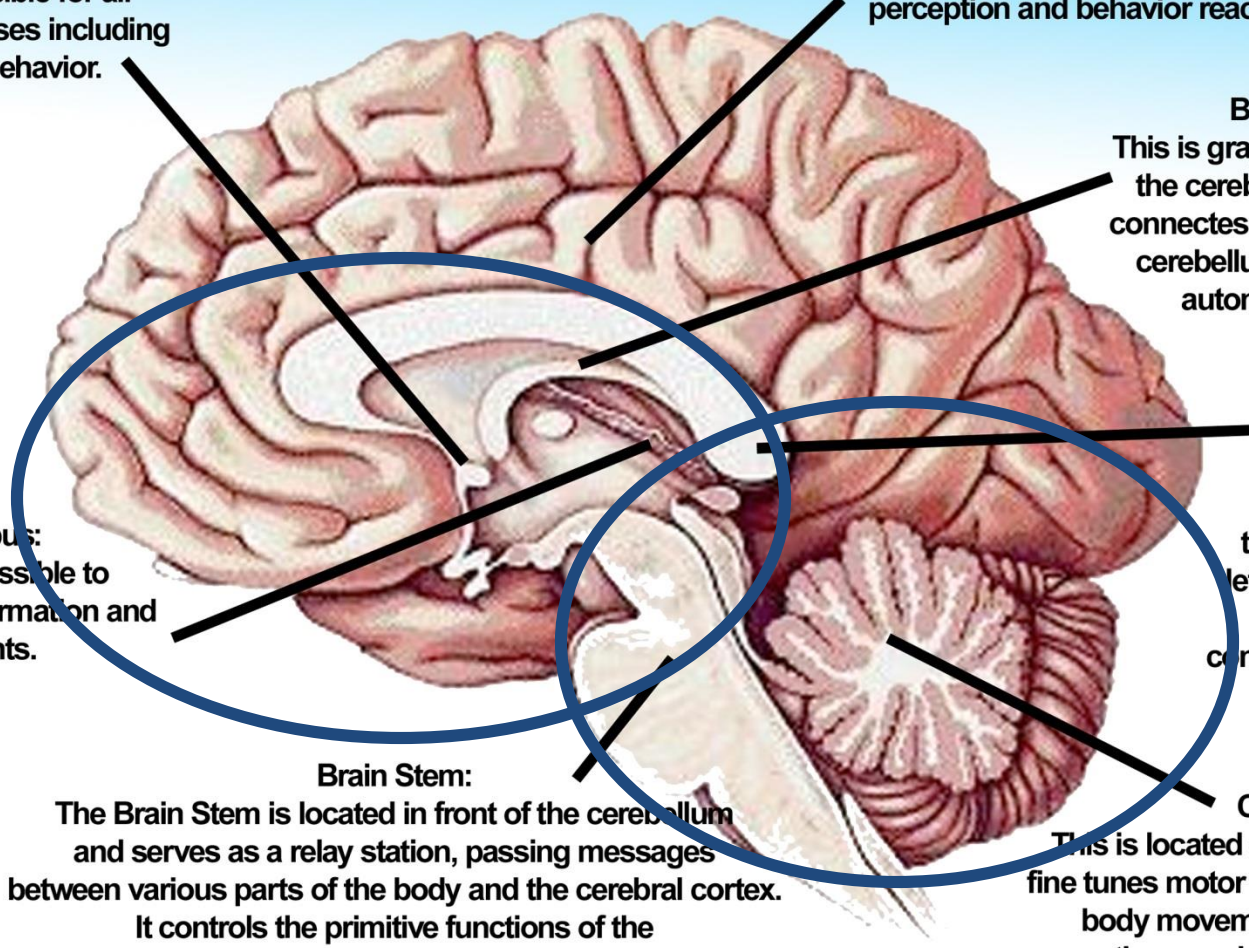
Stoner R., et al. N Engl J Med 2014; 370:1209-1219

Neuropathological Findings in ASD

- **Cerebral cortex** (>50% of the studied cases showed features of cortical dysgenesis).
- **Limbic system** (9 of 14 studied cases showed increased cell density and smaller neuronal size),
- **Cerebellum** (21 of 29 studied cases showed a decreased number of Purkinje cells in cerebellar nuclei and inferior olive)

Saskia J. M. C. Brain Volume 127, Issue 12Pp. 2572-2583 2004

Parts of the Brain Affected by Autism



Cerebral Cortex:
A thin layer of gray matter on the surface of the cerebral hemispheres. two thirds of this area is deep in the tissues and folds. this area of the brain is responsible for higher mental functions, general movement, perception and behavior reactions.

Amygdala:
This is responsible for all emotional responses including aggressive behavior.

Basal Ganglia:
This is gray masses deep within the cerebral hemisphere that connectes the cerebrum and the cerebellum. It helps regulate automatic movement.

Corpus Callosum:
This consists of closely packed bundles of fibers that connect the right and left hemispheres of the brain and allows them to communicate with one another.

Hippocampus:
This makes it possible to remember new information and recent events.

Brain Stem:
The Brain Stem is located in front of the cerebellum and serves as a relay station, passing messages between various parts of the body and the cerebral cortex. It controls the primitive functions of the body essential to survival including breathing and heart rate.

Cerebellum:
This is located at the back of the brain. It fine tunes motor activity, regulates balance, body movements, coordination and the muscles used for speaking

Neurological Disorders

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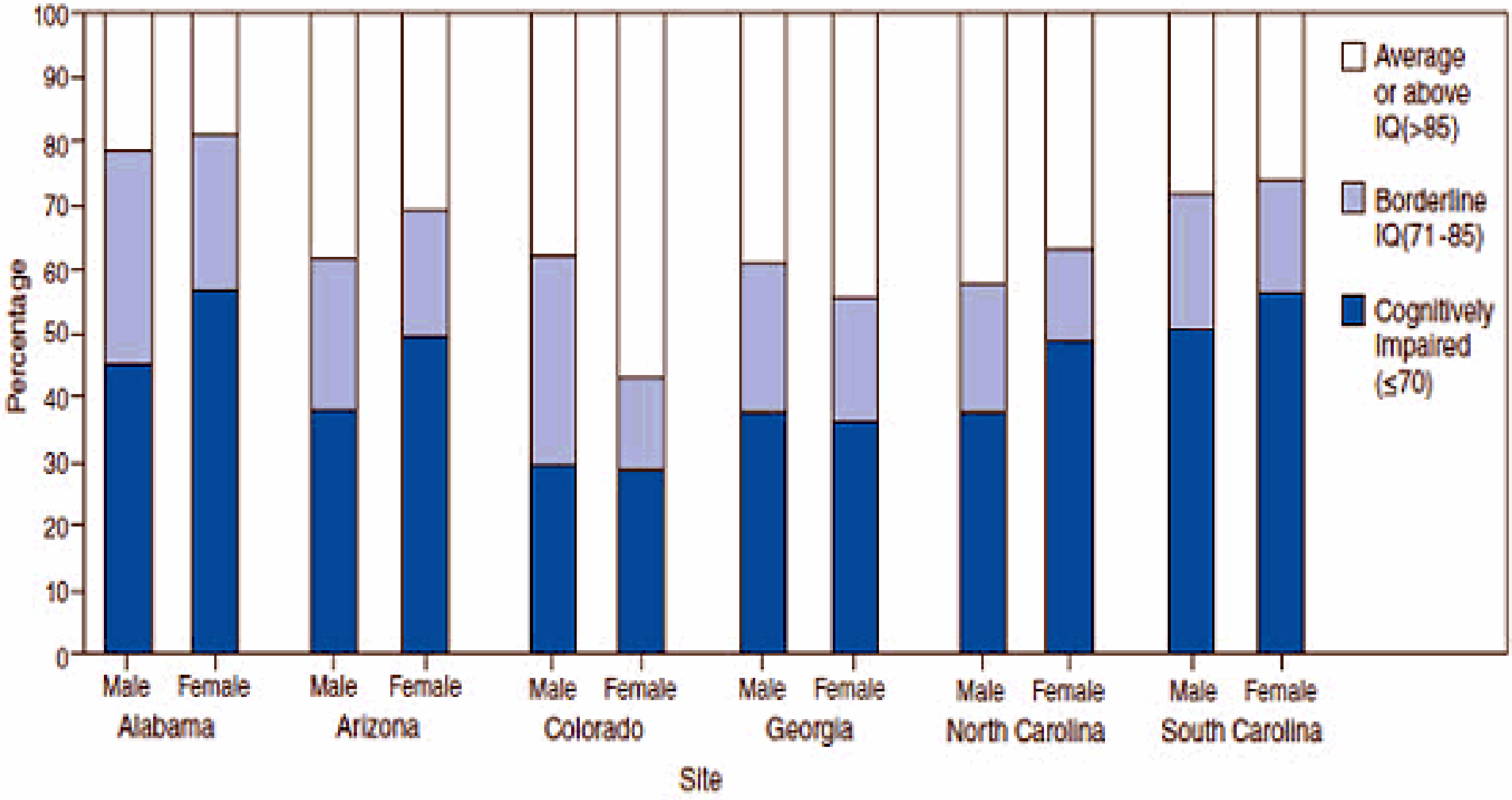
Neurological Disorders

- Intellectual Disabilities
- Seizure Disorders
- Processing Disorders
- Sensory Integration Dysfunction
- Learning Disabilities
- Attention Disorders
- Motor Disorders
- Sleep Disturbances
- Emotional Disturbances
- Challenging Behaviors

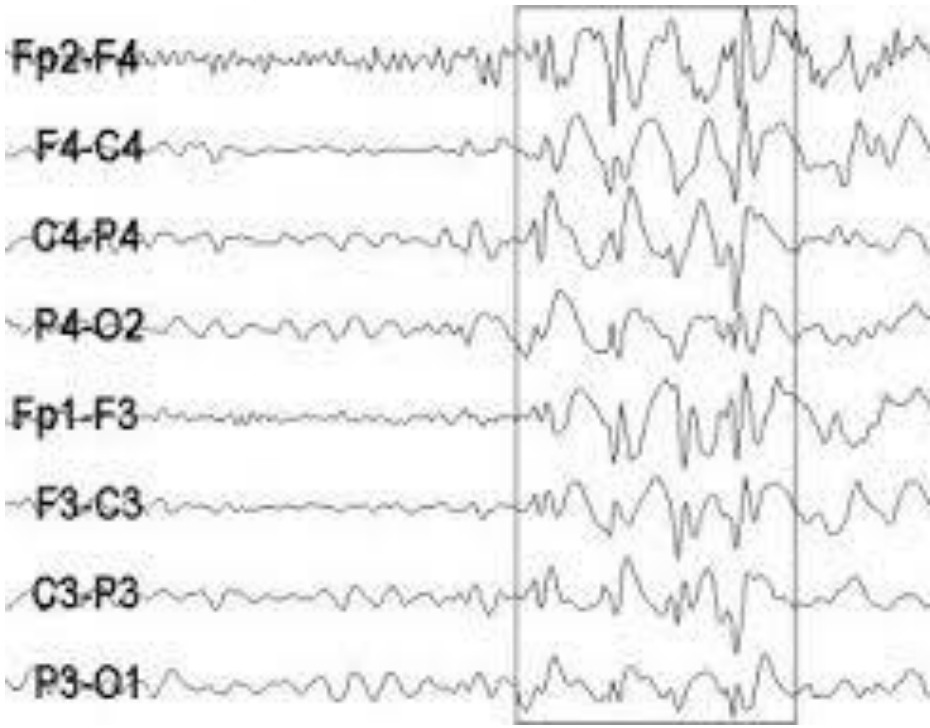
Intellectual Disability



*Sites with psychometric test data on ≥75% of identified cases of ASD were included.

Seizure Disorder

- Seizure Prevalence:
  - 1-2% of children in the general population
  - children with ASD have estimates varying widely from 5% to 38%
- Some children may have staring spells or tic movements that can be confused with seizures



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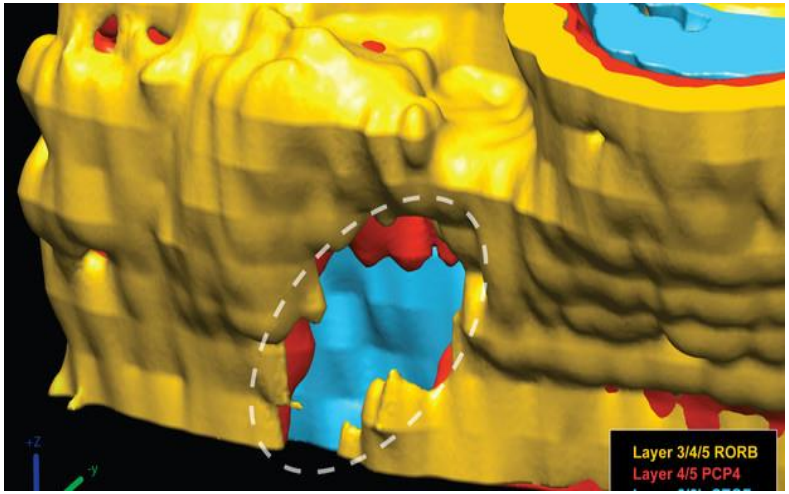
Motor Disorders

- Hypotonia and ligamentous laxity
  - Affects posture
  - Flat feet with pronation
- Coordination and organization
  - Fine motor e.g. writing
  - Gross motor e.g. playing soccer
  - Toe walking – motor vs sensory
- Stereotypic movements
  - Usually hand and finger
- Tics and Tourette's about 6x more likely

Processing of Information



- Assembly patterns and connections perform unique roles in processing information

- Cognitive
- Vision
- Hearing
- Touch
- Taste
- Proprioception
- Balance

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Cognitive Processing

IQ/ Index Scores	Standard Score	Percentile	Range
Full scale IQ	104	61	Average
Verbal Comprehension Index	119	90	High Average
Perceptual Reasoning Index	104	61	Average
Working Memory Index	102	55	Average
Processing Speed Index	78	7	Borderline
General Ability Index	113	81	High Average

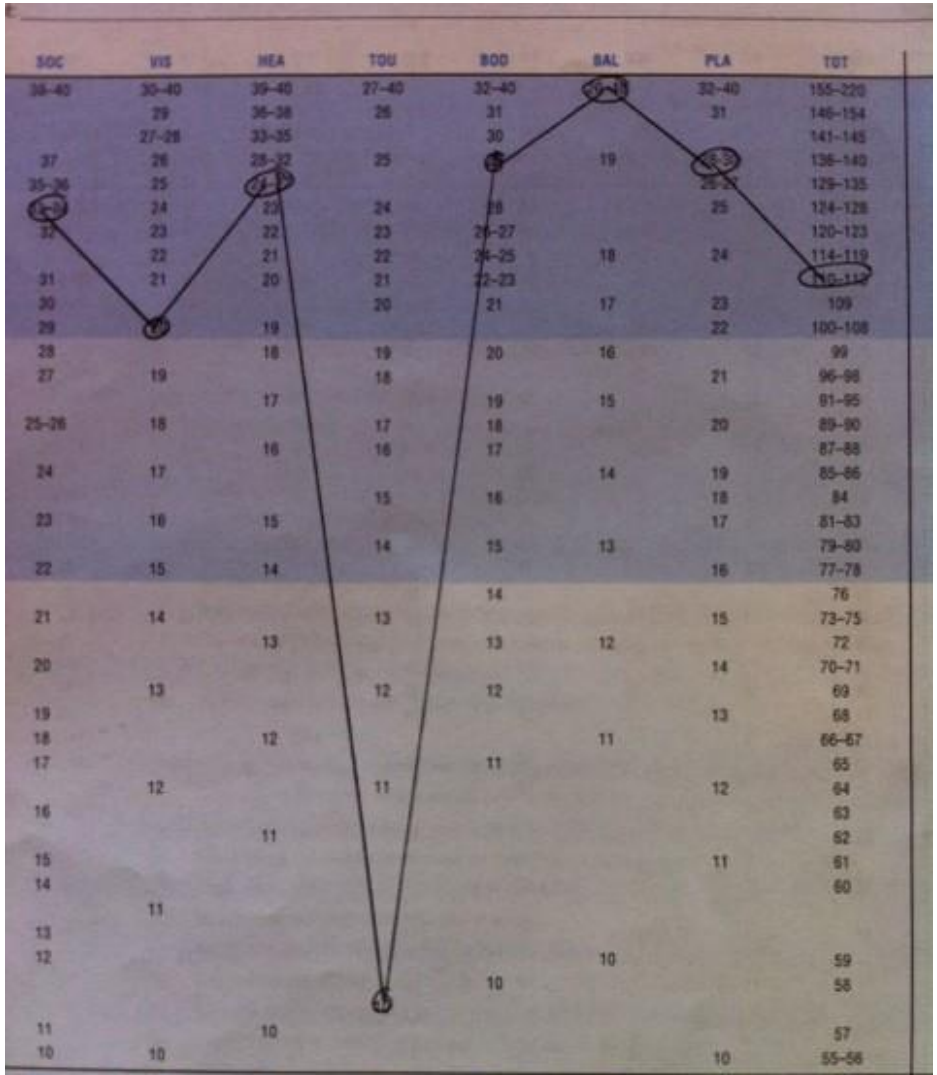
Results:

Cognitive and Academic Functioning

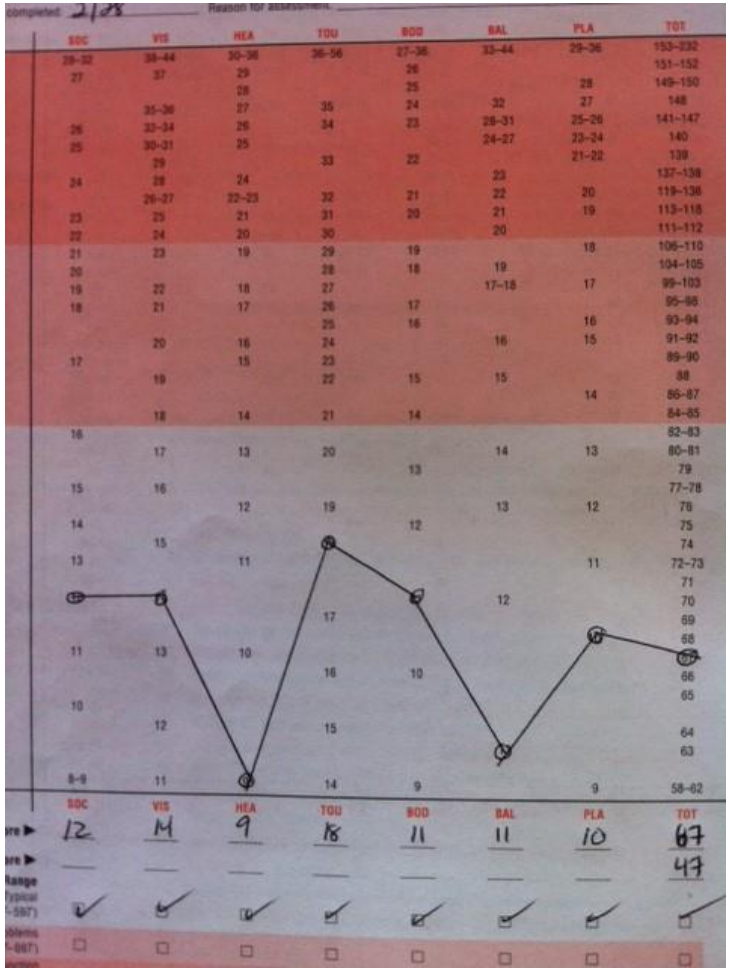
Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV)

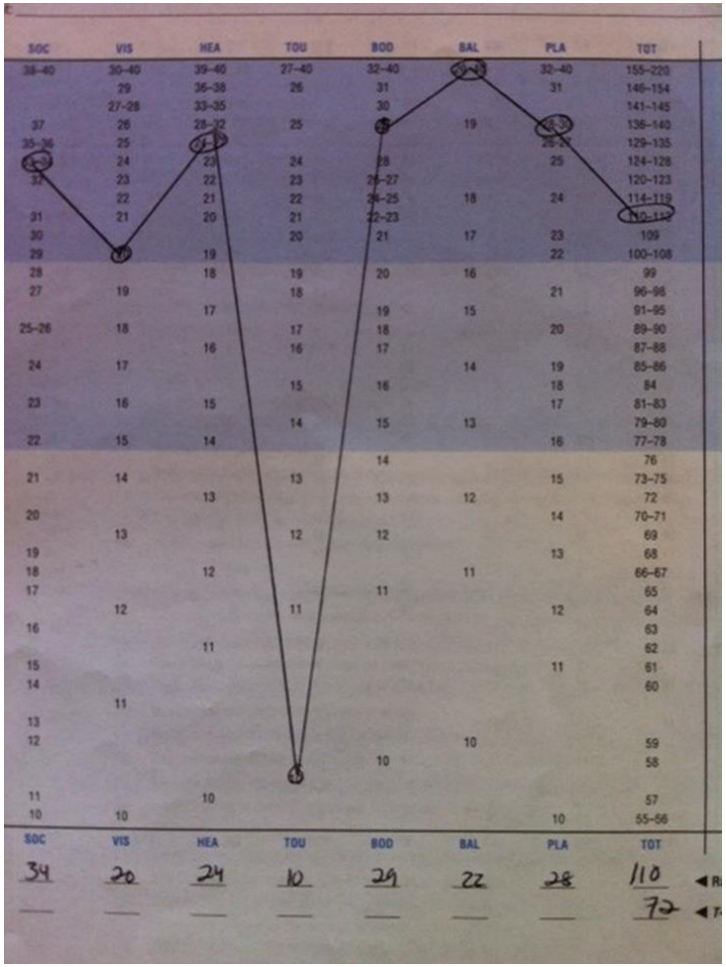
Index	*Standard Score*	*Percentile Rank*	*Descriptive Range*
Verbal Comprehension Index (VCI)	138	99	Very Superior
Perceptual Reasoning Index (PRI)	115	84	High Average
Working Memory Index (WMI)	104	61	Average
Processing Speed Index (PSI)	73	4	Borderline
Full Scale IQ (FSIQ)	114	82	High Average

Sensory Processing



Sensory Processing at Home and at School





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Behavior Perspectives

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Attention Deficit Hyperactivity Disorders

- Autism and ADHD occur together far more than chance would suggest
- About 30 percent of children with autism meet the criteria for ADHD
- The overlap of ADHD symptoms and autism symptoms may be confusing
- Stress can affect attention and focus

Sleep problems in children: Autism vs Typical Developing

- A higher prevalence of sleep problems in the autism group (73%, vs 50%)
- The autism group reported significantly better treatment success with medication
- The autism group also reported significantly better success with behavioral treatment.

. Journal of Intellectual Disability Research 49:260 2005

Types of Sleep Problems

• Difficulty falling asleep	53
• Restless sleep	40
• Will not fall asleep in own bed	39
• Frequent awakenings	33
• Difficulty arousing	31
• Enuresis	27

Effects of Poor Sleep on Children with Autism

- Aggression
- Depression
- Hyperactivity
- Irritability
- Poor Learning and Cognitive Performance
- Increased Behavioral Problems

Approach to Management of Sleep Disorders

- Good History to rule out medical conditions
- Explore emotional situation
- Explore environmental factors
- Good Physical Examination
- Keep a Sleep Graph for at least 2 weeks
- Sleep Study only if necessary

Medical Cause of Sleep Disturbance

- Always ask about snoring
- May be sleep apnea
- Get lateral soft tissue neck x-ray
- Resolved by ENT

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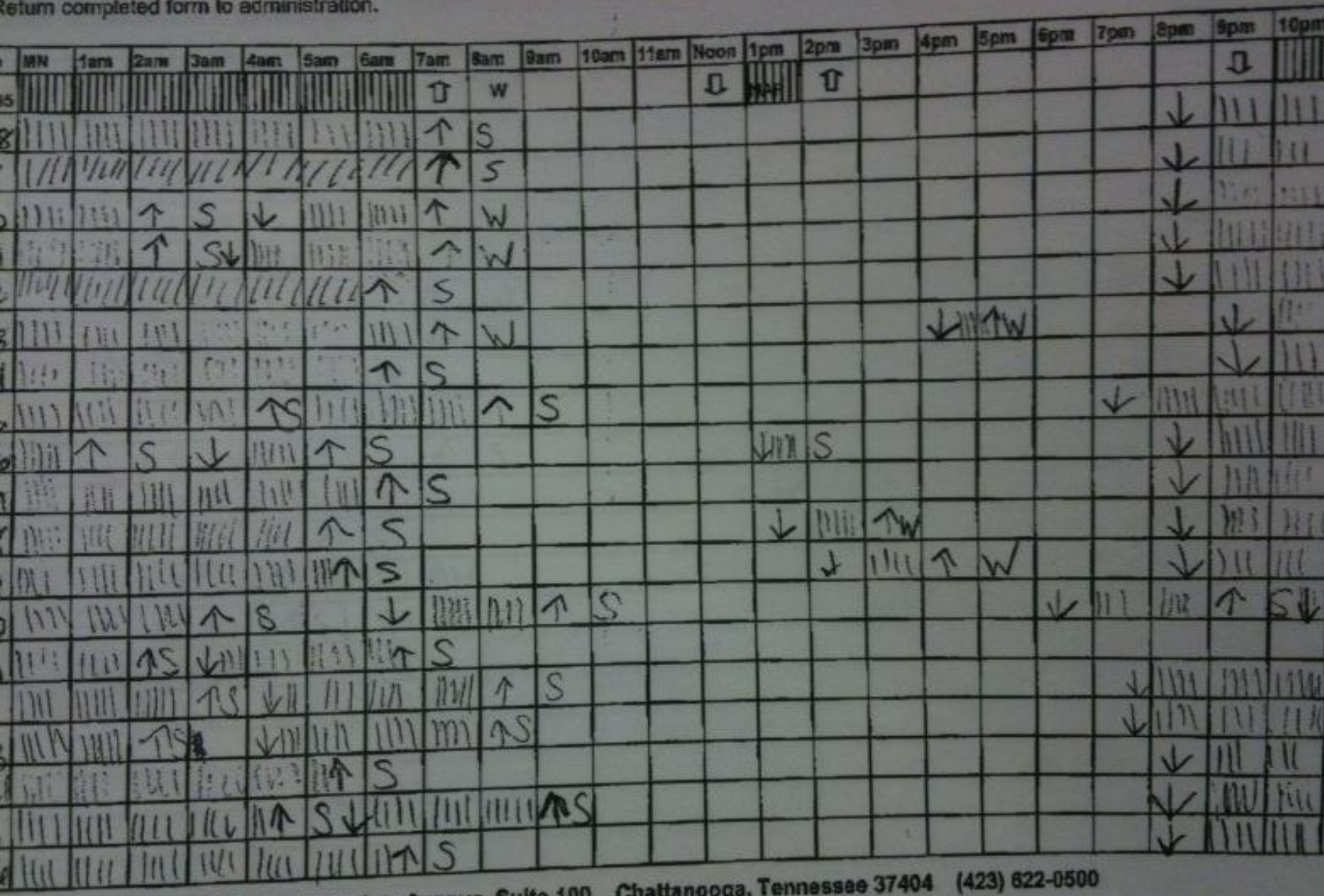
Mark periods of sleep as shaded areas between bars.
Return completed form to administration.



600 North Holtzclaw Avenue, Suite 100 Chattanooga, Tennessee 37404 (423) 622-0500

Name: _____

DOB: _____

Instructions:

1. Mark each time of getting into bed with an arrow pointing downwards.
2. Mark each time of getting out of bed with an arrow pointing upwards.
3. Mark periods of sleep as shadowed areas between vertical bars.
4. Return completed forms to administration.

W=wakened
S=spontaneous

Day	Date																								
Thur	6/26									S															
Fri	6/27									S															
Sat	6/28									S															
Sun	6/29									S															
Mon	6/30				↑	↑	↑																		
Tues	7/1									W															
Wed	7/2					↑	↑	↑	↑		W														
Thur	7/3										S														
Fri	7/4										S														
Sat	7/5									S															
Sun	7/6									S															
Mon	7/7									W															
Tues	7/8																								
Wed	7/9																								
Thur	7/10																								

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Day	Date	8PM	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7
Wed	6/11																								
Thurs	6/12																								
Fri	6/13																								
Sat	6/14																								
Sun	6/15																					↓	↑		
Mon	6/16									S												↓	↑		
Tues	6/17									S												↓	↑		
Wed	6/18									S												↓	↑		
Thur	6/19									S												↓			
Fri	6/20									S												↓			
Sat	6/21																								
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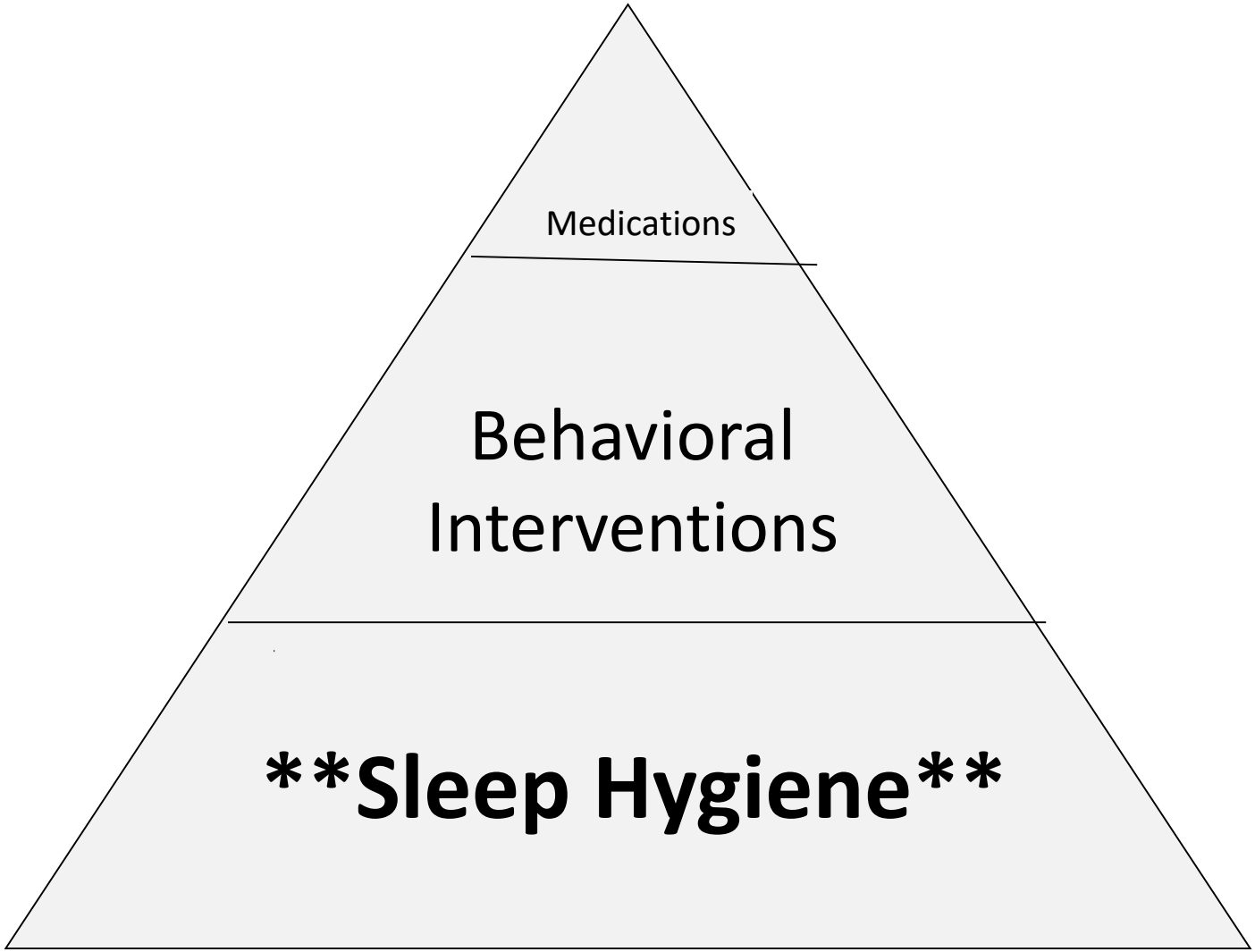
Tues	6/24																								
Wed	6/25																								

THE BEACH!

Sleep Management



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Emotional Reactions

- Need order and predictability
  - Need for routine
  - Difficulty with change
  - Can become focused or obsessed
- Limited ability to communicate emotions and feelings
- Limited ability to manage emotions, especially frustration
- As a result – anxiety can be high!
- With dramatic reactions to minor situations
  - Fight, flight or fright

Case Presentation

- JI is a 45 year old man with the diagnosis of Autism, Intellectual Disabilities and a Seizure Disorder
- He also had problems with constipation
- He liked to be alone rocking in his rocking chair

Suddenly Last Summer….

- He began to have tantrums
- His Seizures spun out of control
- He became more agitated and could not sleep
- He would pace back and forth so much that he sustained a stress fracture of his foot
- He did not eat as much and lost weight

When we first saw him….

- He was in a wheelchair
- He had a cast on his foot
- He was drooling, drowsy and unsteady
- But yet wanted to pace and needed 2 people to support him

He was on Multiple Medications…..

- "Behavior"
  - Ativan and Haldol prn
    - Increasingly given for sleep and agitation
  - Seroquel
  - Prozac
  - Buspar
- Seizure
  - Dilantin
  - Tripleptal
- Gastrointestinal
  - For Gastroesophageal reflux
  - For Constipation

Evaluation Process…

- Review of history and detail of medical conditions
- Review of living arrangements
- Videotape of activities
- Regular weekly visits of the direct care team

Findings…

- Clinical Medical
  - Constipation
  - Gastroesophageal reflux
  - Helicobacter Pylori Gastritis
  - Dysphagia
    - ? Secondary to medications
  - History of [Aspiration] Pneumonias
- Environmental
  - Change in roommate at time of onset of change in behavior

Management Strategy….

- Weekly meetings of both teams
- Limiting prescribing powers to Primary Care MD
- Incremental changes carefully and slowly
- Treating medical conditions
  - Constipation, GERD & Helicobacter
  - Management of Dysphagia
- Reducing psychotropic and seizure medications
- Changing living arrangement to make it quieter and more peaceful

Monitoring progress…

- Less medications
- Improved alertness and awareness
- Improved sleep
- Less tantrums and outbursts
- Improved weight and activity pattern
- Everyone was happier

Lessons….

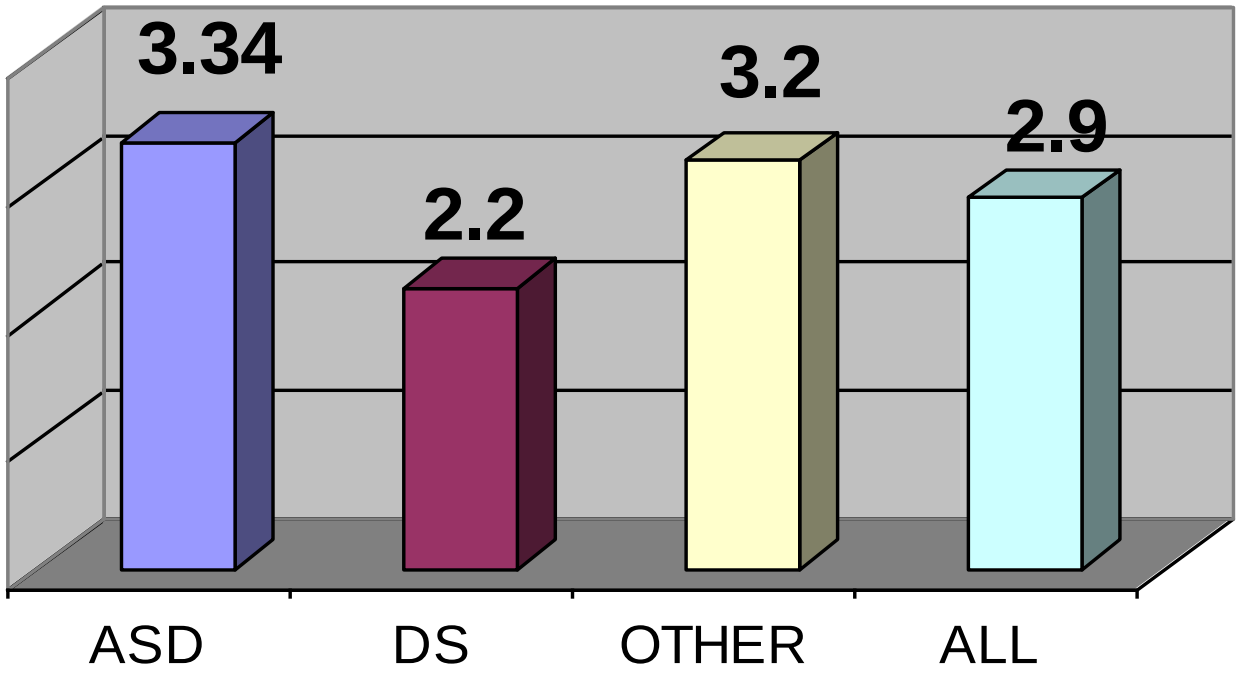
- Understand the underlying neurophysiology and psychology of individuals who have Autism
- Review possibility of medical conditions
- Examine environmental factors
- Work as a team
- Develop thoughtful diagnostic and therapeutic strategies
  - Maintain focus
  - Make changes slowly
- Treat the individual not the “behavior”

OVERVIEW

- Retrospective review of 198 consecutive admissions to and inpatient psychiatry unit for individuals with intellectual and developmental disabilities

Charlot et al, UMASS Medical Center, 2007

Mean Number of Psychoactive Medications per Person for 198 Psychiatric Inpatients with ID



Possible Adverse Neuromotor Drug Effects

	DC DIAGNOSIS	CHART REVIEW
EPS	6%	19%
Dysphagia	**10%**	**13%**
Akathisia	na	7%
Dystonia	4%	15%

Frequency of Health Problems

Group	ASD		DS		OTHER		ALL	
N	60		13		125		198	
	F	%	*F*	%	*F*	%	*F*	%
Constipation	**37**	**62**	**4**	**31**	**76**	**61**	**109**	**55**
GERD	**19**	**32**	**3**	**23**	**52**	**42**	**73**	**37**
Seizure Disorder	**19**	**32**	**0**	**0**	**30**	**24**	**49**	**25**
H/o surgery-any	8	13	1	8	30	24	39	20
Hypothyroidism*	4	7	7	54	26	20	37	19
Hypertension	7	12	2	15	29	23	38	19
Anemia*	6	10	0	0	30	24	36	18
CNS – not sz	6	10	3	23	24	19	33	17
Candidiasis	9	15	4	31	24	19	33	17

Approach to Management

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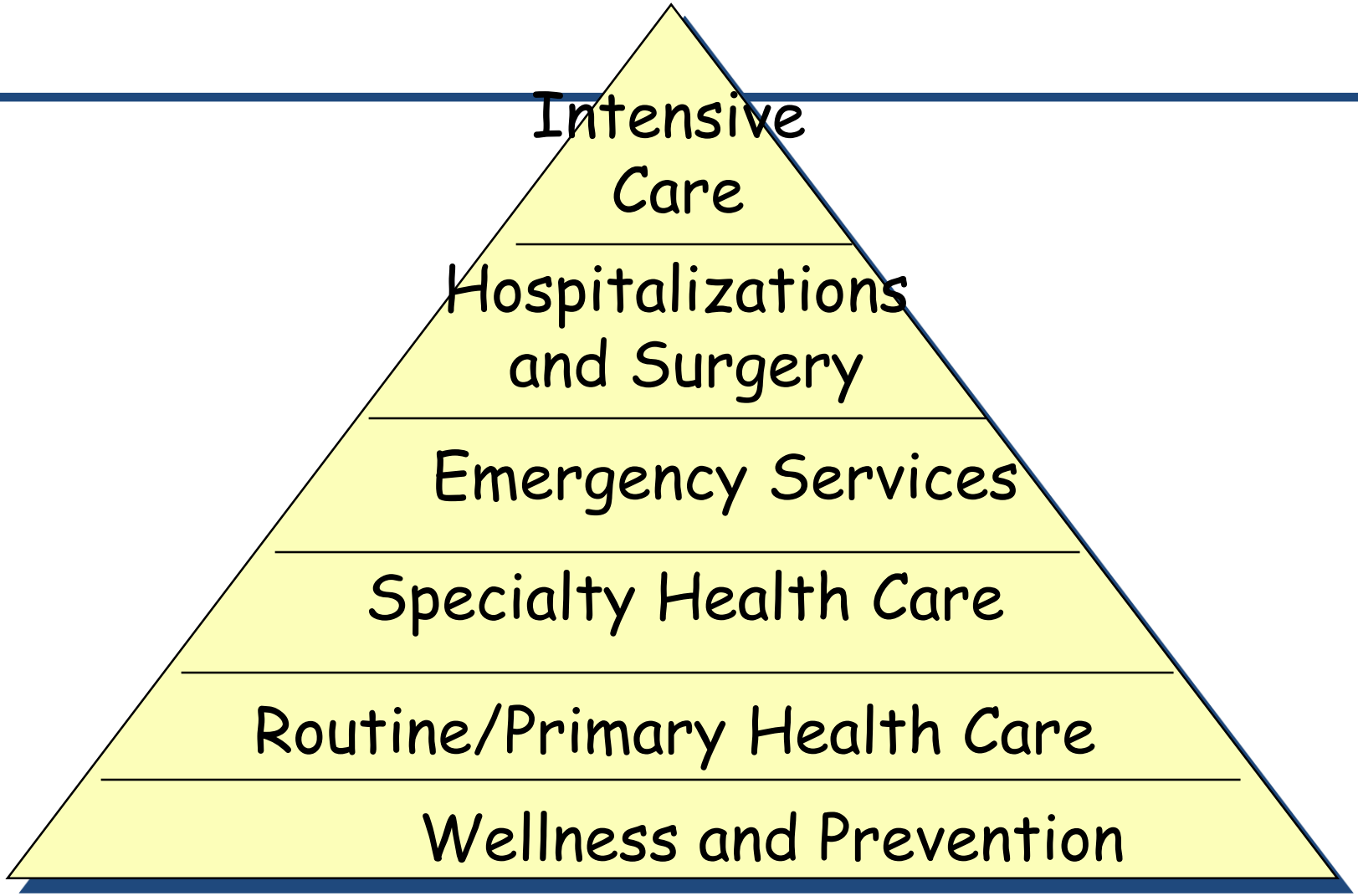
Health Care Infrastructure



WHO Definition of Health

- Not merely freedom from disease but.....

- The promotion of
  - Physical
  - Emotional &
  - Social Well Being

Treatments and Interventions

“A treatment method or an educational method that will work for one child may not work for another child. The one common denominator for all of the young children is that early intervention does work, and it seems to improve the prognosis."

-Temple Grandin

Treatments and Interventions

- Parent Education and Training
- Speech-Language Therapy
- Sensory Integration/Occupational Therapy
- Floortime
- Applied Behavioral Analysis (ABA)
- Social Skills Training
- Appropriate Education
- Medication

Adapted from Autism Speaks

Promoting Health: Medical Perspective

- Screening for at-risk conditions
- Management of existing chronic medical conditions
- Monitoring of medications
- Reducing the gap

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Promoting Health: physical and physiological perspective

- Diet and eating patterns
- Exercise patterns
- Sleep patterns
- Bowel patterns

Promoting Health: medical perspective

- Screening for at-risk conditions
- Management of existing chronic medical conditions
- Monitoring of medications

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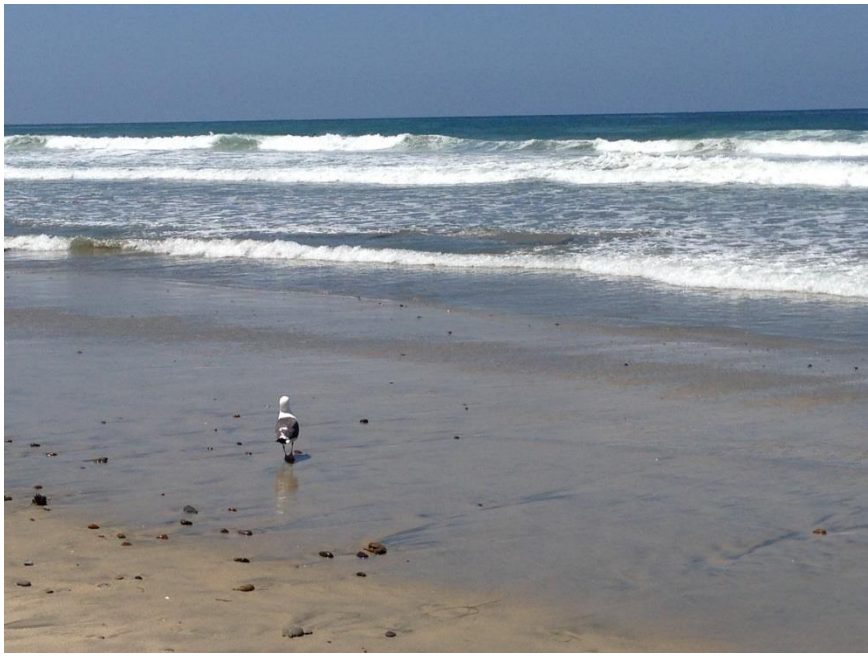
Promoting Health: psychosocial perspective

- Daily activities
- Preferred activities
- Personal relationships
- Social activities
- Personal time



What have we learned?

- Autism is a neurological condition with a genetic basis
- It manifests differently in different people
- There are a variety of neurological manifestation
- There are a variety of behavioral manifestations
- We need to understand and treat individual according to his or her personality and characteristics
- With improved understanding and management we can help each individual to be healthy and to reach his or her own potential

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