Autism spectrum disorder:

A NEURODevelopmental disorder

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Disclosures

- I will discuss non-FDA approved medications used in Autism Spectrum Disorder.
- Member of APA DSM 5 Neurodevelopmental workgroup.
- Current and past grant support from Cure Autism Now, Autism Speaks, MIND Institute, Simons Foundation Autism Research Initiative (SFARI), Nancy Lurie Marks Family Foundation, NIH
- Past consultant for Seaside Therapeutics for Arbacolfen
- Past co-investigator in clinical trial of a novel compound led by Hoffman LaRoche pharmaceuticals.
- Current co-investigator in clinical trial of a novel compound led by Servier pharmaceuticals.
- Consultant to Yanmo pharmaceuticals for new compund being tested in ASD

Overview

- Epidemiology
- Diagnosis
- Heterogeneity
- Etiological theories
- Medical co-morbidities
- Treatments
- Neurodiversity

Epidemiology: 2020 MMWR report

- 2020 data (cohort of 8 year olds from 2016)
- 1 in 54 children or 1.8% or 18.5/1,000 (range 13.1-31.4/1,000)
  - Fist time there were equal rates for most different races/ethnicities
  - Only 33% with ID (IQ<70)
- History
  - 0.4/1,000 when I was in medical school!
  - 6.8/1,000 in 2000
  - 8/1,000 in 2004
  - 11.3/1,000 in 2008
  - 14.7/1,000 in 2010
  - 14.6/1,000 in 2012
  - 16.8/1,000 In 2014
- Why????
  - Increased ascertainment
  - Earlier identification
  - ? true prevalence increase

How do you diagnose autism spectrum disorder?

- Diagnosis comprised of constellation of behavioral symptoms as defined by a group of experts appointed by the APA (DSM 5)
- No biomarkers, no scans, no genetic tests
- Requires comprehensive developmental history AND direct assessment/observation
  - Needs to include assessment of cognitive function and adaptive skills

Common myths

He doesn't have autism because he:

- Talks
- Looks at me
- Interacts with me in the office
- Is interested in other kids
- Doesn't flap or rock

She does have autism because she:

- Doesn't talk
- Doesn't make eye contact
- Flaps or rocks

Concept of a spectrum: Differing presentations:

- 2 year old girl with no interest in parents or other children, ignores any social overtures, no speech or nonverbal communication (gestures or eye contact), almost continuous repetitive behavior (flapping hands, toe walking, flicking string and making a repetitive noise), can only drink out of one sippy cup, tantrums uncontrollably if routine is changed, severe sensory sensitivities, DQ 40
- 15 year old boy with a lot of social interest but makes inappropriate overtures so has no friends, has a hard time changing behavior to suit social context, monotone or unusual high pitched speech, lectures at you rather than conversing with you, performs motor stereotypies only in private now, very literal language (doesn't understand idioms or sarcasm), all play needs to be on his terms – his videogames/his rules, very rigid - thinks in black and white, knows the Paris metro system by heart, IQ 140

What tools do you need to make the diagnosis?

- You and the child
- YOU
  - Have to read the criteria and text.
  - Have to exercise good clinical judgment.
  - Have to have time
    - To take a thorough developmental history
    - To do a behavioral observation
    - Get corroborating information from other sources

Clinical Observation

Look for behaviors that should be there and are missing

- Communicative intent
- Eye contact
- Reciprocal social interaction (shared enjoyment, turn taking, response to and initiation of overtures)
- Insight into social relationships

Look for behaviors that are present and should not be

- Repetitive behaviors
- Restricted interests
- Unusual sensory behaviors

Are there tools that can help?

- Yes
  - Diagnostic criteria can be subjective
  - Screening tests can bring kids to attention
    - M-CHAT R/F (revised with follow-up)
    - Social Communication Questionnaire (SCQ)
  - Standardized instruments developed for research to make sure that we are all studying the same thing
    - Autism Diagnostic Observation Schedule (ADOS)
    - Autism Diagnostic Interview (ADI)
    - Social Responsiveness Scale (SRS)
  - Standardized instruments can help with clinical dx too … but they are not (usually) necessary!
    - Childhood Autism Rating Scale (CARS)
    - Gilliam Autism Rating Scale (GARS)

DSM-5 Criteria for ASD (released 5/2013)

- Major changes:
  - Name change
  - 3 domains become 2
    - Social, communication, restricted interests, repetitive behaviors
  - Autistic Disorder, Asperger and PDD NOS combined into Autism Spectrum Disorder
  - Rett and CDD subsumed under ASD (if appropriate)
  - Adding specifiers and severity ratings

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Other benefits to DSM 5

- In social communication domain
  - Examples allow a better description of the whole range of behaviors seen across the spectrum
  - Examples include descriptions of higher order social communication skills
  - More general language allows mapping of many symptoms onto a given criterion rather than having to see a specific behavior
  - Allows more clinician judgment

Other changes

- In repetitive behavior/restricted interests domain
  - Requirement of meeting 2 of the 4 was necessary for specificity
  - Addition of sensory abnormalities and allowance for symptom presence 'by history' (ie there in the past but no longer showing) captures most patients
- No more requirement for symptoms to be there by age 3 – just in the early developmental period
- The need to differentiate from ID is more clear
  - "Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level."

A single spectrum does not mean lack of specificity

- Specifiers were added to better describe each individual
  - With or without accompanying intellectual impairment
  - With or without accompanying language impairment
  - Associated with a known medical or genetic condition or environmental factor
  - Associated with another neurodevelopmental, mental, or behavioral disorder
  - With catatonia*
    - Not written by the DSM 5 NDD committee

Inclusion of severity ratings

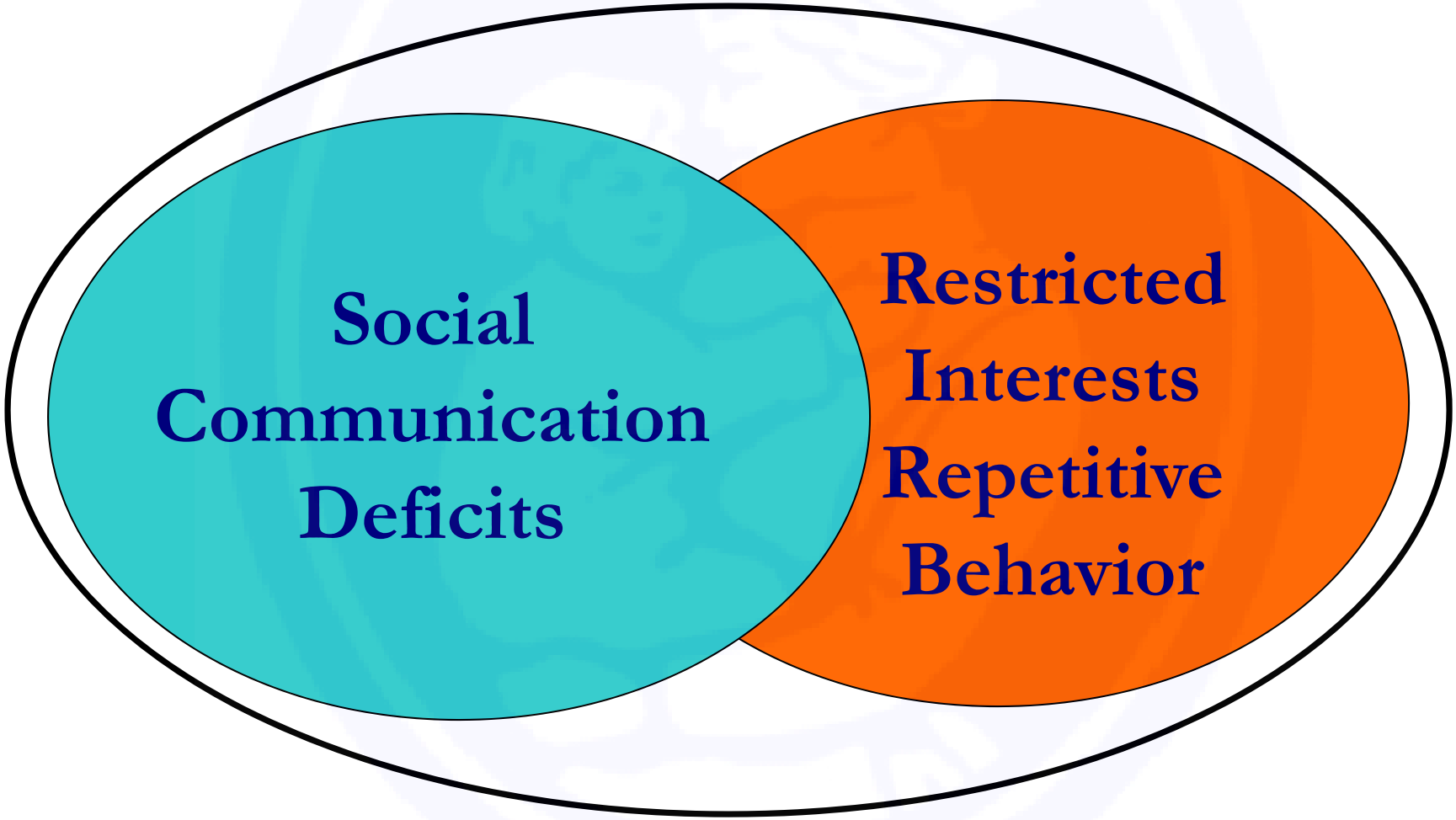
- Previously Asperger used for “milder” ASD
- Recognition that severity in one domain is independent of the other domain
- Avoids “mild” “moderate” “severe”

	Social communication	Restricted interest repetitive behav
LEVEL 1 Requires support		
LEVEL 2 Requires substantial support		
LEVEL 3 Requires very substantial support		

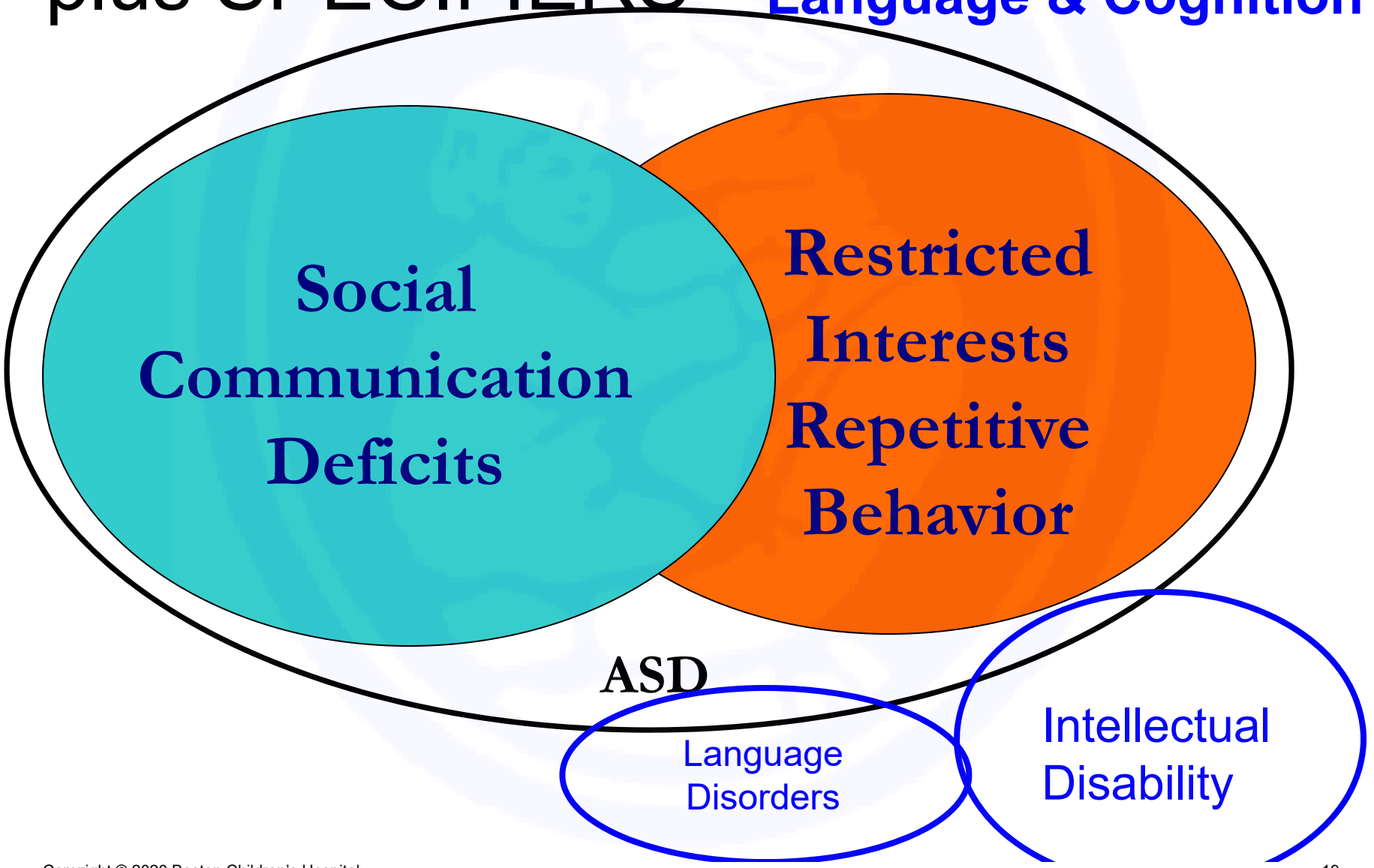
Key Concept: Heterogeneity

- It is a fact
  - If you have known one person with autism … you have known one person with autism!
  - Widely varying presentations
  - “High” and “Low” functioning usually refers to language level & IQ
  - Expressions of symptoms change over time
- It complicates diagnosis and care tremendously … there are implications for and interactions with etiology, co-morbidities, treatment, outcome

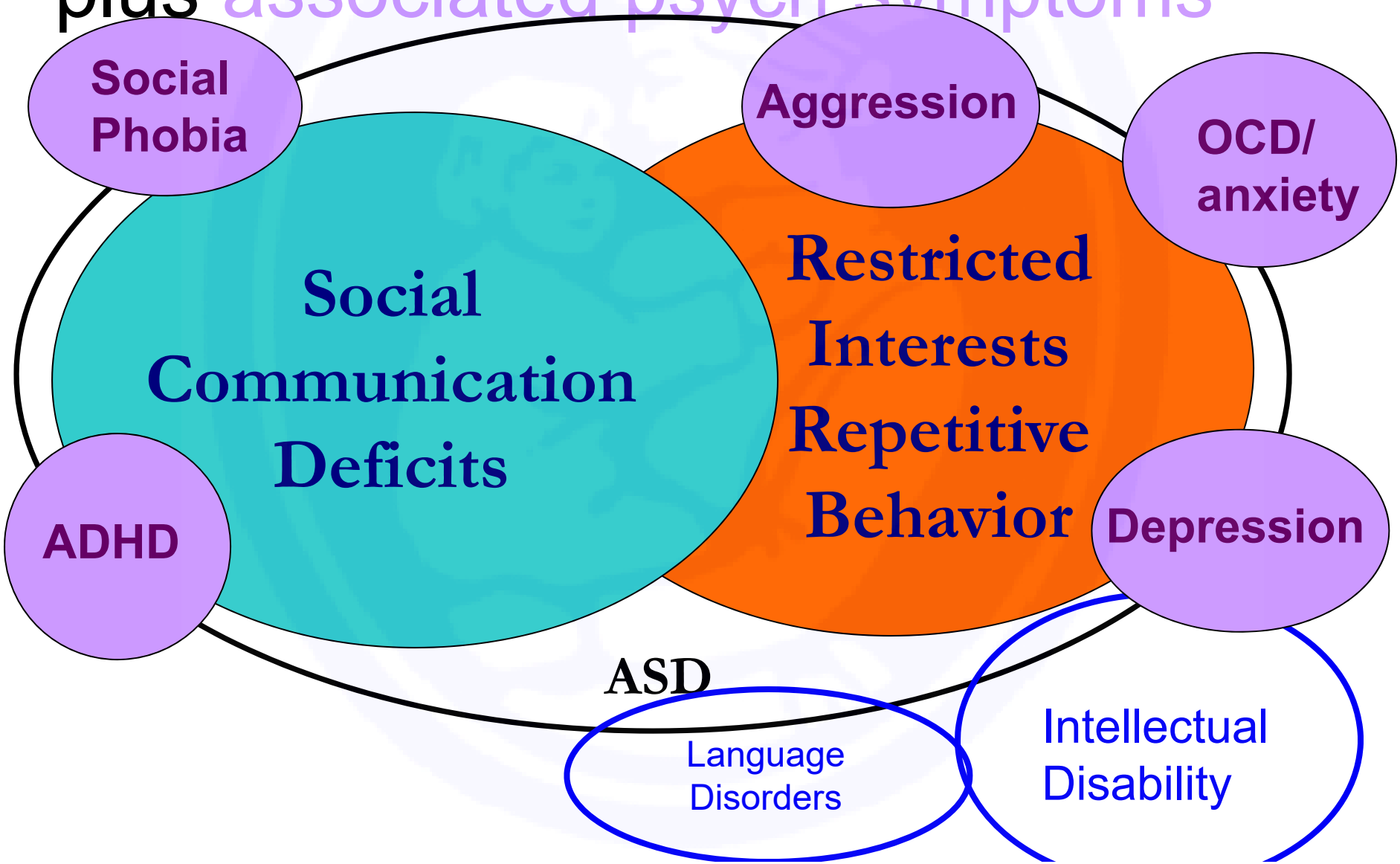
Core Symptom Domains –DSM 5



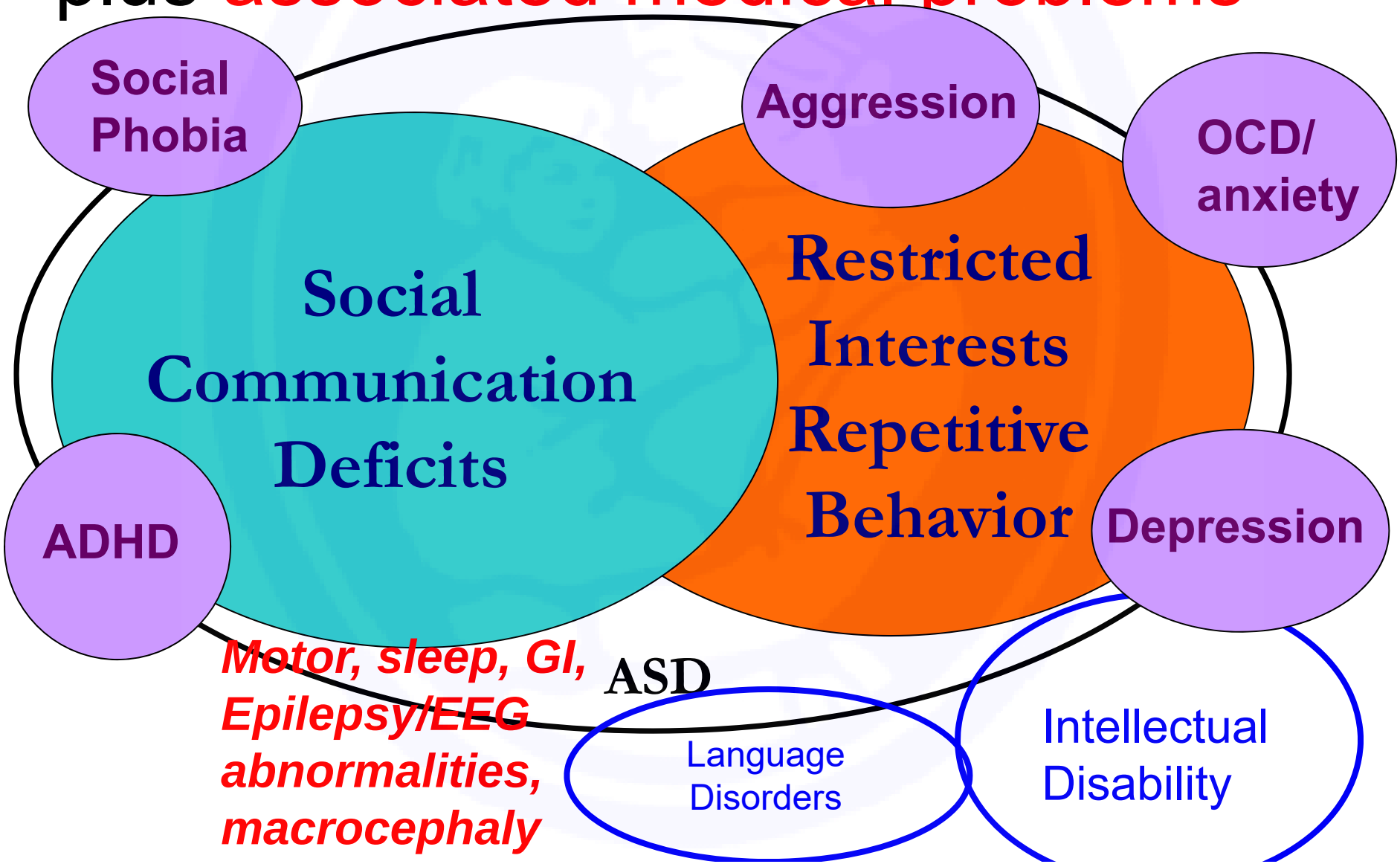
Core Symptom Domains –DSM 5 plus SPECIFIERS



Core Symptom Domains –DSM 5 plus associated psych symptoms



Core Symptom Domains –DSM 5 plus associated medical problems



What we know about etiology

- Not one Disorder
- Not one Cause!
  - Genetic susceptibility
  - Neurobiology
    - Abnormal synapses, excitatory/inhibitory imbalance
    - Abnormal cellular signaling pathways
    - Abnormal functional connectivity
  - Immunologic mechanisms
  - Metabolic abnormalities
  - Interactions amongst all of the above

CO-MORBIDITIES

Determining Genetic Architecture

Observation/ Epidemiological Studies

- Twin studies show high concordance
- Siblings have increased risk (~20%)
- Broader Autism phenotype in family members
- ***Gives heritability estimates but not genes***

RARE VARIANTS de novo /causative

- Syndromes
- Karyotype
- Chromosomal Microarrary
- Whole Exome Sequencing (WES), Whole Genome Sequencing (WGS)
- ***Still low rates so something else is happening***

COMMON VARIANTS frequent low risk

- Very high heritability estimates
- Genome Wide Association Studies (GWAS)
- ***Despite large samples not much reaches genomewide significance***

INTERPLAY

- Gene x Gene
- Gene x environment
- Probably explains phenotypic heterogeniety

Associated Rare Diseases/Syndromes

- Rett syndrome
- Fragile X syndrome
- Tuberous sclerosis complex
- 15q duplication syndrome
- Prader-Willi/Angelman
- Timothy syndrome
- Sotos syndrome
- Noonan syndrome
- Joubert syndrome
- Neurofibromatosis I
- Hypomelanosis of Ito
- Down syndrome
- Williams syndrome
- Congenital myotonic dystrophy
- Duchenne muscular dystrophy
- Velocardiofacial syndrome
- Cohen Syndrome
- ARX mutation
- Smith-Lemli-Opitz syndrome
- Cerebral Folate Deficiency
- Untreated PKU
- Disorders of purine metabolism
- Leber's congenital optic atrophy
- Smith Magenis syndrome
- Moebius Syndrome

Differences in Brain Size

- Macrocephaly is common
  - Kanner's original description of autism documented "large heads" in 5/11 patients.
  - Most studies say ~20%
  - Entire distribution shifted to the right – not just a subgroup.
  - Higher in family members too.
  - Present early in life – early brain growth may be a marker of autism (Courchesne et al., 2003)

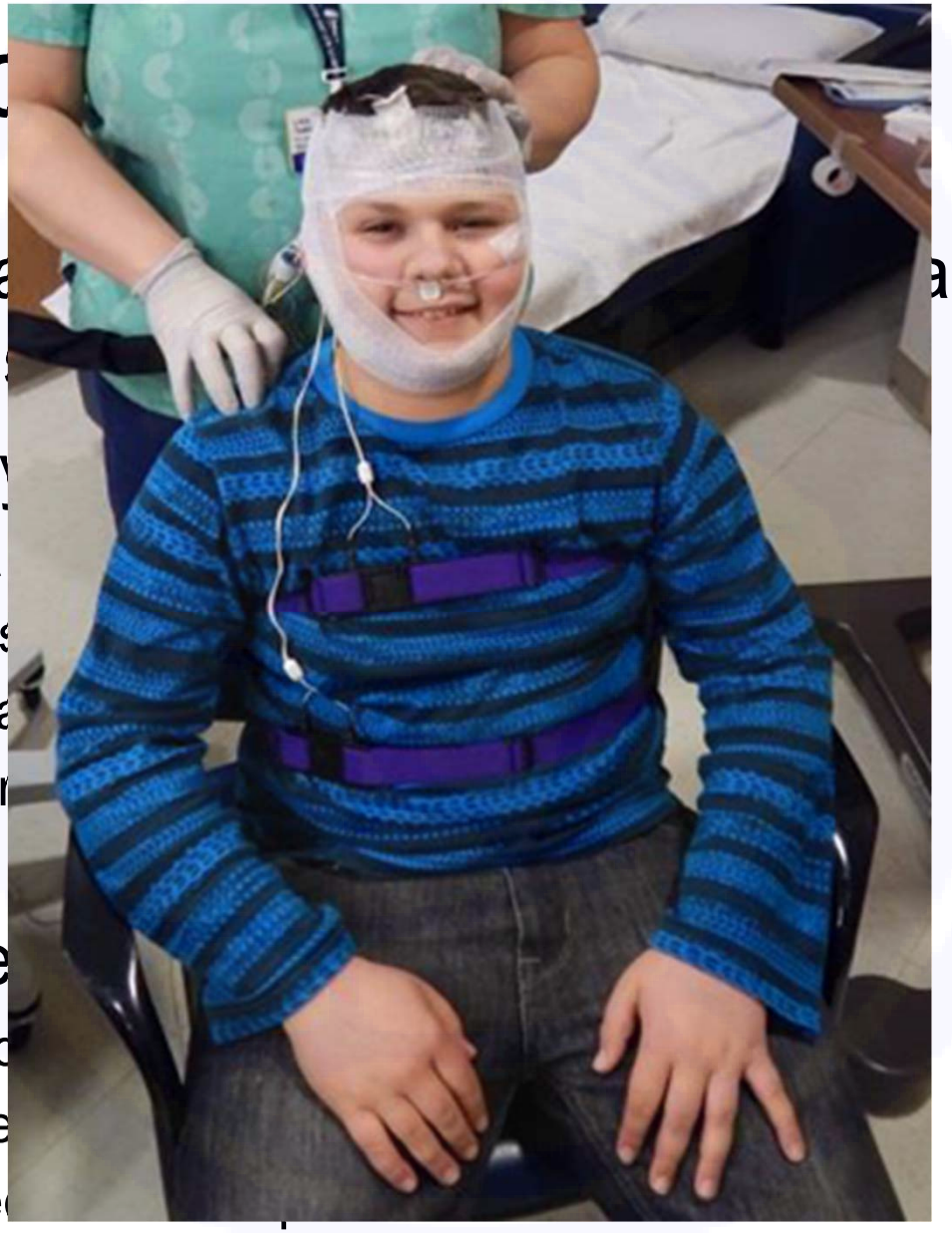
Epilepsy in Autism and ASD

- Increased rates of epilepsy in patients with autism spectrum disorders *(and vice versa!)*
  - But - rates very variable (5-46%)
  - Probably dependent on sample characteristics:
    - AGE: bimodal age of onset (childhood & adolescence/early adulthood).
    - NON-IDIOPATHIC AUTISM: neurogenetic syndromes or brain injury
    - IQ and LANGUAGE skills
      - lower IQ increases the risk of epilepsy but even those with normal IQ have increased risk.
      - language regression and poorer language skills may also predict epilepsy although data are inconsistent.
  - Best estimates from population based studies
    - ~20%

EEG Abnormalities

- No surprise that the kids with epilepsy have them
- But studies started to show that some children with autism had ISOLATED epileptiform EEGs (without clinical seizures)
- Literature in the 90's reported rates 10-20%
- More recent studies are reporting rates ~50-60%
- Overnight or prolonged more sensitive than routine studies
- What to do about it is controversial

Sleep d



- Most data ard to do in these kid
- Extremely
  - Insomnia
  - Delayed s
  - Night awa
  - Early mor
  - Reduced
- Objective
  - Increased
  - Decrease
  - Shortene

Motor impairment

- Repetitive behavior or stereotypies
- Motor Delays
- Hypotonia
- Incoordination
- Gait impairment
- Apraxia
- Motor planning
- Postural control

Known metabolic disorders with ASD phenotypes

- Purine disorders: adenylosuccinase deficiency, adenosine deaminase (ADA) deficiency
- Untreated PKU
- Creatine disorders: arginine-glycine amidinotransferase deficiency, guanidinoacetate methyltransferase deficiency, disorders of creatine transport
- Biotinidase Deficiency
- Cerebral Folate Deficiency
- Succinic semialdehyde dehydrogenase (SSADH) deficiency
- Smith Lemli-Opitz Syndrome
- SCAD deficiency
- Infantile ceroid lipofuscinosis
- Histidinemia
- Urea Cycle Defects: ornithine transcarbamylase deficiency, citrullinemia, argininosuccinic aciduria, carbamoyl phosphate synthetase deficiency
- Sanfilippo syndrome

Intellectual Disability

- Previously quoted as majority of patients
  - Rates variable (40%-100%) median at 70%. *(Fombonne, JADD, 2003)*
- Recent MMWR data only 31%
- Take home message: it's variable!
  - IQ tests hard to perform, many rely heavily on verbal abilities
  - Often a big discrepancy between VIQ and NVIQ
  - Huge variability among subtests.

Sensory

- Unusual behaviors related to auditory, visual, tactile senses.
- Very common finding
- Now part of diagnostic criteria.
- Can be manifested by
  - hyperreactivity (*sensory sensitivity)* to sensory stimulation
  - hyporeactivity (*sensory insensitivity or sensory seeking)* to sensory stimulation

WORK-UP

Genetic testing recommendations

SYSTEMATIC REVIEW | Genetics inMedicine

Open

Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders

Siddharth Srivastava, MD[1], Jamie A. Love-Nichols, MS, MPH[1], Kira A. Dies, ScM[1], David H. Ledbetter, PhD[2], Christa L. Martin, PhD[2], Wendy K. Chung, MD, PhD[3,4], Helen V. Firth, DM, FRCP[5,6], Thomas Frazier, PhD[7], Robin L. Hansen, MD[8], Lisa Prock, MD, MPH[1,9], Han Brunner, MD[10,11,12], Ny Hoang, MS[13,14,15], Stephen W. Scherer, PhD[14,15,16,17], Mustafa Sahin, MD PhD[1], David T. Miller, MD PhD[18] and the NDD Exome Scoping Review Work Group

- Benefits
  - Genetic counseling r.e. recurrence risk
  - Positive findings can end “diagnostic odyssey” for some families
  - May show the way to mechanistic therapies

Recommended medical testing

Audiology
- All children with language delay

Genetics
- CMA and Fragile X for all patients … maybe whole exome
- Consider Tier 2 in special cases

EEG
- Consider if concern for seizures, regression, epileptic encephalopathy

MRI
- Only recommended in cases of microcephaly and/or focal neurological exam

Metabolic testing
- Consider in cases with metabolic red flags: severe hypotonia, lethargy, exercise intolerance, regression with illness

TREATMENT

TREATMENT for ASD

- Applied Behavior Analysis (DTT)
- More naturalistic developmental therapies (DIR floortime)
- Hybrids (Early St Denver model, P TEACCH, SCER

al articulation

communication

imulators

rding (actual typing)

•Group based ther teach individuals respond to and in social interactions

ving skills, iting, play skills y Integration y

What is recommended?

"Educating Children with Autism" (2001)

May be found at: www.nap.edu

Recommendations for intensive therapy:

- 20-25 hours per week
- Individualized
- Trained professionals
- Year round (without substantial breaks in service)
- OT/PT/SLP
- Social skills
- Behavioral supports

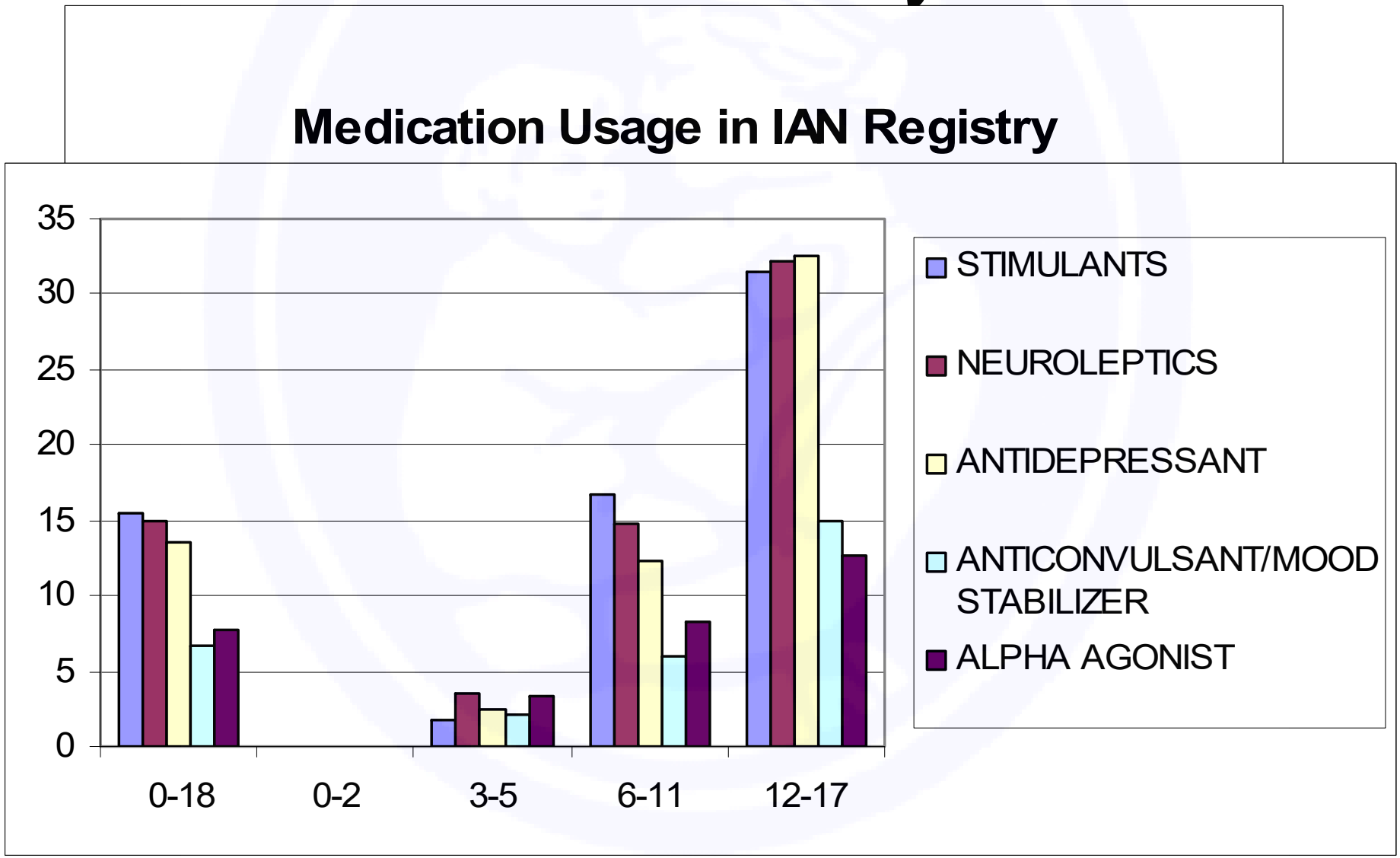
Complementary and Alternative Treatments

Available clinical data?

Traditional Pharmacologic Treatments

- No known pharmacological treatment for core deficits of autism.
  - We don't know the pathophysiology
- But until we figure it out we do symptom modification.
  - Target symptoms that interfere the most
  - Borrow currently used medications from psychiatry

Medication use is very common



Psychopharmacology

- Goal: improve function without side effect
- Rule out other causes (medical, environment)
- Make sure other interventions are in place
  - School program & other therapies
  - Medical care
- Practicalities:
  - Document details of the symptom
  - Start low, increase slowly
  - Monitor closely and reassess over time

Unfortunate Truths

- Only 2 medications currently are FDA approved for children with autism
  - Both atypical neuroleptics – worst side effect profile!
    - risperidone & aripiprazole
    - can be associated with dsykinesias, cause significant weight gain, hyperprolactinemia
    - need to monitor for metabolic syndrome: glucose (HbA1c or fasting insulin), lipids, transaminases, CBC, prolactin
- Most medication use is “off-label”
- The more likely the medication is to be effective, the more likely it is to have substantial side effects

Meds matched to symptoms

- Restricted interests/repetitive behaviors
  - SSRIs: fluoxetine*, citalopram*, sertraline, escitalopram, paroxetine, fluvoxamine
- Aggression/severe behavioral dyscontrol/irritability
  - Atypical neuroleptics: risperidone*, aripiprazole*, ziprasidone, olanzapine, quetiapine
  - Anti-convulsants: valproate*, lamotrigine,* leviteracitam*
- Attention/hyperactivity
  - Stimulants: methylphenidate*, dexmethylphenidate, amphetamine salts, lisdexamphetamine
  - Alpha agonists: clonidine*, guanfacine*
  - Atomoxetine
- Sleep
  - Melatonin*, clonidine, trazodone, mirtazepine, (iron if ferritin <50)

** Those with some randomized placebo controlled data*

Translational medicine and ASD therapeutics

- Novel therapies are showing some promise
  - GABA and glutamate agents (based on E/I imbalance theory)
  - Oxytocin/AVP (based on social affiliation theories)
- Discovery of the underlying pathophysiology in ASD is allowing identification of treatments to target core deficits
- Animal models of single gene disorders are showing the ability to reverse deficits … even in adult animals
- Human trials are underway

GABA and glutamate agents

- Old and new agents tested:
  - Valproate (GABA agonist)
  - Memantine, D-cycloserine, dextromethorphan (glutamate NMDA receptor antagonists)
  - Arbaclofen (known GABA B agonist, ? glutamate receptor modulator)
    - Fragile X trial (Berry-Kravis et al., 2012) found improvements on a social avoidance scale. BUT … it failed to improve study's primary outcome (ABC-irritability)
    - Similar findings in sample of idiopathic ASD (unpublished data from Seaside Therapeutics)

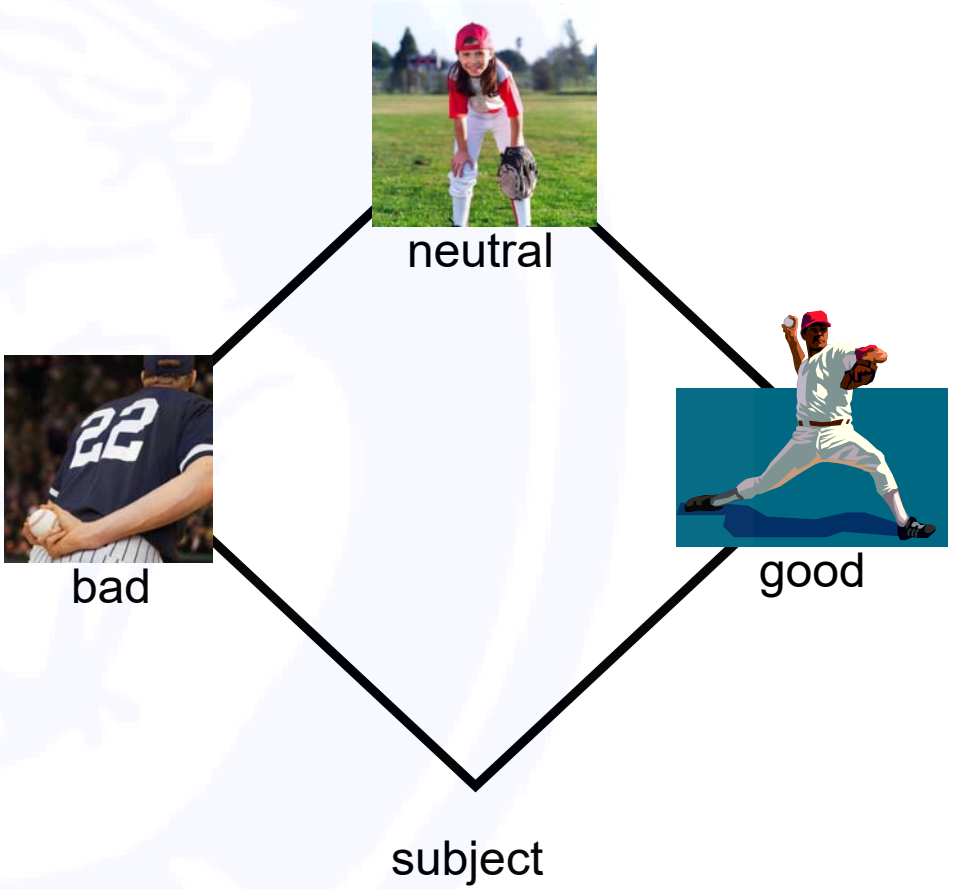
Oxytocin

- Oxytocin is the “pro-social” peptide
  - IV and intranasal preparations
  - Published trials showed improvement in number of behaviors
    - repetitive behaviors, affective speech comprehension, theory of mind, social learning, face processing
    - some effects persisted beyond treatment period

(Hollander et al., 2003; Hollander et al., 2007; Andari et al., 2010 Guastella et al., 2010; Anagnostou et al., 2012; Anagnostou et al., 2014)

Oxytocin

- Small trial of intranasal administration in 13 adults with high functioning autism *(Andari et al., 2010)*
  - Simulated “game of catch” with one neutral player, one good and one bad
  - Then tested preferences for each player & face processing
- Results showed:
  - enhanced ability to process socially relevant cues
  - increasing trust feelings toward the good player
  - Improved time spent looking at socially relevant part of face (eyes)



Arginine Vasopressin (AVP)

- Phase 2 DBRPCT with daily IN preparation
  - improved SRS scores as well as anxiety and some repetitive behaviors
  - improvement associated with baseline AVP levels

  (Parker et al 2019, Science Translational Medicine)
- AVP receptor antagonist trials (oral)
  - VANILLA trial
    - Phase 2 DBRPCT in adult men with ASD
    - Improved Vineland socialization score but not primary endpoint of SRS

    (Bolognani et al. 2019, Science Translational Medicine)
  - AV1ation trial
    - DBRPCT in kids with ASD
    - Ended early for lack of efficacy

NEURODIVERSITY

Concept of Neurodiversity

- Differences vs deficits
  - Temple Grandin talks about her way of thinking in pictures as both a disability and a gift
  - “different not less”
- Focus on the positives, strengths, “autistic intelligence”
- Asperger felt this was not a rare disorder
- The tech sector is full of neurodiverse individuals

Neurodiversity

- Created a rapidly growing civil rights movement
  - More Able Autistic People (MAPP) – don't speak for us
  - Autism Network International (ANI) – came up with the term neurotypical (NT)
  - Autistic Self Advocacy Network (ASAN) – "nothing for us without us"
  - WrongPlanet.net
  - Independent Living on the Autism Spectrum (InLv)
- Important principles
  - They want you to say "Autistic People" – not people with Autism
  - Jim Sinclair "don't mourn for us"
    - *"This is what we hear when your mourn over our existence. This is what we hear when you pray for a cure. This is what we know, when you tell us of your fondest hopes and dreams for us: that your greatest wish is that one day we will cease to be, and strangers you can love will move in behind out faces."*

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Changing the thought process … back!

- THEN - Lovaas: with autism *"you have a person in the physical sense – they have hair, a nose and a mouth - but they are not people in the psychological sense … you have the raw materials, but you have to build the person."*
- NOW - Attwood: *"as I explain to parents, the cure for Asperger's Syndrome is very simple – it is not surgery, medication or intensive therapy. It is taking your son or daughter to the bedroom, leaving the bedroom and closing the door. You cannot have a social deficit when you are alone. You cannot have a communication problem when you are alone. Your repetitive behavior does not annoy anyone when you are alone. That's why teenagers with autism do not want to leave their rooms to go to school: the signs of autism, and the degrees of stress and withdrawal are proportional to the number of people present."*
- THEN AGAIN - Asperger: discussed how some of the defining features could be great gifts:
  - the disregard for authority could be the skepticism that will be crucial for a great scientist
  - they had the potential to be innovators precisely because they were completely unable to take things on faith
  - some of their imaginations anticipated scientific discoveries by decades (eg space travel)

The neurodiversity movement is challenging the long held assumptions

- What is perseveration vs intense curiosity?
- What drives apparent aloofness – is there really a lack of wanting to be with others?
  - A book called NeuroTribes (Steve Silberman) has fascinating exploration of HAM radio operators, Sci-Fi “fandom” and describes individuals feeling like they were “coming home” for the first time.
- Is there really a lack of empathy?
- Do we *need* to or should we *want* to “fix this” or should we be looking to find ways to make the environment acceptable to both neurodiverse and neurotypical individuals

So … where are we?

- What we know:
  - Autism is a neurological disorder
  - Genetic susceptibility
  - Prevalence is increasing
  - Increased co-morbidities (eg epilepsy)
  - Behavioral treatments proved efficacious
- What we don't know:
  - What is the neuropathology/physiology
  - Which genes are involved and how they create the phenotype
  - Why prevalence is increasing
  - What is the significance of the co-morbidities
  - Which treatments are most beneficial for which individuals

For more information…

- Autism information
  - Boston Children's Hospital
    - http://www.childrenshospital.org/autismspectrumcenter
  - NIH
    - http://www.nimh.nih.gov/healthinformation/autismmenu.cfm
  - CDC
    - http://www.cdc.gov/ncbddd/autism/index.html
  - Foundations
    - http://www.autismspeaks.org/
    - http://www.autismsciencefoundation.org/
    - http://www.autism-society.org/site/PageServer
    - http://sfari.org/
- Clinical trials
  - http://clinicaltrials.gov