Autism: Connecting the Dots: Or “What Time of Day is it?”

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Co-Morbidity

While some individuals have a single problem that affects them, many have several that overlap.

For example, people with asthma have a higher chance of having allergic issues, obesity is connected to high blood pressure, and diabetes.

In child development the issue of coexisting problems is even more common.
Obesity

High Blood Pressure

Diabetes
Other Developmental Concerns

Psychiatric Concerns

ASD

Other Developmental Concerns

Psychiatric Concerns

ASD
So when you ask, “What is the problem”

The answer may be, “What time of day is it?”
Psychiatric Disorders in Children With Autism Spectrum Disorders

- Seventy percent studied had at least one co-morbid disorder and 41% had two or more.

- The most common diagnoses
  - Social anxiety disorder 29%
  - Attention-deficit/hyperactivity disorder 28%
  - Oppositional defiant disorder 28%

- Of those with attention deficit/hyperactivity disorder, 84% received a second co-morbid diagnosis

### ASD Co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>In General Population</th>
<th>In ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>7%</td>
<td>38%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5%</td>
<td>39%</td>
</tr>
<tr>
<td>Tics</td>
<td>1%</td>
<td>6-13%</td>
</tr>
<tr>
<td>Mood Disorders</td>
<td>6%</td>
<td>18-36%</td>
</tr>
<tr>
<td>Learning Disorders</td>
<td>5-10%</td>
<td>18-72%</td>
</tr>
</tbody>
</table>
What are these things and how do they affect children?

- Mood Disorders
- ADHD
- Anxiety Disorders
- Learning Disabilities
- Tic Disorders
- Developmental disorders of Coordination
- Language Disorders
Tourette Syndrome

The prevalence of Tourette Syndrome among individuals with autism is estimated at 6.5% but in the general population it is about 1%.

DSM-5 definition

A. Both multiple motor tics and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. (A tic is a sudden, rapid, recurrent, nonrhythmic motor movement or vocalization.)

B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
## Simple Tics

<table>
<thead>
<tr>
<th>Phonic or vocal tics</th>
<th>Motor tics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throat clearing</td>
<td>Eye blinking</td>
</tr>
<tr>
<td>Sniffing</td>
<td>Sticking tongue out</td>
</tr>
<tr>
<td>Barking</td>
<td>Head turning</td>
</tr>
<tr>
<td>Coughing</td>
<td>Shoulder jerking</td>
</tr>
<tr>
<td>Yelling</td>
<td>Muscle tensing</td>
</tr>
<tr>
<td>Hiccuping</td>
<td>Flexing fingers</td>
</tr>
<tr>
<td>Belching</td>
<td>Kicking</td>
</tr>
<tr>
<td>Animal sounds</td>
<td></td>
</tr>
</tbody>
</table>
Complex Tics

<table>
<thead>
<tr>
<th>Phonic or vocal tics</th>
<th>Motor tics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeating parts of words or phrases</td>
<td>Flapping arms</td>
</tr>
<tr>
<td>Prosodic changes</td>
<td>Facial grimacing</td>
</tr>
<tr>
<td>Talking to oneself (multiple characters)</td>
<td>Adjusting or picking at clothing</td>
</tr>
<tr>
<td>Assuming different intonations</td>
<td>Complex touching movements</td>
</tr>
<tr>
<td>Use of obscene words</td>
<td>Jumping</td>
</tr>
<tr>
<td></td>
<td>Shaking feet</td>
</tr>
<tr>
<td></td>
<td>Pinching Poking Kissing self or others</td>
</tr>
</tbody>
</table>
Tourette Syndrome

- High incidence of ADHD, OCD, Anxiety Disorders
- Onset 3-8 years
- Tends to improve over time
Anxiety Disorders

- The most common behavioral health disorder in children and adults in America
  - 13% of children (1 in 8) aged 9-17 years
- 40%-60% of individuals with ASD
Obsessive thoughts

- Mental echolalia (words or phrases)
- Obscene thoughts
- Counting or grouping
- Thinking about forbidden actions (standing on desk in school, kissing teacher, touching others sexually)
Compulsive behaviors

- Arrangement of objects
- Touching things
- Rechecking
- Smelling
- Licking
- Erasing: Writing and rewriting of letters until perfect
- Washing hands repeatedly
Generalized Anxiety

- Excessive worry, occurring more days than not
- Unreasonable worry about a number of events or activities, such as work or school and/or health
- The inability to control the worry
- Are you bothered by a least three of the following
  - Restlessness,
  - feeling keyed-up or on edge
  - Being easily tired
  - Problems concentrating
  - Irritability
  - Muscle tension
  - Trouble falling asleep or staying asleep, or restless and unsatisfying
Mood Disorders: Depression

- Depressed mood
- Markedly diminished interest or pleasure
- Significant weight loss or weight gain, or decrease or increase in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feeling of worthlessness
- Diminished ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
Symptoms of Mania in Children

- Talkative
- Racing thoughts
- Distractability/Hyperactivity
- Euphoria/elation
- Irritability
- Decreased need for sleep
- Appetite changes
- Aggressiveness, Rage
- Grandiosity,
- Hypersexuality,
In a study sample, 36.4% were diagnosed with mood disorder.

Bipolar disorder accounted for 75% of cases.

Learning Disabilities

A disorder in basic psychological processes involved in understanding or using language, spoken or written, that may manifest itself in an imperfect ability to listen, think, speak, read, write, spell or use mathematical calculations. The term includes conditions such as perceptual disability, brain injury, minimal brain dysfunction, dyslexia, and developmental aphasia.
ASD and Learning Disabilities

- Children with ASD showed a significant gap between what they could read and what they could understand when reading.
- Concrete vs. abstract thinking.
“Non Verbal Learning Disability”

- Strong to exceptional vocabulary and more than typical verbal expression.
- Strong to exceptional auditory rote memory skills.
- Excellent attention to detail, but not so for the big picture.
- The individual may be an early reader, OR may have early reading difficulties. Common difficulty with reading comprehension beginning in the upper elementary grades, especially for novel material.
- Difficulties in math are common, especially in the areas of word problems and abstract applications.
- Concept formation and abstract reasoning may be significantly impaired.
- Significant difficulty generalizing information - e.g. applying learned information to new or novel situations.
Attention Disorders

- Inattention
  - Difficulty sustaining attention
  - Difficulty organizing
  - Loses objects, easily distracted, forgetful

- Hyperactivity and Impulsivity
  - Fidgets, runs, excessively loud
  - "On the go," talks excessively, blurts out an answer
  - Difficulty waiting his or her turn
  - Interrupts or act without thinking, impatient
  - Difficult to resist temptations or opportunities
Why Does Autism Have So Many Co-morbid Associations?

- Neurobiology
- Genetics
- The interaction of the environment, experience and genes
An overview of the Neurobiology of Autism

- Autism is a behavioral expression of many different underlying neurologic events and processes that lead to a somewhat similar behavior.
- Autism is primarily a developmental disturbance in neuronal organizational events.
- The final common pathway for the behavior of autism is that disturbance of organization of neurons and their connections. This leads to problems in information processing.
The behaviors of Autism

Neuropsychologic Function

Neurostructural, neuro-organizational status

Molecular Genetics
Neuropsychologic Concerns in Autism

- Face processing, including structural encoding of facial features and face movements, such as eye gaze
- Social affiliation or sensitivity to social reward
- Motor imitation ability
- Memory inequalities
- Executive function, especially planning and flexibility
- Language ability, especially in synthesis

* Dev Psychopathol 2002 14(3):581
## Comparison of Information Processing

<table>
<thead>
<tr>
<th>Non Autistic</th>
<th>Autistic Processing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holistic: information from whole to part; sees the big picture, not the details.</td>
<td>Random: information without priority, jumps from one task to another.</td>
</tr>
<tr>
<td>Intuitive: information based on whether or not it feels right</td>
<td>Concrete: things that can be seen, or touched - real objects</td>
</tr>
<tr>
<td>Fantasy Oriented: creativity; less focus on rules and regulations</td>
<td>Thought as non verbal, “thinking in pictures”</td>
</tr>
</tbody>
</table>
Neuro-cognitive Theories of Autism

- Central coherence and information synthesis
- Executive function
- Categorization
- Abstract reasoning
- Theory of Mind
- Repetitive Thinking
- Mood and Anxiety Regulation
Pick a Theory

- Abstract Reasoning
- Categorization Processing
- Mood Regulation Anxiety
- Theory of Mind
- Coherence
- Repetitive Thinking
Multiple Primary Deficit Model

- There is no single autism lesion, or neuropsychologic dysfunction.
- Not a single primary deficit but multiple primary deficits in which the deficit pattern is reflective of the complexity of the information processing demands.
- “Autism is not primarily a disorder of social interaction, but a global disorder affecting how the brain processes the information it receives-especially when the information becomes complicated.”
- Social information processing is among the most complex set of information the brain must handle.

Neuropsychology. 2002 Jul;16(3):327-34. Minshew
Multiple Primary Deficit Model

- Reasoning
- Mood Regulation & Anxiety
- Abstract Reasoning
- Coherence
- Categorization Processing
- Repetitive Thinking
- Theory of Mind
- Autism
Neuro-cognitive Theories of Intellectual Disability: Another Example of Multiple Deficits
Some of the primary deficits that are included in autistic processing may also be involved with other disorders and lead to co-morbidity.
Neuro-cognitive Theories of Autism

Abstract

Reasoning

Mood

Regulation & Anxiety

Theory of Mind

Categorization Processing

Coherence

Repetitive Thinking

Learning Disability & Intellectual Disability

Mood & Anxiety Disorders

ADD/ADHD

Obsessive Behaviors Tic Disorders
Genetics and Co-morbidity
Correlation of Family History of Autism

- Rate of bipolar affective disorder in families with Asperger syndrome is 4%, 4 times higher than general population
- The parents of children with autism have significantly higher rates of major depressive disorder and social phobia
- Family members have more motor tics, obsessive-compulsive (OCD) and affective disorders.
- The association with OCD may be strongest in families of individuals on the more severe end of the ASD, especially those with prominent repetitive behaviors
Autism Spectrum Disorders and Autistic Traits: A Decade of New Twin Studies

- Significant genetic overlap has been reported in twin studies between autistic traits and ADHD behaviors in the general population.

- The genetic correlations between autistic traits and ADHD behaviors reported in these studies were all substantial.

Rare Structural Variations of Synapse and Neurotransmission Genes in Autism

- Synapses are the contact points at which nerve cells communicate with other nerve cells, while neurotransmitters are the chemical messengers carrying those signals.

- This large study is the first to demonstrate a statistically significant connection between genomic variants in autism and both synaptic function and neurotransmission.

- Molecular Psychiatry, published online March 1, 2011.
Connections and Transmission

- Synapses are the contact points at which nerve cells communicate with other nerve cells, while neurotransmitters are the chemical messengers carrying those signals.

- This is the same model considered for many disorders such as mood disorders, ADHD, learning disabilities.
Tourette syndrome is associated with recurrent exonic copy number variants

- In Tourette Syndrome 5 exon-affecting rare CNVs that are either de novo or recurrent in 10 out of 111 patients with TS
- Three out of the 5 CNVs have been implicated previously by other studies in schizophrenia, autism, and attention-deficit hyperactivity disorder, suggesting that these CNVs produce a continuum of neuropsychiatric disturbances that manifest in different ways depending on other genetic, environmental, or stochastic factors.
- Senthil K. Sundaram *Neurology*® 2010;74:1583–1590
Tourette Syndrome

- A breakpoint in 7q31 has been recently associated with TS and is also implicated in autism and speech-language disorder.
Parent–child DRD4 genotype as a potential biomarker for oppositional, anxiety, and repetitive behaviors in children with ASD

- A common polymorphism of the D4 receptor gene (DRD4) is located on chromosome 11.
- The 7-repeat allele purportedly results in less D4 receptor responsiveness (reduced dopamine binding efficiency).
- Specifically, mother–child and father–child 7-repeat genotypes were associated with ODD, social anxiety, tics and repetitive problems.
- In addition, youths who did not have a parent who was a 7-repeat carrier were less likely to have severe tic-like behaviors than those who did.

GABA(A) receptor alpha5 subunit as a candidate gene for autism and bipolar disorder

- Genetic studies implicate linkage of one autism subgroup to the chromosome 15q11–13 region, especially to the GABA(A) receptor subunit genes GABRB3 and GABRA5
- Also associated with
  - ‘savant’ characteristics
  - ‘need for sameness’,
  - bipolar disorder
  - alcoholism

*Autism* 2007 11: 135
Chromosome 17 Deletion

Individuals missing a chromosome 17 sequence comprised of 15 genes are about 14 times more likely to develop autism or schizophrenia.

This is a genetic variation that confers a very high risk for ASD, schizophrenia and neurodevelopmental disorders.

May increase risk for other psychiatric conditions such as bipolar disorder.
Dysfunctional gene splicing as a potential contributor to neuropsychiatric disorders

- During transcription, removal (splicing of small segments of the genetic code (exons) are removed.
- There is some evidence for specific splicing abnormalities in a wide range of neuropsychiatric disorders, including psychotic disorders (schizophrenia), affective disorders (bipolar disorder and major depressive disorder), suicide, substance abuse disorders (cocaine abuse and alcoholism), and neurodevelopmental disorders (autism).

The Environment and Co-morbidity

- ADHD
- Autism
- Tourette Tics
- Anxiety Disorders
- Learning Disabilities
- Mood Disorders
Environment and Genes

Fig. 1 Environmental factors only lead to a disorder in presence of a specific genetic make-up

Fig. 2 An individual with a susceptible genetic make-up will only develop a disorder if there are additional environmental pathogens
Parental Age

- Maternal and paternal age are independently associated with autism.
- Firstborn offspring of 2 older parents were 3 times more likely to develop autism than were third- or later-born offspring of mothers aged 20–34 years and fathers aged <40 years.
- Also found for Bipolar Disorder.
Birth Spacing

- Children born less than two years after their siblings are considerably more likely to have an autism diagnosis than those born after at least three years. The sooner the second child is conceived, the greater the likelihood of that child later being diagnosed with autism.

- Also found in schizophrenia.
Exposure to Toxins

- Maternal exposure to air pollution can be related to low infant birth weight (particularly <1500 g) and prematurity.
- Children born to mothers who live close to freeways have twice the risk of autism.
- Also found in learning disabilities,
Birth Complications

- Autism and other behavioral issues can stem from complications during pregnancy and shortly after birth.
- Premature babies have a higher risk of autism and ADHD if they have a high rate of complications.
- Exposure to jaundice in newborns is associated with increased risk of disorders of psychological development for children born at term including autism.
Children can inherit cytokine profiles that tend toward pro-inflammation and are exposed to high levels of cytokines in utero that can affect brain development.
Biological risk factors in pediatric bipolar disorder

- Some bipolar individuals experience increased stressful events prior to onset or subsequent episodes of their disorder.
- Pregnancy is a particular stress for women with a manic-depressive illness history and increases the possibility of postpartum psychosis.
- Drug and medication exposures can be triggers.
- For every additional perinatal risk factor such as prenatal exposure to drugs or birth complications, the risk of having a PBD diagnosis increased more than six-fold.

Biol Psychiatry. 2006 Nov 1;60(9):936-41
Pavuluri, Henry
Autism: Connecting the Dots

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Why Does Autism Have So Many Co-morbid Associations?

- Neurobiology
- Genetics
- The interaction of the environment, experience and genes