

AD/HD and Autism

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AD/HD and Autism are neurobehavioral and neurodevelopmental

Objectives

- Review the neurobehavioral aspects of both AD/HD and Autism
- Discuss AD/HD and Autism as neurodevelopmental disorders: how and why these disorders emerge with respect to brain development.
- Phenotype overlap in AD/HD and Autism: the importance of sleep.

Neurobehavioral Disorders

- Both Autism and AD/HD are neurologically based.
- BUT we cannot currently base our diagnosis on more traditional medical or biological markers.
- Thus, we rely on behaviors to help us clarify diagnosis (looks like a duck, quacks like a duck...)

What Behaviors Define AD/HD and Autism?

....And How Do We Measure Them?



AD/HD as Classified by Behavior

Inattention: careless mistakes, trouble sustaining attention, daydreaming, difficulty completing tasks, disorganization, reluctance to put forth mental effort, misplacing things, and forgetfulness

AD/HD as Classified by Behavior

Hyperactivity/Impulsivity (Disinhibition): fidgeting, difficulty staying seated, restlessness, difficulty being quiet, always moving, talking excessively, blurting out, a lack of patience, and intrusive social behavior



*HERE'S A PRAYER I HEARD MY MOM SAY...
LORD, WHY DID WE INVITE THESE PEOPLE TO DINNERS?*

Quantifying AD/HD Behaviors

- Rating Scales: NICHQ Vanderbilt Assessment Scales, Conners 3, Behavior Assessment Scales for Children-3rd Edition, Behavior Rating Inventory of Executive Function-2nd Edition
- Direct Assessment: Conners Continuous Performance Test-3, Test of Variables of Attention, Quotient, Test of Everyday Attention for Children, Delis-Kaplan Executive Function System, Wisconsin Card Sorting Test, etc

Autism Spectrum Disorder (ASD) as Classified by Behavior

- “Persistent deficits in social communication and social interaction” must be manifested in three different ways:
 - deficits in social-emotional reciprocity.
 - deficits in nonverbal communicative behaviors
 - deficits in developing, maintaining, and understanding relationships

Deficits in Social-Emotional Reciprocity

- A connected back and forth exchange, or the ability to engage with others and to share thoughts and feelings.
- Early signs : disinterest in interactive games like peek-a-boo, lack of a social smile, and failure to imitate facial expression, vocalizations, and actions.
- In older children: one-sided communication, little give and take in conversation



Deficits in Nonverbal Communicative Behavior



- Abnormalities in eye contact, limited use of gestures, facial expressions, and other body language
- Unusual speech intonation and difficulty coordinating speech with nonverbal forms of communication.
- Early signs: lack of interest in faces and the behavior of others, failure to reference parents to see how they react in novel situations, a lack of pointing or following a point

Deficits in Developing, Maintaining, and Understanding Relationships

- Abnormal social interest, ranging from complete disinterest in others to inappropriate, aggressive and disruptive approaches to social interaction.
- In young children: a lack of social and imaginative play with others and in inflexibility in play
- Preference for solitary activities or interactions with younger or older individuals.
- Lacking theory of mind



Early Signs of ASD from Autism Speaks

- No big smiles or other warm, joyful expressions by six months or thereafter
- No back-and-forth sharing of sounds, smiles or other facial expressions by nine months
- No babbling by 12 months
- No back-and-forth gestures such as pointing, showing, reaching or waving by 12 months
- No words by 16 months
- No meaningful, two-word phrases (not including imitating or repeating) by 24 months
- Any loss of speech, babbling or social skills at any age

ASD as Classified by Behavior

- **BUT WAIT!** Individuals must also exhibit behaviors from at least 2 out of 4 categories that refer to restricted, repetitive patterns of behavior, interests, or activities.

Restricted/Repetitive Patterns of Behavior, Interest, or Activities

- Stereotyped or repetitive motor movements, use of objects, or speech
- Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior
- Highly restricted, fixated interests that are abnormal in intensity or focus
- Hyper or Hypo reactivity to sensory input or unusual interest in sensory aspects of the environment

Stereotyped or repetitive motor movements, use of objects, or speech

- Simple motor movements like hand flapping and finger flicking
- Repetitive use of objects such as lining up toys
- Repetitive/stereotypical speech patterns including echolalia, misuse of pronouns, and repeating phrases



Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior



- Resistance to change
- Insistence upon following rules
- Inflexible, black and white thinking

ASD as Classified by Behavior

- highly restricted, fixated interests that are abnormal in intensity or focus
- hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment

Quantifying ASD Behaviors

- Rating Scales: Childhood Autism Rating Scale-Second Edition, Autism Spectrum Rating Scales, Autism Screening Questionnaire, Autism Diagnostic Interview-Revised, Behavior Assessment Scales for Children, Third Edition
- Direct Assessment: Autism Diagnostic Observation Schedule-Second Edition, NEPSY-II, Test of Problem Solving Elementary and Adolescent

What is Happening in the Brain in AD/HD and Autism?

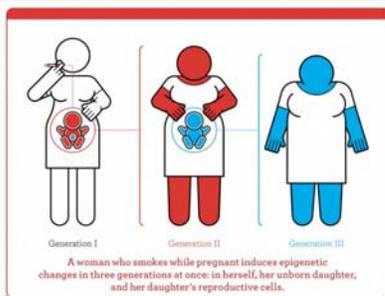
Where does the term “neurodevelopmental” fit?

Neurodevelopmental Disorders

- Both AD/HD and ASD are neurodevelopmental disorders.
- They are believed to be caused by differences in the way the brain grows and develops.
- The behaviors that classify both AD/HD and ASD emerge early in a child's development, and they have a high level of comorbidity with other neurodevelopmental disorders.
- Both children with AD/HD and children with ASD can present with abnormalities in attentional functioning, hyperactivity, social dysfunction, and externalizing behavior.

“Typical” Brain Development

- Nature AND Nurture
- Behavioral development reflects an interaction between neurology (brain) and context (environment).
- It is also dependent upon epigenetics. Genes are never expressed outside of an environmental context.

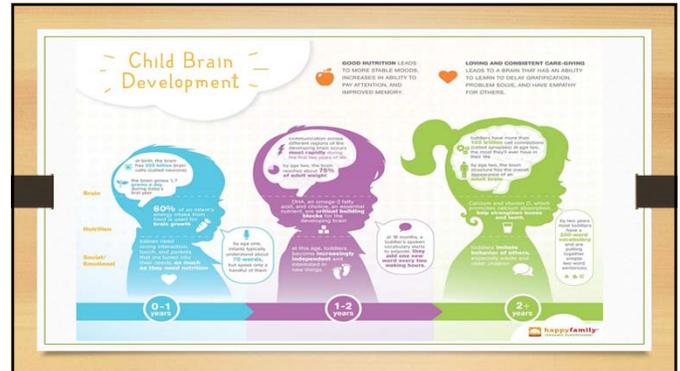


“Typical” Brain Development

- The brain has a great deal of plasticity and it can recover over time, but it is also highly vulnerable during the early years.
- Early care is crucial for healthy brain development.
- Children thrive when they receive warm, responsive care, and early care has been shown to have decisive, long lasting impacts.

“Typical” Brain Development

- The brain grows from the inside out and from the bottom up
- Brain development occurs in 2 basic stages
 - Growth spurts and overproduction
 - Pruning
- Critical phases of growth are in utero, 0-3 years, and 10-13 years



“Typical” Brain Development

- Pruning
 - By the second decade of life, the brain undergoes a process during which it prunes and organizes its neural pathways.
- Learning
 - Learning happens when a synapse is created and strengthened by frequent use.
 - The brain holds onto the most efficient and strong synapses, and it discards the synapses that are not used.
 - What a child “feeds” their brain, makes a direct impact on which synapses flourish and which are pruned away.



AD/HD and Neurodevelopment

- AD/HD is by definition a disorder of age-inappropriate inattention and disinhibition (hyperactivity/impulsivity).
- We see the behaviors of inattention and disinhibition, and these are more prevalent than would be expected given the child's age and developmental level. Thus, we see immaturity.
- More specifically, in AD/HD, we see immaturity in executive function.

AD/HD and Neurodevelopment

- Executive Dysfunction (ED) often becomes apparent with shifts in developmental expectations
- Elementary school: remember and follow classroom rules, stay seated and pay attention for longer periods of time, interact with their peers in prosocial ways, control basic emotional reactions
- Middle school: keep up with assignments and materials in multiple classes, navigate the hallways, use a locker, dress out for PE, manage social status and image.
- High school: growing independence, managing impulses related to drugs, sex, driving, and social media.

AD/HD and Neurodevelopment: Russell Barkley, PhD

- Barkley argues that inhibitory control is responsible for increases in advanced executive control during brain maturation.
- Barkley posits that in AD/HD, we see three specific weaknesses in inhibitory control that lead to early and later executive dysfunction:
 - stopping of an ongoing response
 - interference control
 - prepotent response inhibition

AD/HD and Neurodevelopment: Russell Barkley, PhD

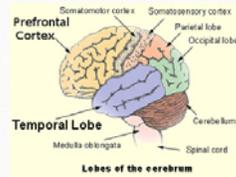
- In the preschool period, symptoms of AD/HD are highly predicted by deficits in inhibitory control, but the relationship between symptoms of AD/HD and working memory deficits is not yet clear.
- By the time children reach elementary school age, working memory deficits start to discriminate well between children with AD/HD and their typically developing peers.

BUT WHAT IS HAPPENING IN THE BRAIN?



AD/HD and Neurodevelopment

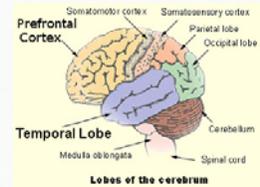
- The more severe the AD/HD symptoms or behaviors—as rated by parents and clinicians—the smaller their
 - frontal lobes
 - temporal gray matter
 - caudate nucleus
 - cerebellum.



www.ADHDbasics.com

AD/HD and Neurodevelopment

- The prefrontal cortex is believed to be particularly important in AD/HD.
- Lesions to the PFC produce a profile of distractibility, forgetfulness, impulsivity, poor planning, and locomotor hyperactivity- or symptoms of AD/HD.



AD/HD and Neurodevelopment

- The PFC regulates behavior, attention, and affect by using representational knowledge, or working memory, to guide movement and attention, and to inhibit inappropriate responding.
- Single-unit recording studies have shown that PFC neurons are able to hold modality-specific information “on-line” over a delay and use this represented information to guide behavior in the absence of environmental cues. (Goldman-Rakic PS, 1995)
- PFC neurons can maintain delay-related firing even in the presence of distracting stimuli, which protects performance from interference.

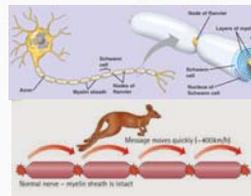
AD/HD and Neurodevelopment

- The PFC is one of the last areas of the brain to fully develop, perhaps reaching maturity around age 24.
- As the PFC matures, through experience and practice, teens gradually learn to reason better, develop more impulse control, and make better judgments.
- In AD/HD, underdevelopment, or delayed development in the PFC is believed to make children and teens more prone to “behave emotionally or with ‘gut’ reactions.”
- They require more, not less structure, support, and guidance during this time.

No Neuron is an Island

What about Brain Connectivity and Circuitry?

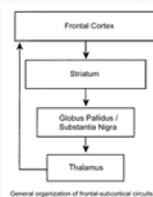
AD/HD and Neurodevelopment: Connectivity



- White matter maturation is delayed in children with AD/HD.
- White matter contains myelin, a layer of insulation that progressively insulates cells and is whitish in color.
- Insufficient insulation, with delayed production of myelin, is believed to contribute to some of the inefficiencies in processing that we see in AD/HD.

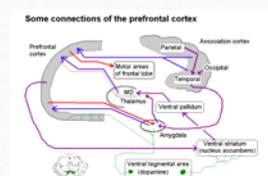
AD/HD and Neurodevelopment: Circuitry

- Children and adults with AD/HD have been shown to exhibit structural changes in networks that involve the prefrontal PFC and its connections to the striatum and cerebellum.
- These changes have been shown to be associated with cognitive impairments, such as distractibility, forgetfulness, impulsivity, poor planning, and locomotor hyperactivity. (Seidman et al., 2005; Arnsten, 2006).



AD/HD and Neurodevelopment: Circuitry

- The PFC also has extensive connections to sensory and motor cortices.
- The PFC receives inputs from sensory association areas, and thus is well-positioned to inhibit processing of stimuli that is irrelevant and to regulate attention.
- The PFC is a critical area of integration of sensory information and plays a prominent role in regulating movement and inhibiting inappropriate behavioral responses in light of this information.



AD/HD and Neurodevelopment: Circuitry

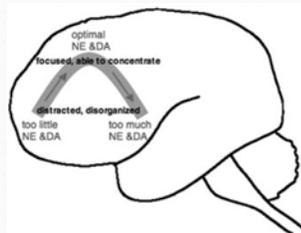
- The temporal cortex, which is also reduced in volume in AD/HD, is specialized for processing visual and auditory features.
- Neuronal activity in this area is increased when stimuli are novel, but repeated experience with that same visual stimulus leads to decreased firing (habituation).
- “Top-down” projections from the PFC can override the intrinsic habituation process and allow for sustained, directed selective attention even if the stimuli is boring or challenging.

Does Neurodevelopmental Theory Match up with Treatment?

AD/HD and Neurodevelopment: Treatment

The operations of the PFC are greatly influenced by its neurochemical environment.

Both DA and NE exhibit an inverted U influence on cognitive functions of the PFC, where either too little or too much impairs working memory and attention. (Brennan and Arnsten, 2008)



AD/HD and Neurodevelopment: Treatment

- Medications for the treatment of AD/HD all increase catecholamine transmission from neuron to neuron.
- Amphetamine and methylphenidate enhance the release of and/or inhibit the reuptake of both DA and NE, making it more available.
- Methylphenidate can improve PFC working-memory function and enhance the efficiency of PFC activation.

AD/HD and Neurodevelopment: Treatment

- Methylphenidate is often (falsely) referred to as a selective DA drug, leading to the dopamine hypothesis of ADHD, but NE is actually increased more than DA in the PFC with methylphenidate.

AD/HD and Neurodevelopment: Treatment

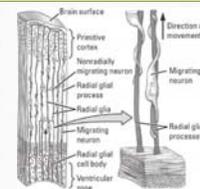
- What about non-stimulants?
 - Atomoxetine increases both NE and DA in the PFC.
 - Guanfacine acts specifically as an agonist for NE at the alpha2A receptor.
- AD/HD has been associated with genetic alterations in a specific enzyme that synthesizes NE: dopamine beta hydroxylase (DBH).
- AD/HD is also associated with an increased incidence of the 7 repeat polymorphism of the D4 receptor.

It's More Complicated in Practice

- AD/HD is often the default diagnosis for children with attentional and behavior problems, particularly when diagnosis is based on AD/HD specific rating forms alone.
- Factors other than developmental AD/HD can mimic the behaviors of AD/HD.
- Fatigue can lead to insufficient catecholamines and stress can lead to excessive catecholamines.

“Typical” Brain Development

- Neural migration occurs between 4 and 9 months of gestational age
- Some neuroblasts begin to move to the outer edges of the growing wall of the neural tube, forming the spinal cord, brain stem, cerebellum, and cerebral hemispheres.
- The distance to be traveled from the inner boundary to the outer portions becomes increasingly longer and more difficult.
- Radial glial cells provide support and directional guidance for the migrating neuroblasts.



“Typical” Brain Development

- The greatest thickening of the neural tube occurs in the developing cerebral hemispheres, where this process results in the formation of six cortical layers.
- Each new layer of the cortex forms from neuroblasts that have migrated all the way through the previously formed layers, resulting in an inside-out sequence of development.



ASD and Neurodevelopment

- Migration-associated problems can be detected in the brains of individuals with ASD. These include:
 - changes in neuronal density and volume
 - aberrant minicolumn cytoarchitecture
 - heterotopias
- (reviews DiCicco-Bloom [2006](#); Casanova and Pickett [2013](#); Chen *et al.* [2015](#)).

ASD and Neurodevelopment

- Evidence that neurogenesis is dysregulated, along with neuronal migration and neuronal maturation in multiple regions of the cortex.
- Evidence of cell clustering with less distinct boundaries between gray and white matter.
- Disruption of organization of cells in minicolumns
- Wegiel *et al.* [2010](#); Hutsler *et al.* [2007](#); Avino and Hutsler [2010](#); Casanova *et al.* [2002](#); Buxhoeveden *et al.* [2006](#).

ASD and Neurodevelopment

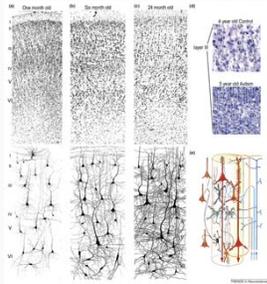
- In another study, focal patches of abnormal cytoarchitecture and cortical disorganization of neurons were detected in prefrontal and temporal cortical tissue. While the neurons were disorganized, the glial cells were not. (Stoner *et al.* [2014](#)).
- No cortical layer was uniformly spared, with the clearest signs of abnormal expression most often in layers IV and V.

ASD and Neurodevelopment

Evidence of early brain overgrowth in individuals with ASD.

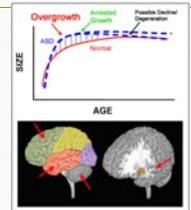
This has been shown to be associated with a narrower neurophil area between columns (Casanova et al, 2006).

When these neurons are packed in so closely together, this disrupts the arborization of dendrites.



ASD and Neurodevelopment

- Following overgrowth, we see a sudden arrest of growth between 2 and 4 years of age
- We also see an earlier brain degeneration and decline in ASD



ASD and Neurodevelopment: Courchesne et al, 2007

- Early overgrowth leads to an excess of excitatory neurons in the frontal and temporal cortex
- Overgrowth results in a mismatch in the number of afferent axons coming to this large pool of frontal and temporal cortex neurons
- This leads to broad and sporadic connectivity, as well as to too much processing in the cortical areas
- This could profoundly disrupt the major event of circuit formation

ASD and Neurodevelopment: Language Acquisition

- Toddlers typically demonstrate a burst in language acquisition
- This skill development requires recruitment of large-scale networks that involve frontal, temporal, occipital, and cerebellar regions
- Functional connectivity is crucial for this development to occur.

Neurotransmitters and ASD

- Excitatory and inhibitory neurotransmitters are implicated in ASD: serotonin, GABA, and glutamate
- Serotonin is known to play a role in the development of social skills
- GABA plays a key role in regulating stages of cell migration, neuronal differentiation, and maturation
- In adults, GABA is important for cognition and for processing sensory information

Neurotransmitters and ASD

- Certain genetic variants that code for GABA and GABA receptors are associated with increased risk for ASD
- GABA concentration in the sensorimotor cortex correlates with performance on touch discrimination tasks
 - Could the relationship between GABA and touch explain sensory sensitivities in ASD?
 - What would this mean for treatment?

AD/HD and ASD: Lessons from Neurodevelopmental Theory

- Functional connectivity between and among brain regions is crucial and implicated in both disorders
- Differences in neurotransmitter function are implicated in both disorders
- Small, but complicated changes in brain development lead to a wide array of neurobehavioral symptoms

Behavioral Pediatrics in ASD and AD/HD

- Behavioral pediatric issues are relevant when working with families of children who have neurodevelopmental disabilities
- We see a high level of comorbidity of symptoms in the areas of sleeping, eating, toileting, physical activity, and externalizing behavior

Sleep and AD/HD

Sleep problems are frequently reported in children and adolescents with AD/HD

Restless sleep was once listed as a diagnostic criteria for AD/HD, but the relationship between sleep and AD/HD is not straightforward



Sleep and AD/HD

- CNS centers that regulate sleep and attention/arousal overlap
- Catecholamine pathways are implicated in AD/HD and in sleep problems
- A primary circadian rhythm disruption in AD/HD?
- Children with AD/HD demonstrate increased sleep propensity
- Is hyperactivity an adaptive behavior that counteracts hypoarousal?

Sleep and AD/HD: Objective Measures

- Most objective studies fail to find consistent differences in sleep between children with AD/HD and controls
- Some evidence of subtle changes in sleep microarchitecture in AD/HD (Miano et al, 2006)
- Overall activity levels during sleep may be greater in AD/HD
- More night to night variability in sleep patterns is noted in AD/HD (Gruber, Sadeh, & Raviv, 2000)

Sleep and AD/HD: Subjective Measures

- Parents report a high frequency of sleep problems in children with AD/HD and so do mental health providers
- These most often include problems with sleep initiation and maintenance
- Problematic night-time behaviors are also commonly reported



Sleep and AD/HD:

Why the difference between objective and subjective reports?

- Possible “negative halo” effect
- Caregivers and clinicians may be vigilant about monitoring because of beliefs about sleep and AD/HD
- Night to night variability may play a role in clinical settings
- Methodological issues, including definition of “sleep problem”

Sleep and ASD

- 40-80% of children and adolescents with ASD experience sleep problems:
 - 54% bedtime resistance
 - 56% insomnia
 - 53% parasomnias
 - 25% sleep disordered breathing
 - 45% morning arising problems
 - 31% daytime sleepiness

Sleep and ASD

- The last enzyme needed to synthesize melatonin is less active in children with ASD
- Serotonin and GABA are important for establishing the sleep-wake cycle
- PSG studies of children with ASD show abnormalities in REM sleep
- In one study, 5/11 children with ASD and disrupted sleep had nocturnal awakenings, REM sleep behavior disorder, and lack of muscle atonia during sleep (Thirumalai Shubin, & Robinson, 2002)

Sleep and ASD

- Reduced Total Sleep Time (TST) correlates with severity ratings on the Childhood Autism Rating Scale (CARS)
- Lower REM percentage is related to higher CARS scores
- AD/HD in ASD studies.....
 - Children with moderate to severe AD/HD symptoms also show increases in sleep onset latency and REM latency

Sleep and Clinical Practice

- We should start our assessment of sleep problems earlier and in the diagnostic phase of treatment
- We should routinely screen for primary and comorbid sleep disorders
- The BEARS screening tool is readily available online
- Before using, refresh your knowledge of symptoms and risk factors for sleep problems (family history of OSA and/or RLS, enlarged tonsils and adenoids, obesity, and iron deficiency)

Sleep and Clinical Practice

- Assess severity (e.g. time to fall asleep), frequency (e.g. nights per week), and duration (e.g. number of months/years the symptoms have been present)
- Also assess these points of intervention:
 - Sleep hygiene
 - Anxiety and mood symptoms that impact sleep
 - AD/HD and ASD symptoms at bedtime
 - Timing of sleep onset relative to bedtime
 - Degree and persistence of bedtime resistance

Conclusions: Facts about AD/HD and Autism?

- As always, we have much to learn
- We have considered what the terms neurobehavioral and neurodevelopmental mean within the context of AD/HD and ASD.
- We have started a conversation about areas of overlap in the phenotype of AD/HD and ASD

Questions?

