

*Infant and Early Childhood Conference
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Pharmacology in Autism

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Autism: Practice Parameters

2000

P.A.Filipek, MD, et al. Practice Parameter: Screening and Diagnosis of Autism. *Neurology*, 55:468-479, 2000. (101 references)

2007

C. P. Johnson, S. M. Meyers, and the AAP Council on Children with Disabilities. Identification and Evaluation of Children with Autism Spectrum Disorders. *Pediatrics*, 120:1183-1215, 2007 (334 references).

2007

S. M. Meyers, C. P. Johnson, and the AAP Council on Children with Disabilities. Management of Children with Autism Spectrum Disorders. *Pediatrics*, 120:1162-1182, 2007 (245 references).

2008

Schafer and Mendelsohn. Genetics evaluation for the etiologic diagnosis of autism spectrum disorders. *Genetics in Medicine*, Vol 10 (1):4-12 (2008).

2009

Caring for Washington Individuals with Autism Task Force. *Autism Guidebook for Washington State*. Revised/printed: 2009.

Autism Spectrum Disorder

- Common **neurobiological** disorder with impairments in social interaction, communication, and repetitive and stereotypic behaviors.
- Multifactorial causation (genetic + ??)
- Gender differences (males 4:1 females)
- Variable expression (spectrum)
- Positive treatment responses

Autism: Diagnostic Criteria (DSM-IV-TR)

1. Social interaction:

- Non-verbal behaviors
 - eye contact
 - expressions
 - body postures
- Forming peer relationships
- Sharing interests with others
- Social/emotional reciprocity

- *Two (2) or more of the above present*
- *Total of six (6) items for 1, 2, and 3.*
- *Onset prior to three (3) years of age*
- *Not Rett or CDD*

2. Communication:

- Delayed spoken language
- Conversational speech
- Repetitive use of idiosyncratic language
 - Echolalia
- Social imaginative play

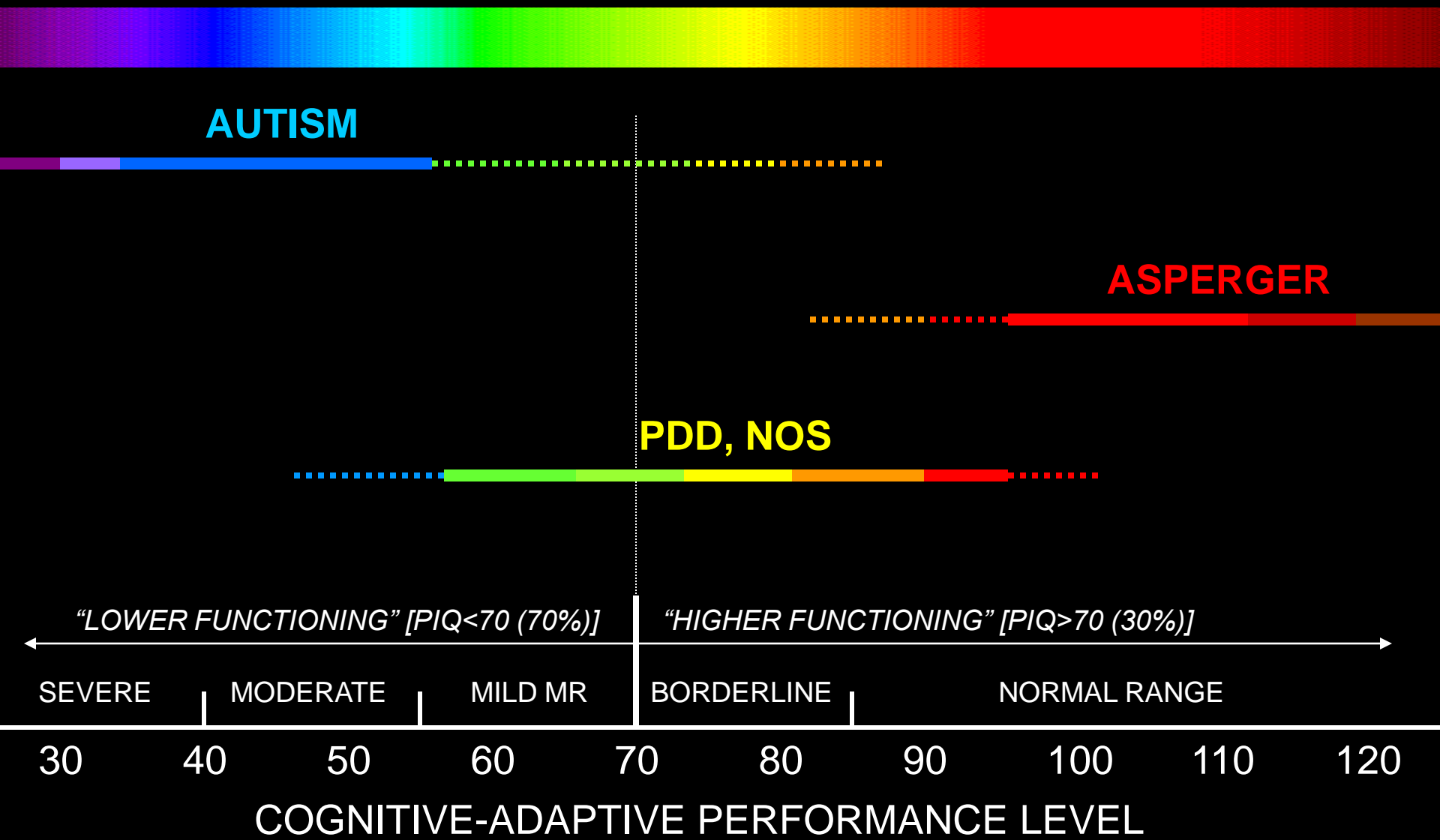
- *One (1) or more of the above present*

3. Repetitive behavior:

- Preoccupation with behavior(s)
- Nonfunctional rituals or routines
- Repetitive motor mannerisms
 - hand-flapping
 - spinning
- Preoccupations with parts of objects

- *One (1) or more of the above present*

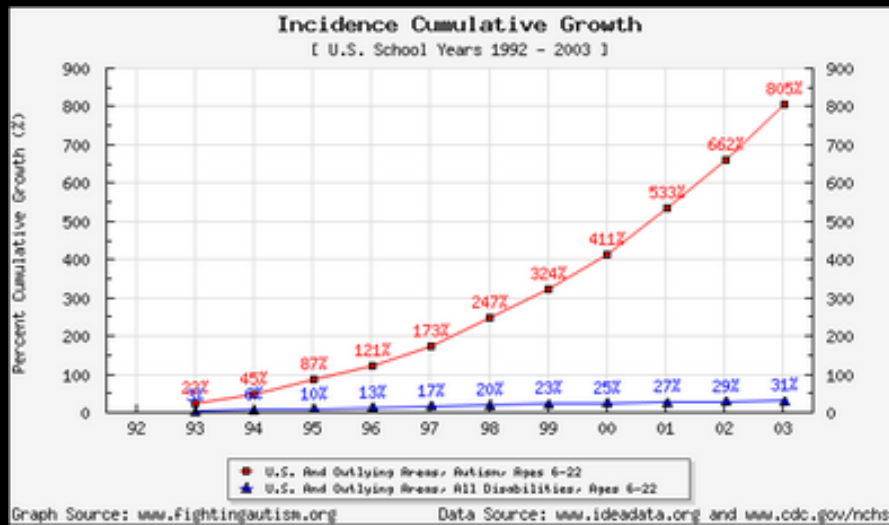
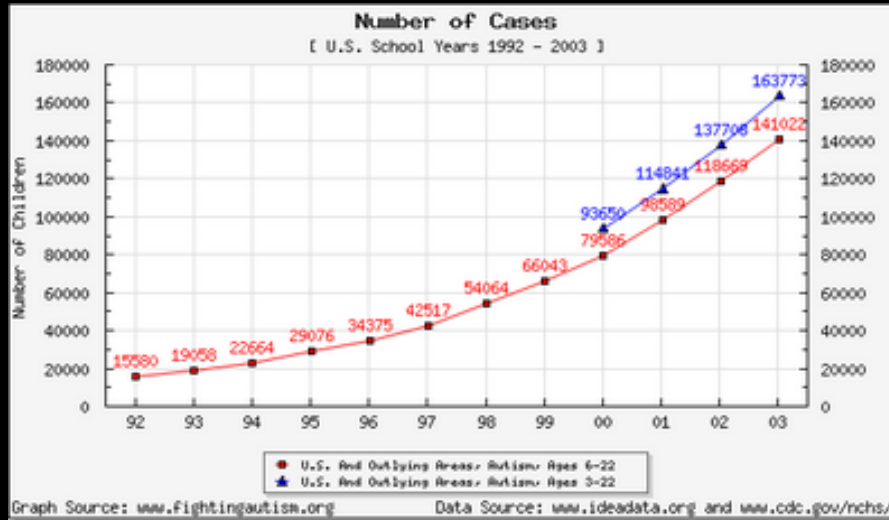
Autism Spectrum Disorders



Autism: Coding Classifications

ICD-9-CM	DSM-IV-TR	ICD-10-CM	DSM-V (2011)
299.0x (0, 1) Autistic Disorder Infantile Psychosis	299.00 Autistic Disorder	F84.0 Autistic Disorder Infantile Psychosis	XXXX Autism spectrum disorder
299.1x (0, 1) Childhood Disintegrative Disorder	299.10 Childhood Disintegrative Disorder	F84.2 Rett Syndrome	
299.8x (0, 1) Other Pervasive Devel Disorders Asperger Disorder Atypical Child Psychosis Borderline Child Psychosis	299.80 Asperger Disorder Rett Syndrome Pervasive Devel Disorder NOS	F84.3 Childhood Disintegrative Disorder Dementia Infantilis Symbiotic Psychosis	
299.9x (0, 1) Pervasive Devel Disorders NOS Childhood psychosis NOS Schizophrenia, child NOS		F84.5 Asperger Disorder Autistic Psychopathy Schizoid Disorder, Child	
		F84.8 Other Pervasive Devel Disorder "Overactive Disorder with MR and Stereotyped Movements"	
		F84.9 Pervasive Devel Disorder NOS	

Autism: Increasing Prevalence Rate



100?

Autism strikes
1 in ~~156~~ children
every year

150

The challenges last a lifetime.
Help make sure
the solutions do too.

www.researchautism.org
(866) 366-9710

Center for Disease Control (CDC):
<http://www.cdc.gov/od/media/pressrel/2007/r70208.htm>

Autism: Early Detection

B	2	4	6	8	10	12	14	16	18	20	22	24
*	*	*	*	*		*		*	*			*

By 6 months:

- Turn to name
- Smile at person
- Respond to sound with sounds
- Social play (peek-a-boo)

Red Flags (6 months):

- Lack of eye contact
- Lack of social interest
- Too passive

By 12 months:

- Use simple gestures (bye-bye)
- Makes consonant sounds
- Imitates actions
- Responds to "no"

- Follows parent pointing (Avg: 10-12 months)

Red Flags (12 months):

- No babbling
- No pointing/gestures

By 18 months:

- Simple pretend play ("talk" on telephone)
- Point to out of reach objects (Avg: 12-14 months)
- Bring objects to show parent
- Uses several words
- Spontaneous point to interesting objects (Avg: 14-16 months)

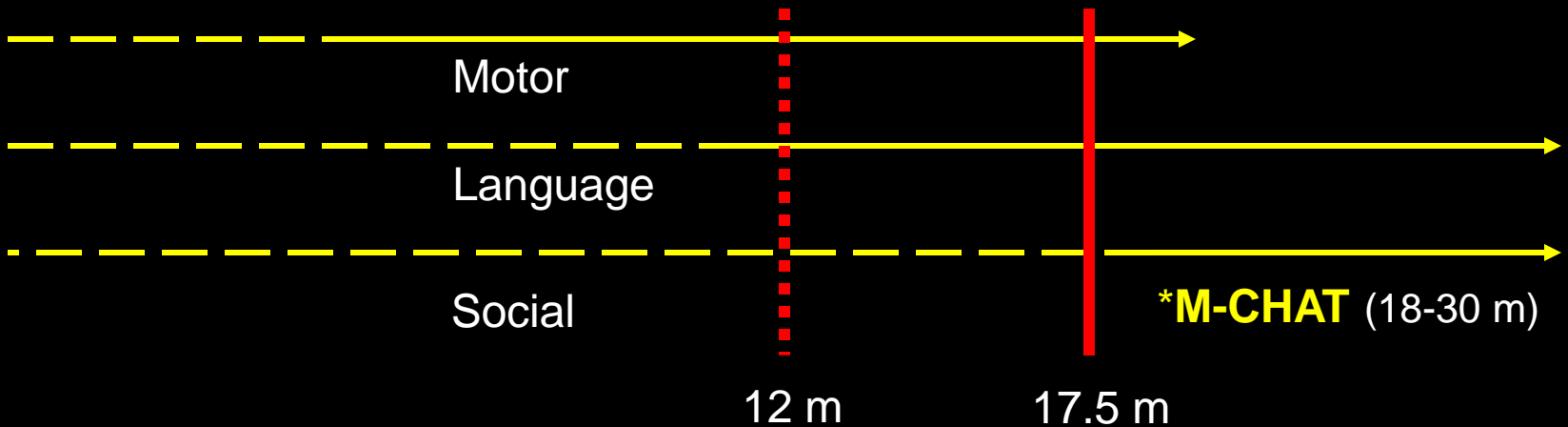
Red Flags (18-24 months):

- No words by 16 months
- No 2-word phrases by 24 months

Developmental regression at any age!

Autism: Presentation

B	2	4	6	8	10	12	14	16	18	20	22	24
*	*	*	*	*		*		*	*			*

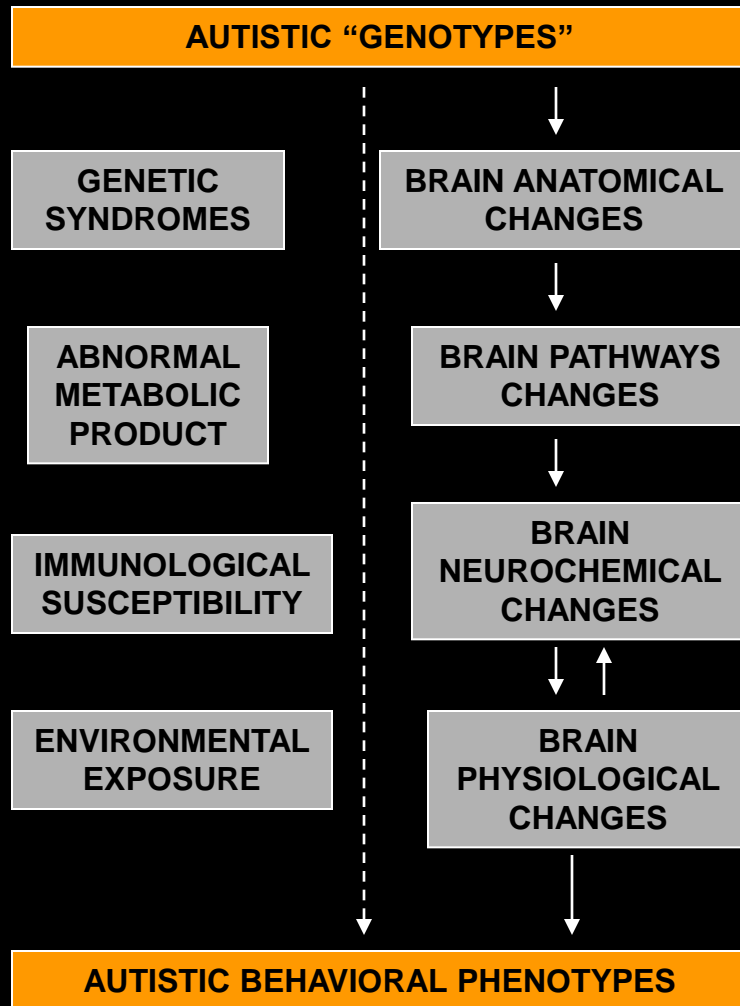


70% *Mixed developmental delays with autistic symptoms*

30% *“Normal” developmental progress*

Autistic regression (12-18 m)

Autism: Genetic factors



•Multiple candidate genes

- Embryogenesis (midbrain, cerebellum)
- Neuron proliferation/determination
- Neuron migration/synapse formation
- Neurotransmitter systems

Miles, J. and McCathren, R. Autism Overview. GeneReviews. 1 Dec 2005

*"The nature of the genetic risk for ASD is not well understood; whatever is transmitted from parents to children is not "classic autism", but rather a **risk for social, communication, and behavioral difficulties** that may manifest as autism, PDD-NOS, or Asperger syndrome, or as less pervasive language delays, social deficits, or restricted interests".*

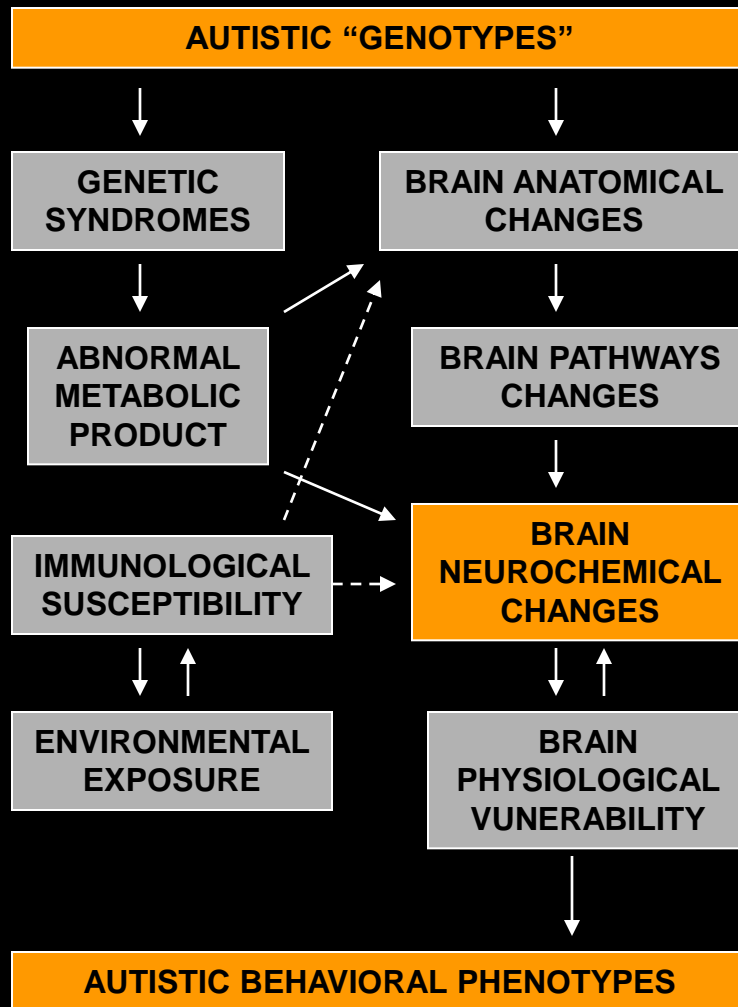
Lord, C. Detecting Autism in a Toddler. Medscape. 2007

•Recurrence risk in siblings: **~10%**

- Idiopathic autism: **4%**
- Broader phenotype: additional **4-6%**

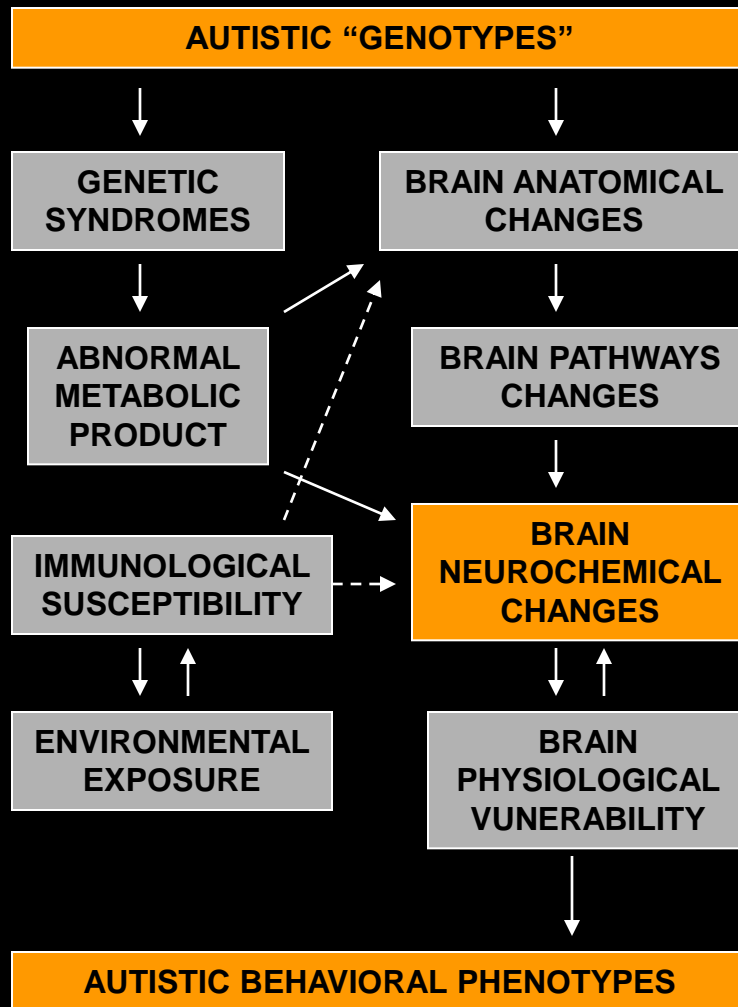
Miles, J. and McCathren, R. Autism Overview. GeneReviews. 1 Dec 2005

Possible Neurochemistry in Autism



- Complex and largely unknown mechanism
- Hypothesized differences in brain neurotransmitter systems:
 - Core autism symptoms
 - Co-existing symptoms:
 - Intellectual impairment (70%)
 - Sleep problems (~60%)
 - Seizures (~30%)
 - Disordered attention
 - Sensory/emotional regulation
 - Overanxious; OCD] + tics = TS?
 - Mood disorders
 - Aggressive, self-injury

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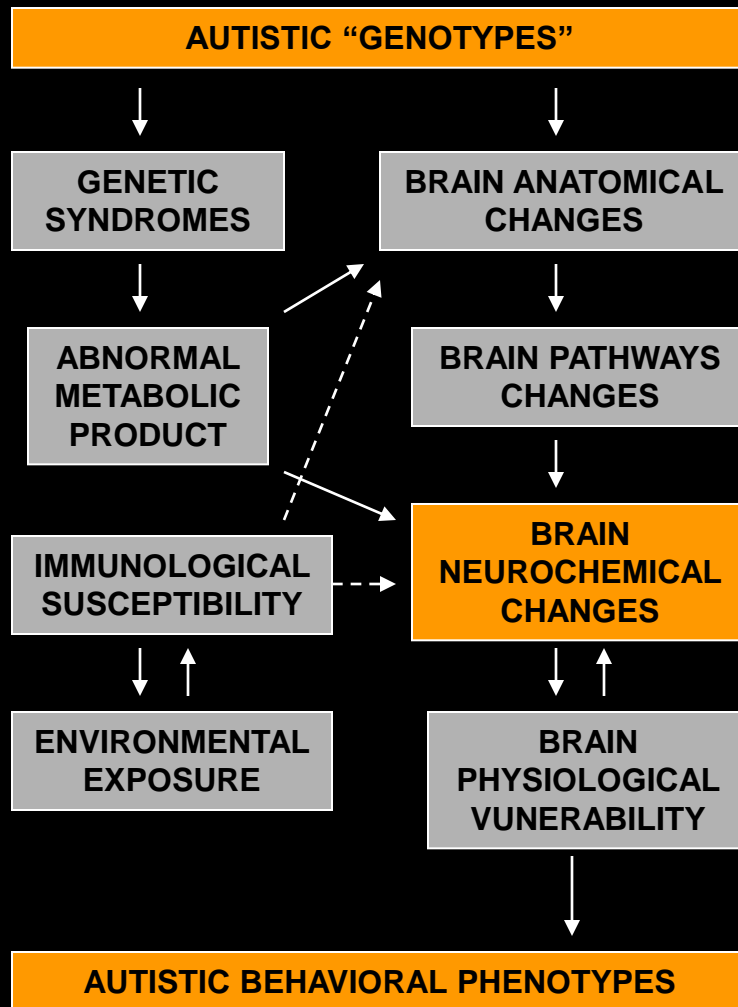
Sleep Problems in Autism

- Sleep problems common in ASD; all types represented
- Variable relationship to cognitive level
- Highest incidence in young (< 8yrs)
- Usually chronic and refractory to therapy
- Increased incidence of anxiety
- Sleep routines affected by stereotypic behaviors, rigid behavioral routines, and atypical social awareness
- Possible melatonin production disturbance or primary arousal dysfunction

“Off-label” Sleep Aids in Children

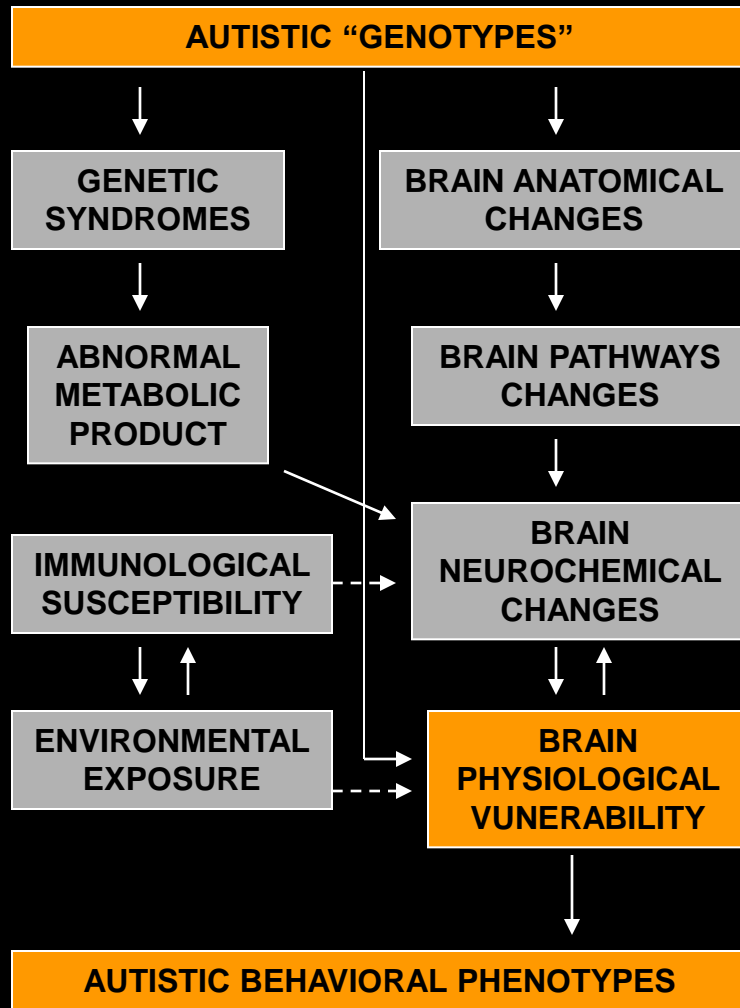
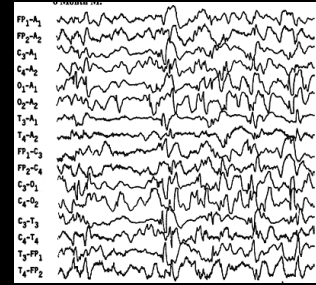
Class	Medication	Duration	Adverse effects
Antihistamines	diphenhydramine	8 to 12 hrs	Daytime drowsiness
Hormonal	melatonin	3 to 4 hrs	Short duration No FDA approval
Alpha-2 adrenergic agonists	clonidine guanfacine	3 to 4 hrs 8 hrs	Hypotension Cardiac rhythm
Antidepressants	trazodone	8 hrs	Drowsiness Priapism
“Anything else that makes you sleepy”	Multiple Rx and OTC agents	Variable	No research in children or not FDA regulated

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Electroencephalography in Autism

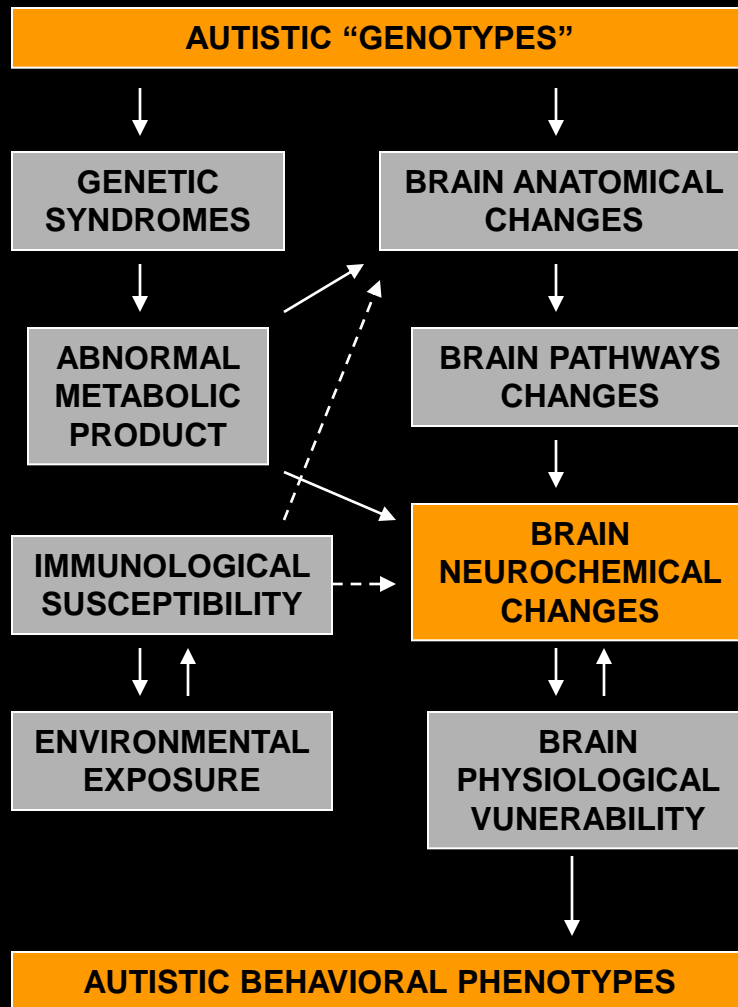


- **Abnormal EEGs common**
 - ~5% “typical” children
 - 15% - 80% autistic children
 - Who? What type EEG?
- **Incidence of seizures in autism highly variable:**
 - ~25% lifetime risk in autism
 - Higher incidence with:
 - Genetic syndromes
 - Structural brain lesions
 - Mental retardation
 - Motor impairments
 - Tuberous sclerosis (85%)

Antiepileptic and Mood Stabilizers

Brand (Generic)	On-label uses	Off-label uses	Preparations	Initial (mg/day)	Target (mg/day)
Depakote (valproic acid)	Seizures, mania >10 yrs	Mania, DBD	Multiple tabs, sprinkles	10-15 mg/kg tid	Plasma 50-125
Lithium (lithium carbonate)	Bipolar >12 yrs	Severe DBD	Multiple tabs, solution	Dose by weight/kg	Plasma 0.6-1.2
Klonopin (clonazepam)	Seizures, panic >18 yrs	Anxiety insomnia	Multiple tabs, wafers	0.01-0.03 mg/kg bid/tid	0.02-0.2
Lamictal (lamotrigine)	Bipolar, seizure >18	Bipolar MDD	Multiple tabs, solution, chew	Dose by weight/kg	Titration schedule
Neurontin (gabapentin)	Seizures >3 yrs	Anxiety PTSD	Multiple tabs, solution, chew	100-300 mg tid	400-2400 tid
Tegretol (carbamazepine)	Seizures (All ages)	Mania Rage	Multiple tabs, solution, chew	7-10 mg/kg	Plasma 8-12
Topomax (topiramate)	Seizures >2 yrs	Bipolar	Multiple tabs, sprinkles	1-3 mg/kg 20-50 mg/d	5-9 mg/kg <200-400
Trileptal (oxcarbazepine)	Seizures	Mania Rage	Multiple tabs, solution	8-10 mg/kg <600 mg bid	Based on weight

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ADHD: Diagnostic Criteria (DSM-IV-TR)

Hyperactivity:

- Fidgets
- Runs excessively
- Constant movement
- Problems playing quietly
- Talks excessively

Impulsivity:

- Blurts out answers
- Often interrupts others
- Problems waiting turn

- Six (6) or more of the above present
- Less than six (6) inattention symptoms
- Symptoms persisted at least six (6) months
- Onset prior to seven (7) years of age

Inattention:

- Poor close attention, many careless mistakes
- Poor sustained attention
- Doesn't seem to listen
- Fails to finish tasks
- Difficulty organizing tasks
- Avoids difficult mental tasks
- Often misplaces things
- Distracted by external stimuli
- Often appears forgetful

- Six (6) or more of the above present
- Less than six (6) hyperactive/impulsive symptoms
- Symptoms persisted at least six (6) months
- Onset prior to seven (7) years of age

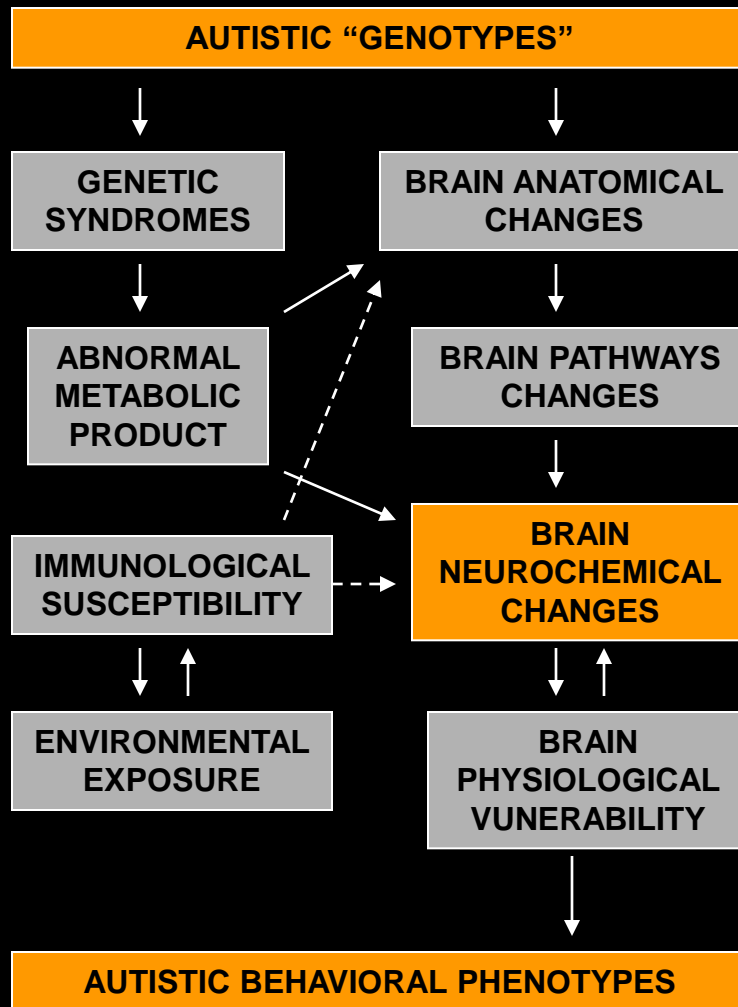
ADHD: Long-Acting Medications

Brand Name	Generic Name	NT	Duration of Action	Delivery System	Sprinkle Option	Available Dosages (mg)	Dosage (mg/kg/day)	C-II	Diversion [+ / +++++]	FDA Approved
Metadate CD	MPH (d + l)	NE DA	8 hr	Capsule (beads) (30/70%)	Yes	10, 20, 30	1 - 2	Yes	+++	> 6 yrs < 60 mg/d
Ritalin LA	MPH (d + l)	NE DA	8 hr	Capsule (beads) (50/50%)	Yes	10, 20, 30, 40	1 - 2	Yes	+++	> 6 yrs < 60 mg/d
Concerta	MPH (d + l)	NE DA	12 hr	Tablet (OROS pump) (22/78%)	No	18, 27, 36, 54	1 - 2	Yes	++	> 6 yrs < 108 mg/d
Daytrana	MPH (d + l)	NE DA	12 hr (worn 9 hr)	Patch (DOT matrix)	[NA]	10, 15, 20, 30	1 - 2	Yes	+	6-12 yrs < 30 mg/d
Focalin XR	d-MPH (d)	NE DA	12 hr	Capsule (beads) (50/50%)	Yes	5, 10, 15, 20	0.5 - 1	Yes	+++	> 6 yrs Adults < 30 mg/d
Adderall XR	AMPH (d + l) (d + l)	NE DA	12 hr	Capsule (beads) (50/50%)	Yes	5, 10, 15, 20, 25, 30	0.5 - 1	Yes	+++	> 6 yrs Adults < 30 mg/d
Vyvanse	AMPH (d + l) + L-lysine	NE DA	12 hr	Capsule (powder; soluble in water)	Yes	30, 50, 70	0.5 - 1	Yes	++	6-12 yrs < 70 mg/d
Strattera	ATOM	NE	24 hr	Capsule (powder) (100%)	No	10, 18, 25, 40, 60, 80, 100	1.2 - 1.4	No	+	> 6 yrs Adults < 100 mg/d
Intuniv	GUANF	NE	24 hr	Tablet	No	1, 2, 3, 4	0.5 - 0.8	No	+	6-12 yrs < 4 mg/d

MPH: methylphenidate AMPH: amphetamine ATOM: atomoxetine GUANF: guanfacine

Glenn C. Tripp, MD, FAAP; 2010

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Anxiety Disorders in Children and Adolescents

DEFINITIONS:

- **Anxiety:** Emotional uneasiness associated with anticipated danger
- **Fear:** Normal reaction to a real or imagined danger or threat
- **Phobias:** Excessive, specific, persistent fear of a stimulus that causes significant distress and/or avoidance.
- **Anxiety disorder:** Irrational fears or worries that cause significant distress and/or avoidance

Anxiety Disorders in Children and Adolescents

Epidemiology:

- *10-20 % of children have overanxious symptoms*
- *13% of children and adolescents have ADs*
- *1/3 will have “co-existing” conditions:*
 - *Other anxiety disorders*
 - *Depression*
 - *Attention deficit hyperactivity disorder*
 - *Sleep disorders*
- *70% of adults report first symptoms during childhood*

Generalized Anxiety Disorder (GAD)



- *3% of school-age children*
- *10% of adolescents*
- *Mean age of onset: 10-13 years
(as early as 4 years old)*
- *Males = females in childhood; higher
in females in adolescence*
- *Risk for future anxiety disorders,
depression, suicide, and psychiatric
hospitalizations*

Separation Anxiety Disorder (SAD)



- *4% of school-aged children and young adolescents*
- *Mean age: 7.5 years*
- *Males = females*
- *Higher incidence in:*
 - *Lower socioeconomic status*
 - *Single parent families*

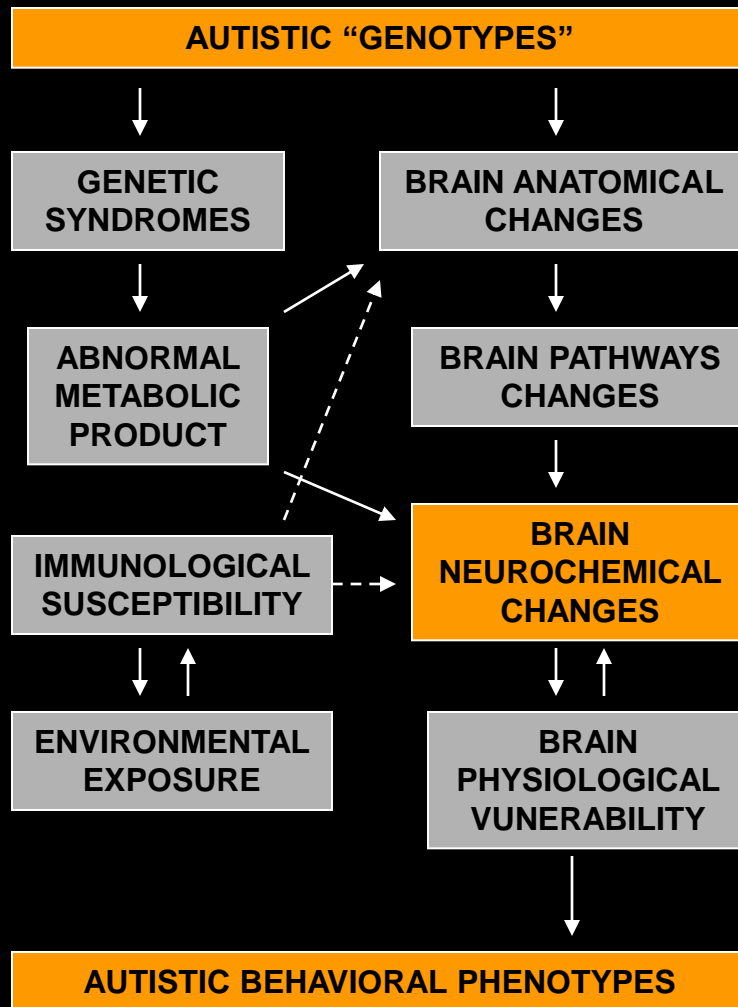
Autism: Obsession or Fixation?

- Obsession:
 - Intrusive thoughts
 - Bothersome
 - Increase anxiety
 - “Must” complete correctly
- Behavior:
 - Excessive hand-washing
- Fixation:
 - Favorite activity
 - Enjoyable
 - Reduce anxiety
- Behavior:
 - Hand-flapping
 - Lining objects

SSRI Antidepressants

Brand (generic)	On-label (<18y)	Off-label (<18 y)	Metabolism	Preparation (mg)	Initial (mg/day)	Target (mg/day)
Prozac (fluoxetine)	OCD >7y MDD	Anxiety	2D6, 3A3, 3A4, 2C19	10, 20, 40 20mg/5ml	2.5-10	2.5-40 (c) 10-80 (a)
Zoloft (sertraline)	OCD >6y	Anxiety MDD	2D6 (weak) 2C19	25, 50, 100 20mg/ml	12.5-50	25-200
Luvox (fluvoxamine)	OCD >8y	Anxiety MDD	1A2, 3A3, 3A4, 2C19	25, 50, 100	12.5-25	25-300
Paxil (paroxetine)	None	Anxiety	2D6	10, 20, 30, 40 10mg/5ml	5-10	10-60
Celexa (citalopram)	None	Anxiety MDD	2D6 (weak)	10, 20, 40 10mg/5ml	5-10	10-60
Lexapro (escitalopram)	None	Anxiety MDD	2D6 (weak)	10, 20 5mg/5ml	1.25-5	2.5-20

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Atypical Neuroleptics

Brand (generic)	On-label uses	Off-label uses	Metabolism	Preparations (mg)	Initial (mg/day)	Target (mg/day)
Abilify (aripiprazole)	Schizophrenia (adults)	Mania, aggression	2D6, 3A4	5, 10, 15, 20, 30	2.5-5 mg	10-30 mg
Clozaril (clozapine)	Schizophrenia (adults; resistant)	Severe psychosis	1A2, 2D6, 3A4	25, 100	12.5 mg	50-900 mg
Geodon (ziprasidone)	Schizophrenia (adults)	Mania, aggression	3A4, 1A2	20, 40, 60, 80	20 mg bid	1-3/mg/kg (160/day)
Risperdal (risperidone) (FDA: 10/06)	Schizophrenia (adults) Autism (DBD) (5-16 yr)	Mania, aggression	2D6 <u>Caution:</u> (Prozac, Paxil, Strattera)	0.25, 0.5, 1, 2, 3, 4	0.25 mg bid	0.5-6 mg bid-tid (<2 mg/d)
Seroquel (quetiapine)	Schizophrenia (adults)	Mania, aggression	3A4	25, 100, 200, 300	25 mg	25-500 mg bid
Zyprexa (olanzapine)	Schizophrenia; bipolar (adults)	Mania, aggression	1A2, 3A4	2.5, 5, 7.5, 10, 15, 20	2.5 mg	5-20 mg qd-tid

