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Making Sense of Autistic Spectrum Disorders



DSM5 is here: Now What?

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Revised 5/3/2014



Outline

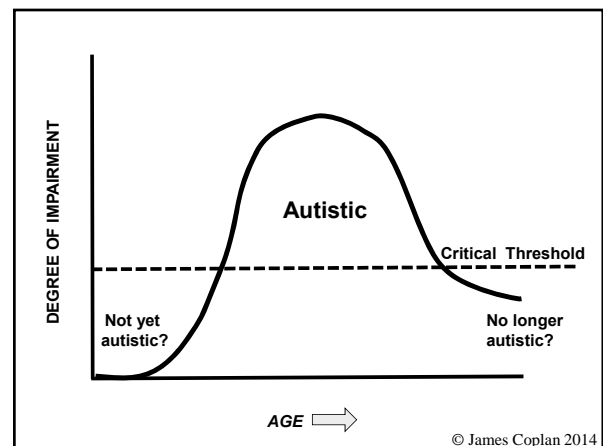
- **Implications of the DSM-V**
 - What do we mean by “ASD”?
 - Clinical definition
 - Kanner
 - Administrative and Research definitions
 - The changing faces of the DSM
 - Potential impact of recent changes to the DSM
 - Service Eligibility
 - Apparent prevalence
 - Research (treatment efficacy and longitudinal outcome studies)

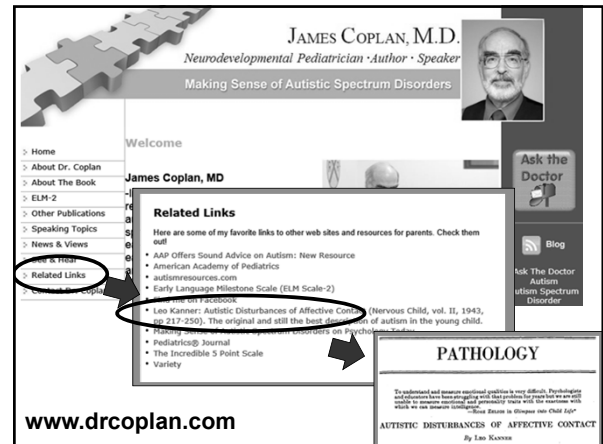
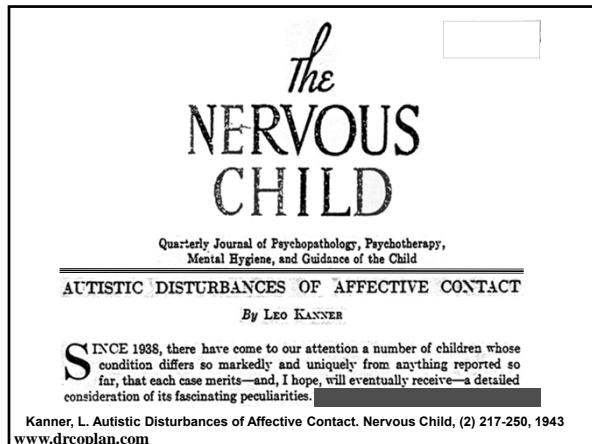
Outline

- **Potpourri of New Developments**
 - Behavior Management and Psychopharmacology
 - New Drugs and Lost Opportunities
 - The Arbaclofen story
 - Other GABA-ergic agents / Glutamate Antagonists
 - Etiology: New clues, new suspects
 - Adult outcomes and services
 - New initiatives

Disclosures

- Dr. Coplan is author of *Making Sense of Autistic Spectrum Disorders: Create the brightest future for your child with the best treatment options* (Bantam-Dell, 2010), and receives royalties on its sale
- This presentation will include a discussion of off-label drug treatments





Kanner, 1943

- N = 11 (M 8; F 3)
- Age: 2 to 8 yr.
- Clinical Features: FOUR Domains
 1. Impaired socialization
 2. Idiosyncratic language
 3. Repetitious behaviors
 4. Unusual responses to sensory stimuli

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943
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Impaired Socialization

- “Aloof”
- “Withdrawn”
- Limited eye contact
- Indifferent to others

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Impaired Socialization “In his own little world”



Age: 22 months. Nonverbal. CARS=44.
www.drcoplan.com MRN 11-0741

Idiosyncratic Language

- Echolalia
 - Delayed Echolalia
 - Pronoun Reversal
 - Odd inflection
- These behaviors are grouped under “Pragmatics” and “Prosody”.

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Pragmatics

(Use of language for social interaction)

- **Normal Pragmatics**
 - Framing
 - Topic Maintenance
 - Conversational repair
- **Impaired Pragmatics**
 - Person talks “at” you rather than “with” you
 - Echolalia
 - Delayed Echolalia (“scripting”)
 - Verbal perseveration

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Repetitious Behaviors

- **Rigid Routines**
 - “Insistence on sameness”
- **Stereotypies**
 - Flapping, spinning, etc.
- **Lining up / spinning objects**

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Unusual sensory responses

- “Petrified of vacuum cleaner”
- Drawn to, or afraid of, spinning objects
- Mouthing behavior
- Ingesting inedible materials
- Food selectivity

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Abnormal responses to sensory stimuli



© Coplan, J. Making Sense of Autistic Spectrum Disorders. Bantam-Dell, 2010

Kanner, 1938 → 1943

- **Gradual improvement in early childhood**
 - ↑Social skills
 - ↑Language
 - ↑Cognitive flexibility
 - ↓Sensory Aversions & Food Selectivity

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Kanner, 1938 → 1943

“Between the ages of 5 and 6 years, they gradually abandon echolalia and learn spontaneously to use personal pronouns.

“Language becomes more communicative, at first in the sense of a question-and-answer exercise, and then in the sense of greater spontaneity of sentence formation....

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

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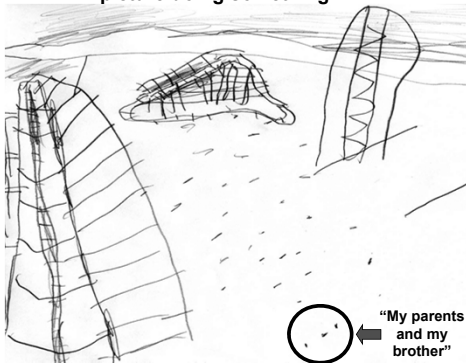
Kanner, 1938 → 1943

“Food is accepted without difficulty. Noises and motions are tolerated more than previously. The panic tantrums subside. The repetitiousness assumes the form of obsessive preoccupations...

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

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“Draw a picture of your family, with everybody in the picture doing something.”



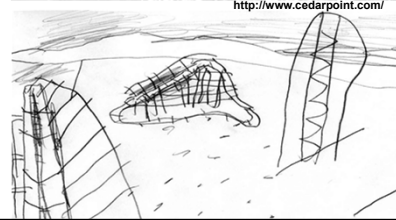
“Cedar Point Park, with the ocean and Canada in the background.”

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<http://www.cedarpoint.com/>



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Kanner, 1938 → 1943

“Reading skill is acquired quickly, but the children read monotonously, and a story or a moving picture is experienced in unrelated portions rather than in its coherent totality...*

* “Central coherence”

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

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Q: What's happening in this picture?

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Q: What's happening in this picture?
A: The kitten is on the boy's back and is about to eat him.

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Q: What's happening in this picture?
A: The boy is hoarding animals.

© Coplan, J. Making Sense of Autistic Spectrum Disorders. Bantam-Dell, 2010

Kanner, 1938 → 1943

“Between the ages of 6 and 8, the children begin to play in a group, still never with the other members of the group, but at least on the periphery alongside the group.

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

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Kanner, 1938 → 1943

“People are included in the child's world to the extent to which they satisfy his needs...

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

www.drcoplan.com

Kanner, 1938 → 1943

All of this makes the family feel that, in spite of recognized ‘difference’ from other children, there is progress and improvement.

Leo Kanner, 1943

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

www.drcoplan.com

Kanner, 1943

[T]here is a great deal of obsessiveness in the family background. The very detailed diaries and reports and the frequent remembrances, after several years, that the children had learned to recite twenty-five questions and answers of the Presbyterian Catechism, to sing thirty-seven nursery songs, or to discriminate between eighteen symphonies, furnish a telling illustration of parental obsessiveness.

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

Kanner, 1943

One other fact stands out prominently. In the whole group, there are very few really warmhearted fathers and mothers. For the most part, the parents, grandparents, and collaterals are persons strongly preoccupied with abstractions of a scientific, literary, or artistic nature, and limited in genuine interest in people.

The question arises whether or to what extent this fact has contributed to the condition of the children....

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

Kanner, 1943

The child's aloneness from the beginning of life makes it difficult to attribute the whole picture exclusively to the type of early parental relations with our patient.

We must, then, assume that these children have come into the world with innate inability to form the usual, biologically provided affective with people, just as other children come into the world with innate physical or intellectual handicaps.

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

Kanner, 1943

If this assumption is correct, a further study of our children may help to furnish concrete criteria regarding the still diffuse notions about constitutional components of emotional reactivity. For here we seem to have pure-culture examples of *inborn autistic disturbances of affective contact*. (italics in the original)

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

Kanner's contributions

- **Clinical Description**
 - Social, Language, Repetitious behavior, & Sensory aversions / attractions
- **Attribution**
 - An “inborn disturbance of affective contact”
- **Described the *Natural History* of improvement over time**

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Leo Kanner's Other Paper:

Kanner, L., Follow-up study of eleven autistic children originally reported in 1943. Journal of Autism & Childhood Schizophrenia, 1971. 1(2): p. 119-45

Kanner, 1971

- Deceased: 1
- Lost to follow-up: 2
- Institutionalized: 5
- Living on work farm: 1
- Living at home: 2
 - BA degree / bank teller
 - Sheltered workshop / machine operator

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Time Passes.....



1943 → → →

DSM III

Yr	Event	Comment
1980	DSM-III: First appearance of: •Infantile autism •Autism-residual state: Children who once met criteria for infantile autism but no longer do.	6 mandatory criteria: I. Onset < 30 mo. II. Pervasive lack of responsiveness to other people III. Gross impairment in communication skills IV. Peculiar speech patterns if speech is present V. Bizarre responses to various aspects of the environment VI. Absence of delusions / hallucinations / incoherence

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DSM III-R

Year	Event	Comment
1987	DSM-III-R: • "Infantile autism" replaced by "Autistic Disorder" • "Autism-Residual State" replaced by PDD-NOS	• PDD-NOS encompasses children who <i>never met full criteria for Autism</i> , as well as children who once met such criteria but improved over time

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DSM IV

Year	Event	Comment
1994	DSM-IV: • Broader menu for diagnosis • Sx in 3 Domains: •Social •Language •Repetitive Behavior • Asperger's Disorder first appears ("No delay in language")	6 of 16 milder criteria, such as: •Lack of spontaneous seeking to share achievements with other people •Difficulty sustaining a conversation •Lack of varied social imitative play •Persistent preoccupation with parts of objects

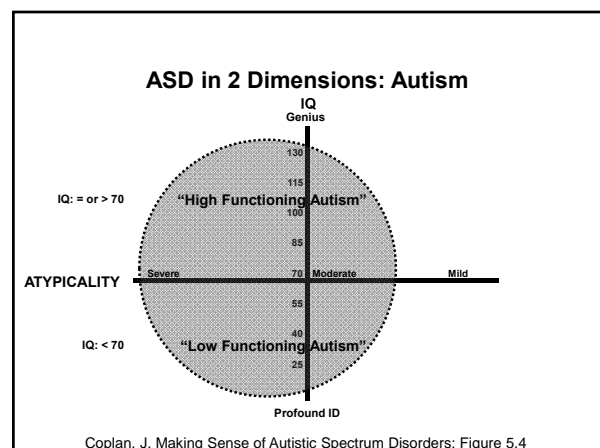
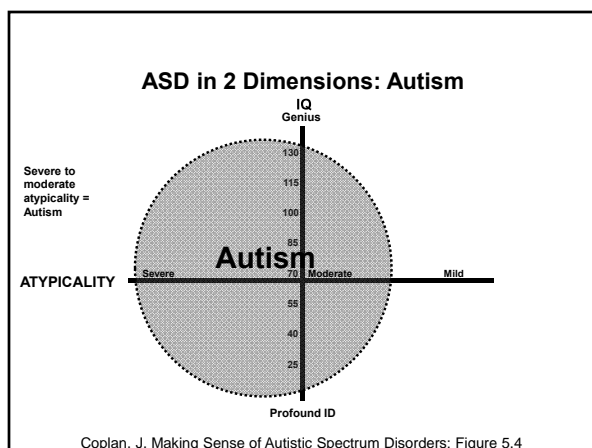
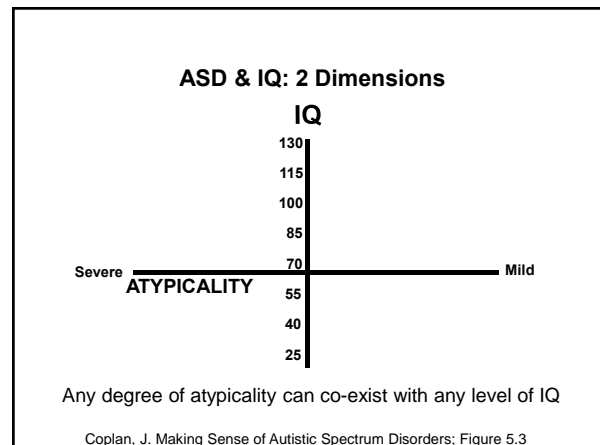
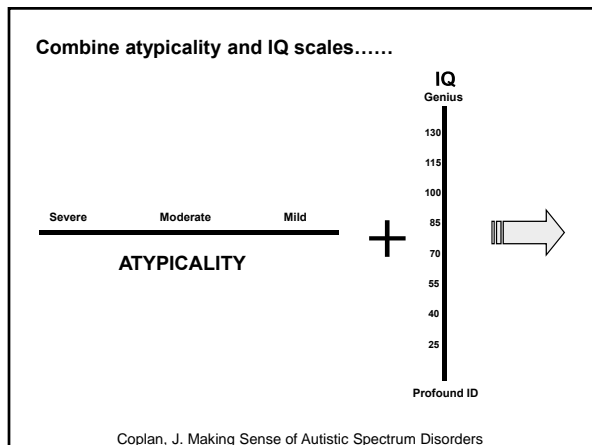
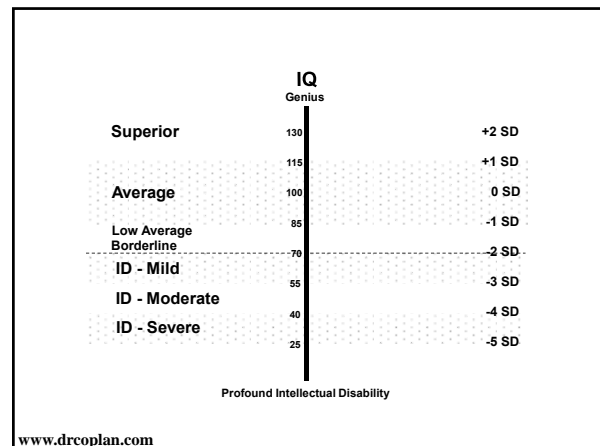
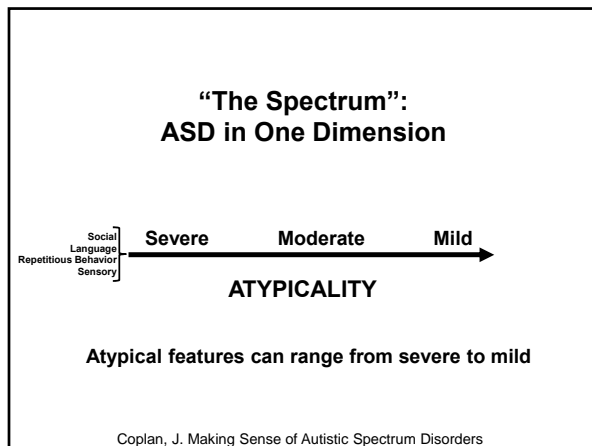
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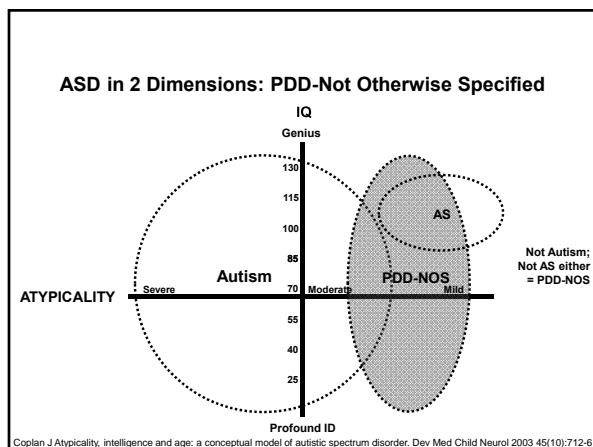
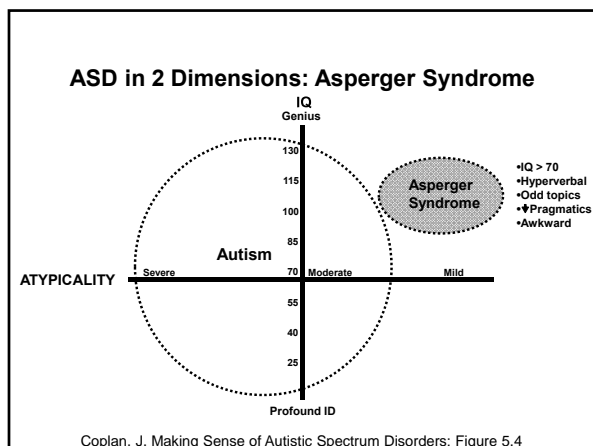


Natural History of ASD (still barely recognized in DSM)

- ASD changes over time
- Relevant variables include:
 - Degree of atypicality
 - Nonverbal IQ
 - Intervention?

Coplan, J., Counseling parents regarding prognosis in autistic spectrum disorder. *Pediatrics*, 2000. 105(5): p. E65

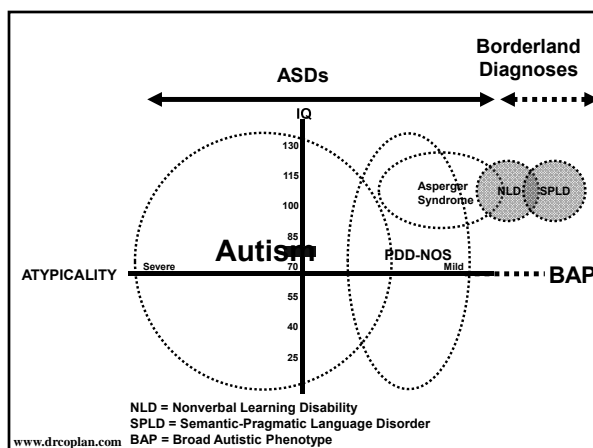




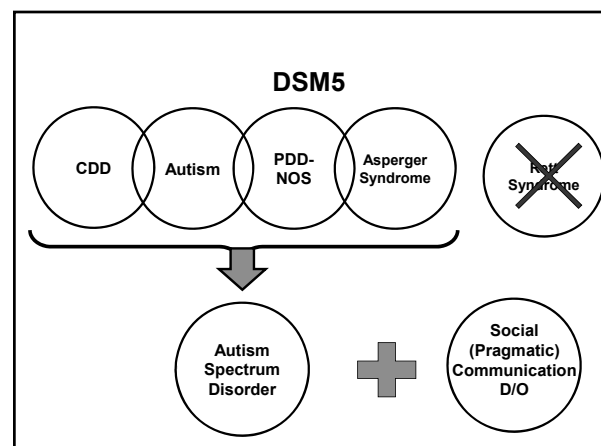
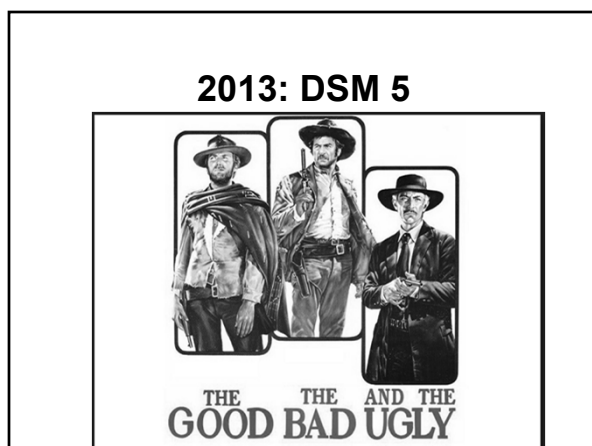
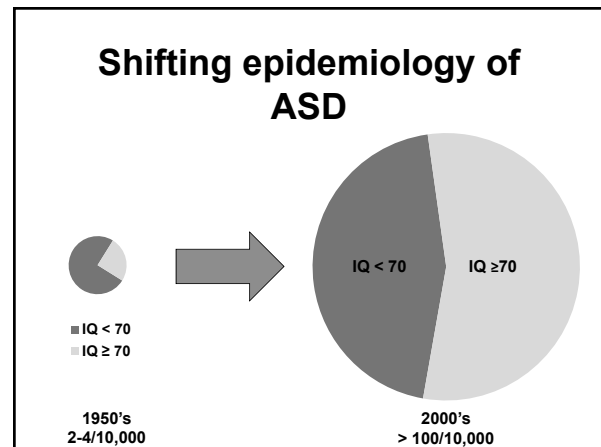
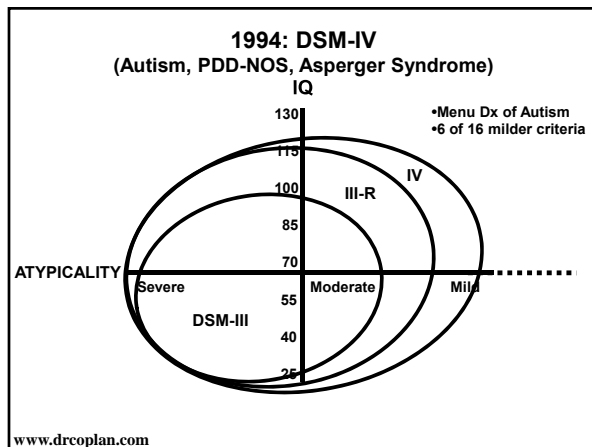
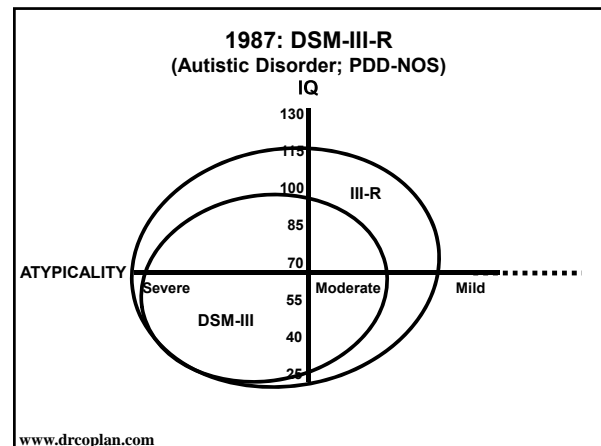
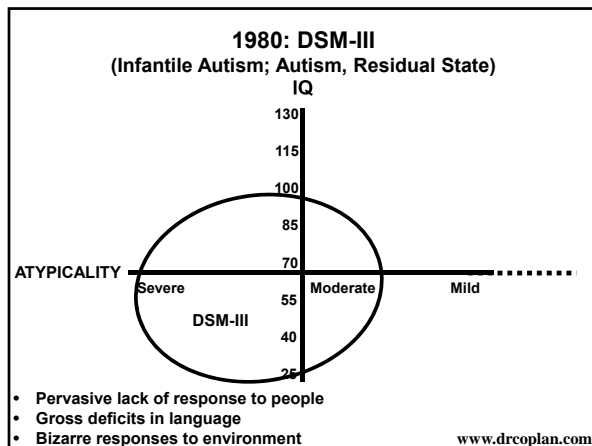
At the “Borderland” of ASD

- **Nonverbal Learning Disability (NLD)**
 - ↓ Language pragmatics
 - ↓ Social skills
 - Disregard for personal space
 - ↓ Coordination / Sensory processing
 - Verbal IQ > Performance IQ
- **Semantic-Pragmatic Language Disorder (SPLD)**
 - ↓ Language pragmatics only
- **(Broad Autistic Phenotype: Traits, not disorder)**

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DSM Criteria and the ASD “Explosion”



Autism Spectrum Disorder

Clinical Domains: 3 → 2

A. Deficits in Social Communication & Interaction

B. Restricted, Repetitive, Behaviors, Interests, and Activities

DSM5 - ASD

A. “Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive):...”

Social Communication & Interaction

- “Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.”

Social Communication & Interaction

- “Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.”

Social Communication & Interaction

- “Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.”

DSM5 - ASD

B. “Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive)...”

Restricted, repetitive patterns of behavior, interests, or activities

- “Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases)”

Restricted, repetitive patterns of behavior, interests, or activities

- “Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day)”

Restricted, repetitive patterns of behavior, interests, or activities

- “Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests)”

Restricted, repetitive patterns of behavior, interests, or activities

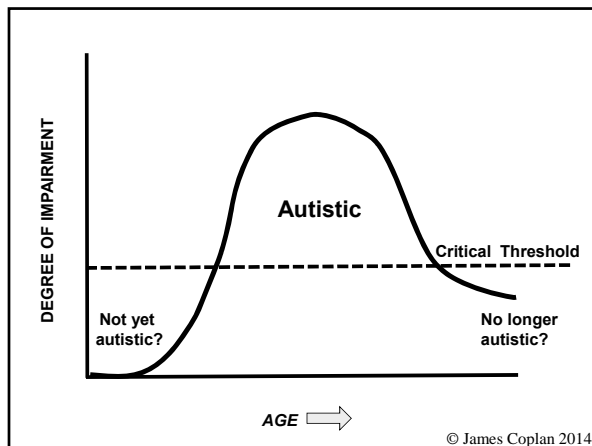
- “Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain / temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement)”

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability or global developmental delay.

- “Criterion D requires that the features must cause clinically significant impairment in social, occupational, or other important areas of current functioning.
- “Because symptoms change with development and may be masked by compensatory mechanisms, the diagnostic criteria may be met based on historical information, although the current presentation must cause significant impairment.

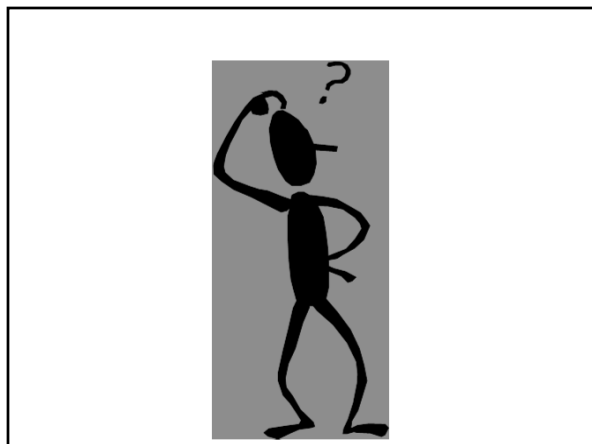


“Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger’s disorder, or PDD-NOS should be given the diagnosis of ASD. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for ASD, should be evaluated for social (pragmatic) communication disorder”

ASD vs. Social (Pragmatic) Communication D/O		
Symptom Domain	Autism Spectrum D/O	Social (Pragmatic) Communication D/O
Social and Language	<ul style="list-style-type: none"> ✓deficits in <i>social-emotional reciprocity</i> ✓<i>nonverbal communication</i>, and ✓<i>maintaining / understanding relationships</i> 	“Deficits in social communication resulting in functional limitations in effective communication, social participation, development of social relationships, academic achievement, or occupational performance”
Restricted, repetitive patterns of behavior, interests, or activities	<ul style="list-style-type: none"> ✓Stereotyped or repetitive motor movements, use of objects, or speech ✓Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal beh. ✓Highly restricted, fixated interests that are abnormal in intensity or focus ✓Hyper- or hyporeactivity to sensory input (at least 2 out of 4) 	Never

ASD vs. Social (Pragmatic) Communication D/O

“Current absence of symptoms would not preclude a diagnosis of autism spectrum disorder, if the restricted interests and repetitive behaviors were present in the past. A diagnosis of social (pragmatic) communication disorder should be considered only if the developmental history fails to reveal any evidence of restricted/repetitive patterns of behavior, interests, or activities”



DSM5

- **The Good**
 - Emphasis on Developmental History, and ability to qualify for a Dx based, in part, on symptoms that may have resolved over time

DSM5

• The Good

- Abnormal sensory processing is now a symptom that counts towards the dx

DSM5

The Bad

• Lack of awareness of Language as a developmental domain

- Combining Language and Social into one domain
 - No mention of pragmatics, apart from impaired socialization
 - Echolalia is listed as a “repetitive behavior”

DSM5

The Bad

• Lack of awareness of Language as a developmental domain

- DSM-IV mischaracterized Asperger syndrome (“No gross delay in language” rather than “relentlessly hypervocal”)
- DSM5 compounds the error by jettisoning Asperger Disorder

Asperger’s Disorder will be Back[1]

Journal of autism and developmental disorders [0162-3257]
Tsai, Luke: 2013 vol:43 iss:12 pg:2914 -2942 Luke Y. Tsai¹

128 publications were identified through an extensive search of major electronic databases and journals. Based on more than 90 clinical variables, 94 publications concluded that there were statistically significant or near significant differences between Asperger’s Disorder (AspD) and Autistic Disorder / HFA groups; 4 publications found both similarities and differences between the two groups; 30 publications concluded with no differences between the two groups. DSM-5 will eliminate Asperger’s Disorder. However, it is plausible to predict that the field of ASD would run full circle during the next decade or two and that AspD will be back in the next edition of DSM.

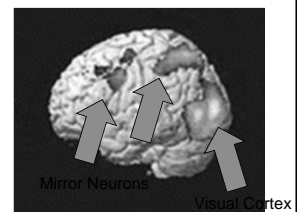
DSM5

The Bad

• Lack of awareness of sensory processing and fine motor clumsiness as a developmental domain

- Mirror neurons: The basis of motor imitation and empathy?
 - Mostofsky, S.H. and J.B. Ewen, *Altered connectivity and action model formation in autism is autism*. Neuroscientist, 2011. 17(4): p. 437-48

Mirror Neurons: The Missing Link?



“The observation of actions done by another individual activates, besides visual areas, also areas that have motor properties.”

Mirror Neurons: From discovery to autism
Rizzolatti & Fabbri-Destro; Exp Brain Res 2010

DSM5

The Bad

- **Lack of 2 sets of criteria**
 - Research: Restrictive, in order to achieve homogeneity within research sample
 - Clinical: Inclusive, in order to assure that nobody who needs services is overlooked

DSM5

- **The Ugly**
 - Introduction of Social Pragmatic Language Disorder, and setting it *apart from* (rather than *within*) the Autism Spectrum

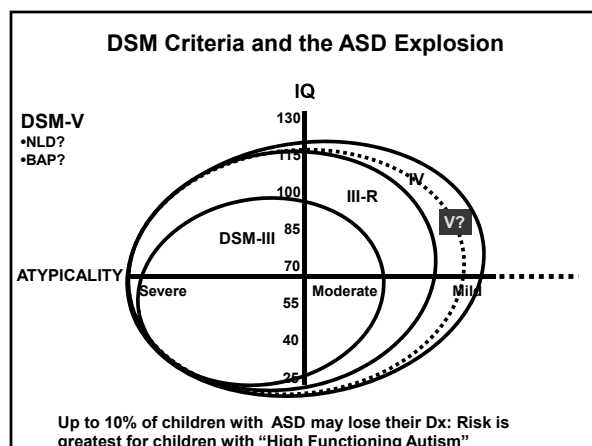
DSM5

- **The Ugly**
 - In order to get a Dx, one must be *impaired*. “Compensated” ASD is not recognized.
 - Therapies “Mask” rather than “treat”
 - Bring back “ASD, residual state”?
 - Mental health issues still present (anxiety, depression, mood, schizophrenia)
 - Genetic risk for recurrence still present

DSM5

The Ugly

- **Up to 10% of children with “high functioning autism” may not meet DSM5 criteria**



How Will DSM-5 Affect Autism Diagnosis? A Systematic Literature Review and Meta-analysis
Kulage, KM et al J Aut Dev Dis 2/2014

- **Method: Meta-analysis of Dx rates: pooled data on 14 studies**
- **Results:**
 - ↓ ASD diagnosis (range 7.3–68.4 %) using DSM-5 criteria
 - “DSM-5 will likely decrease the number of individuals diagnosed with ASD”

**Brief Report: Comparability of DSM-IV and DSM-5
ASD Research Samples**

C. A. Mazefsky, et al
Published online: 26 September 2012

Subjects:

- 498 high-functioning participants with ASD research Dx

Methods:

- Autism Diagnostic Observation Schedule (ADOS)
- Autism Diagnostic Interview-Revised (ADI-R)

Results:

% meeting all DSM-5-requirements, based on:

- ADOS alone: 33%
- ADI-R alone: 83 %
- Both: 93 %

Molecular Autism



<http://www.molecularautism.com/series/dsm5>

<http://www.molecularautism.com/content/4/1/13>

Review

Autism in DSM-5: progress and challenges

Fred R Volkmar* and Brian Reichow

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Molecular Autism 2013, 4:13 doi:10.1186/2040-2392-4-13

The electronic version of this article is the complete one and can be found online at:
<http://www.molecularautism.com/content/4/1/13>

Autism in DSM-5: progress and challenges

Fred R Volkmar* and Brian Reichow

- DSM-IV: Three categories (Language, Social, Repetitive Behavior) and a menu of qualifying criteria within each category gave >2,000 combinations of criteria that would yield an autism diagnosis
- Combining Social and Language into one category, and requiring 3 out of 3 criteria to be met for Repetitive Behavior results in many fewer potential combinations

Autism in DSM-5: progress and challenges

Fred R Volkmar* and Brian Reichow

- “ASD” as defined in DSM5 might more closely resemble the more classic autism described by Kanner than the broader autism spectrum that might be captured with polythetic criteria...
- “Despite the name change to Autism Spectrum Disorder, the concept actually proposed is apparently more restricted than the DSM-IV approach”

Autism in DSM-5: progress and challenges

Fred R Volkmar* and Brian Reichow

- “The impact is probably greatest among the most cognitively able cases and those with less classic autism presentations;” up to 10% may lose Dx of ASD
- Impact will be greatest in settings where reliance is placed exclusively on testing, w/o diligent review of early developmental history

ADOS Abuse

RF:

- 10 y.o. male
- Superior IQ
- Preschool h/o repetitive language & play
- Dx'd with Autism at age 4 (CARS 30.5)
- Recurrent AOM and OSA; T&A at age 6
- Invades personal space; no friends
- Impulsive ⇄ Obsessive & perfectionistic
- Disruptive behavior

MRN 13-0890

ADOS Abuse

“R’s testing with the ADOS2 rules out the presence of Autism Spectrum Disorder; R’s social communication and behaviors are not consistent with the criteria for ASD. Given that his prior diagnosis of ASD was given before medical intervention for ENT issues, it is possible that his presentation at that time was related to medial complications and ADHD versus a true Autism Spectrum Disorder.”

MRN 13-0890

	Change From DSM-IV-TR	Change To DSM-5
Title	Autistic disorder	Autism spectrum disorder
No. of criteria	12	7
Minimum criteria	6	5
No. of domains	3	2
Social Interaction Domain Combined With Communication To Form New Domain: Social Interaction and Social Communication		
Minimum required	2 of 4	All 3
Criterion 1A	Marked impairments in the use of multiple nonverbal behaviors to regulate social interaction	Criterion A.2: deficits in nonverbal communicative behaviors used for social interaction
Criterion 1B	Failure to develop peer relationships appropriate to developmental level	Criterion A.3: deficits in developing and maintaining relationships appropriate to developmental level
Criterion 1C	A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people	(Subsumed into criterion A.1)
Criterion 1D	Lack of social or emotional reciprocity	Criterion A.1: deficits in social emotional reciprocity
Communication Domain Combined With Social Interaction To Form New Domain: Social Interaction and Social Communication		
Minimum required	2 of 4	All 3
Criterion 2A	Delay in, or total lack of, the ability to use spoken language	(Criterion removed)
Criterion 2B	Marked impairment in the ability to initiate or sustain a conversation with others	(Subsumed into criterion A.1)
Criterion 2C	Stereotyped or repetitive use of language or idiosyncratic language	(Subsumed into criterion B.1)
Criterion 2D	Lack of varied, spontaneous make-believe or social imitative play appropriate to developmental level	(Subsumed into criterion A.3)
Restricted Interests and Repetitive Behaviors Domain		
Minimum required	2 of 4	2 of 4
Criterion 3A	Encompassing preoccupation with ≥1 stereotyped and restricted pattern of interest abnormal in intensity or focus	Criterion B.3: highly restricted fixated interests that are abnormal in intensity or focus
Criterion 3B	Apparently inflexible adherence to specific routines or rituals	Criterion B.2: excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change
Criterion 3C	Stereotyped and repetitive motor mannerisms	Criterion B.1: stereotyped or repetitive speech, motor movements, or use of objects
Criterion 3D	A persistent preoccupation with parts of objects	(Criterion removed or possibly subsumed into criterion B.3)
New criterion		Criterion B.4: hyperactivity or hyperactivity to sensory input or unusual interest in sensory aspects of environment
Additional Criteria for DSM-5		
New criterion	Criterion C: symptoms must be present in early childhood (but may not fully manifest until social demands exceed limited capacities)	
New criterion	Criterion D: symptoms together limit and impair everyday functioning	

Hollon. JAMA Pediatr. 2013;167(7):508-513. doi:10.1001/jamapediatrics.2013.2168

COMMUNIQUE

“Implications for School Psychology”
Stephen E. Brock & Shelly R. Hart

“Ultimately, we ask the question as school psychologists: *What does this mean for us?*...The short answer is: Nothing...

The work of school psychologists is, and always has been, *informed* by DSM. DSM has never been a controlling authority....

COMMUNIQUE

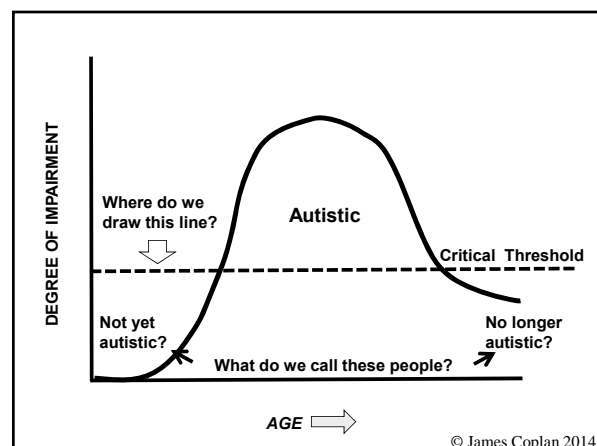
“The simple presence of a DSM diagnosis for a student we serve can and should direct our attention, but it never should direct our action.

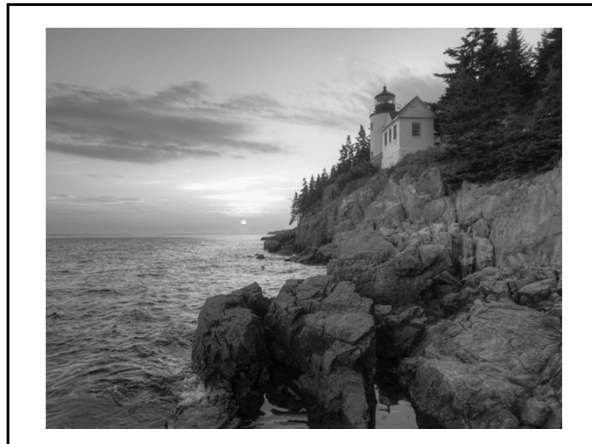
The education codes and regulations that do direct our action (i.e. IDEA) require clear evidence of an adverse effect on educational functioning, and, as a result, some might argue are more restrictive in this setting than DSM*...”

(* Some of us would beg to differ: Anxiety w/o academic failure, e.g.)

The bottom line

- Most persons with moderate-severe ASD (with or w/o ID) will still meet criteria
- Persons with mild ASD and normal IQ are at the greatest risk for exclusion
- Evaluation in borderline cases must include a diligent search for early Sx of repetitive behavior
- If you're not impaired, you can't have ASD (per DSM5)





Outline

- **Potpourri of New Developments**
 - Behavior Management and Psychopharmacology
 - New Drugs and Lost Opportunities
 - The Arbaclofen story
 - Other GABA-ergic agents / Glutamate Antagonists
 - Etiology
 - Adult outcomes and services
 - New initiatives

Results *Probi Cell Differ*, 2012;54:297-335. doi: 10.1007/978-3-642-21649-7_17.

Fragile X syndrome and targeted treatment trials.

Hagerman R¹, Lauterborn J, Au J, Berry-Kravis E.

RUSH UNIVERSITY MEDICAL CENTER IT'S HOW MEDICINE

ABOUT RUSH | CONTACT US | NEED APPOINTMENT | NEWSLETTER SIGN-UP | QUALITY OF CARE

CLINICAL SERVICES **Fragile X Syndrome Research**

Rush Fragile X Clinic and Research Program Description

STX209 is a new drug developed by Seaside Therapeutics... Baclofen and STX209 activate the GABA system which is the main inhibitory neurotransmitter in brain ... STX209 and baclofen reverse many of the problems seen in the fragile X mouse and fly, by increasing GABA activity and presumably reversing the defective inhibition. Thus STX209 may be helpful for humans with fragile X syndrome...

The New York Times **Business Day**

WORLD U.S. N.Y. / REGION BUSINESS TECHNOLOGY SCIENCE HEALTH

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An Experimental Drug's Bitter End

Seaside Therapeutics Announces End of Arbaclofen (STX209) Extension Study

Late yesterday afternoon the NFXF, along with all of the study locations, was contacted by Seaside Therapeutics and informed that the "Study 209FX303 [An Open-Label Extension Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of STX209 (arbaclofen) in Subjects with Fragile X Syndrome] is being terminated. The closure of the study is due to resource limitations at Seaside Therapeutics, Inc., and is not related to any known safety issue in patients taking the drug."

Two patients even sued, but a court ruled the company had no obligation to continue to supply the drug to participants in its trials.

Controversial study touts blood pressure drug for autism

Virginia Hughes

19 February 2013

E-mail Print

Quiet time: Bumetanide decreases the level of chloride ions inside cells, which in turn affects the cell's ability to fire.

<http://sfari.org/news-and-opinion/news/2013/controversial-study-touts-blood-pressure-drug-for-autism>

Etiology

- **Genetics: Pleiotropy, Phenocopies, and the expanded spectrum**
- **DSM6: "Mapping autism from the inside out" (King & Lord)**

The History of Science in 1 Slide

Description & Classification*

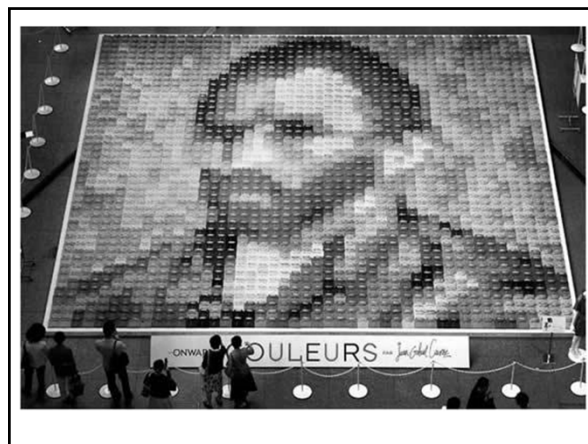
(Group items into *categories*, based on externally visible characteristics)



Analysis

(Explain & predict, based on an understanding of why and how things happen. *Newton, Einstein*)

* *Plato (428-328 BCE): "Carve Nature at its joints." We can't explain why or how things happen, but if we observe carefully, and group similar items into categories, eventually the big picture will emerge.*



Psychiatry

Description & Classification

(based on externally visible characteristics)



Analysis

(based on an understanding of fundamental mechanisms)

1700's to DSM 5

(categories based on symptoms → quest for symptom homogeneity within categories)



DSM 6

(classification based on causation and brain systems; *Mapping ASD from the inside out – King & Lord 2011*)

Psychiatry

Description & Classification

(based on externally visible characteristics)



Analysis

(based on an understanding of fundamental mechanisms)

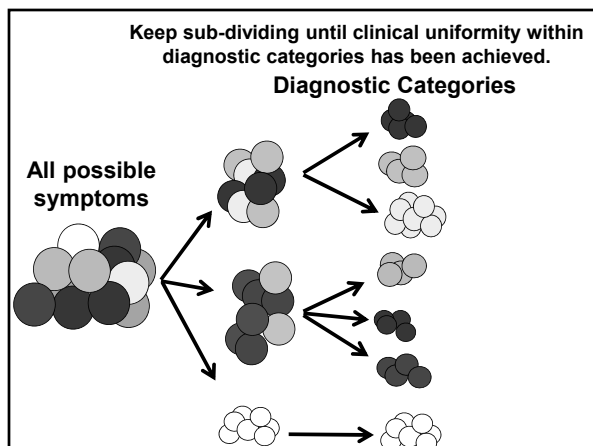
1700's to DSM 5

(categories based on symptoms → quest for symptom homogeneity within categories)

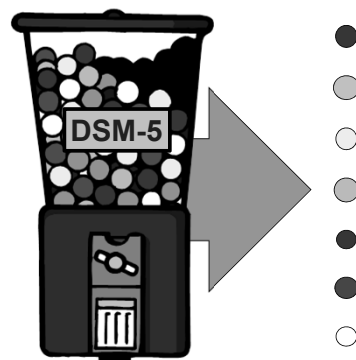


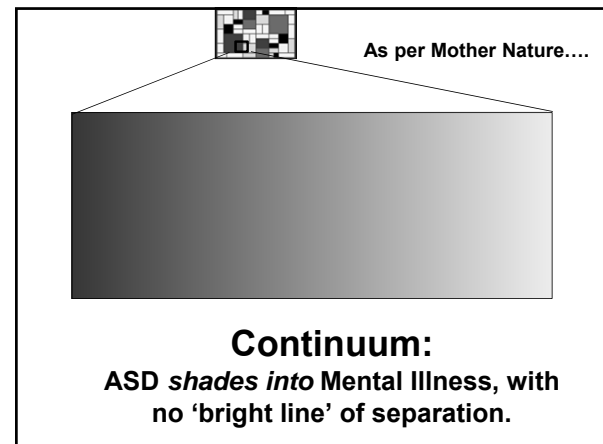
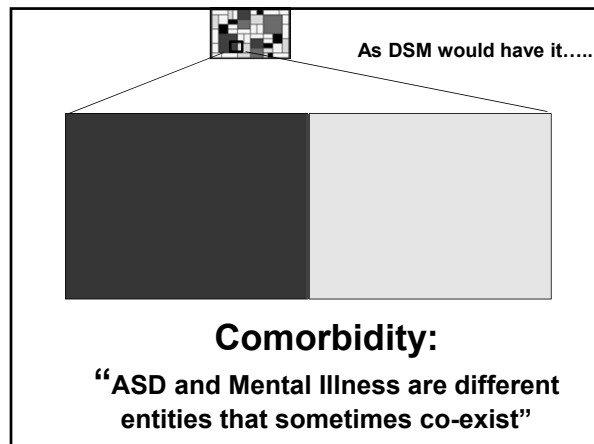
DSM 6

(classification based on causation and brain systems; *Mapping ASD from the inside out – King & Lord 2011*)



Make Diagnoses





Two more terms

- **Phenocopy:** Similar-appearing conditions that arise from different genetic mechanisms
 - Ex: Many different genetic defects cause “ASD”
- **Pleiotropy:** Different clinical conditions due to the same genetic mechanism
 - Ex: Trisomy 21: Can produce ID with or w/o ASD

Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence

Andreas Meyer-Lindenberg, Scott M Myers, Thomas D Challman, Daniel Moreno-De-Luca, David W Evans, David H Ledbetter

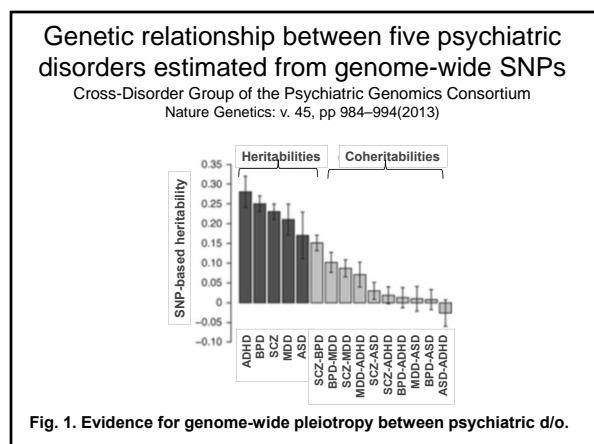
Pleiotropy (Same gene, different disorders)

Phenocopy (Different genes, same disorder)

	Frequency in clinical cohorts*	Intellectual disability or developmental delay	Autism spectrum disorder	Schizophrenia	Epilepsy
22q11.2	1 in 167	✓	✓	✓	✓
16p11.2	1 in 241	✓	✓	–	✓
1q21.1	1 in 309	✓	✓	✓	✓
15q13.2-q13.3	1 in 358	✓	✓	✓	✓
7q11.23	1 in 415	✓	✓	–	✓
15q11.2-q13	1 in 553	✓	✓	✓	✓
17q21.31	1 in 700	✓	✓	–	✓
16p13.11	1 in 788	✓	✓	✓	✓
17q12	1 in 985	✓	✓	✓	✓
17p11.2	1 in 985	✓	✓	–	✓
8p23.1	1 in 1854	✓	✓	–	✓
5q35	1 in 1970	✓	✓	–	✓
3q29	1 in 2101	✓	✓	✓	–

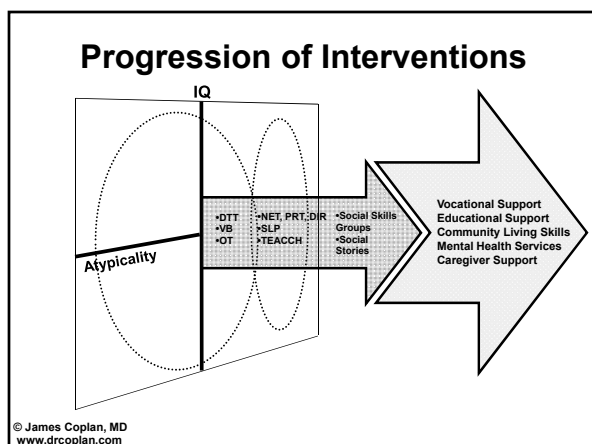
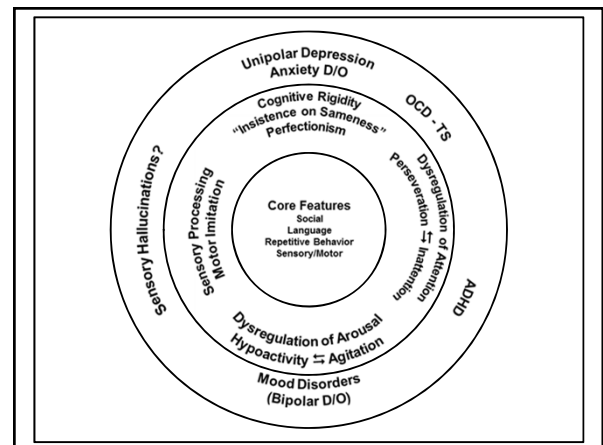
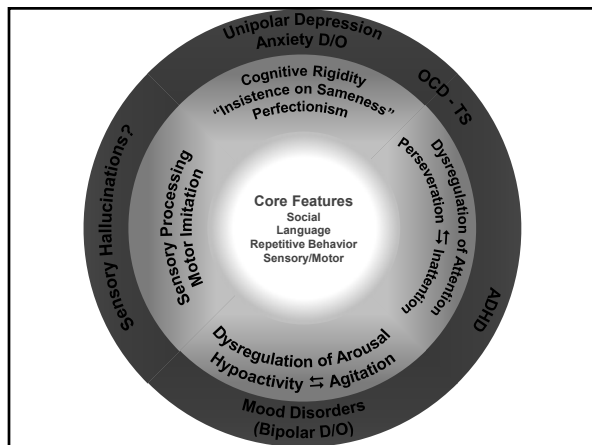
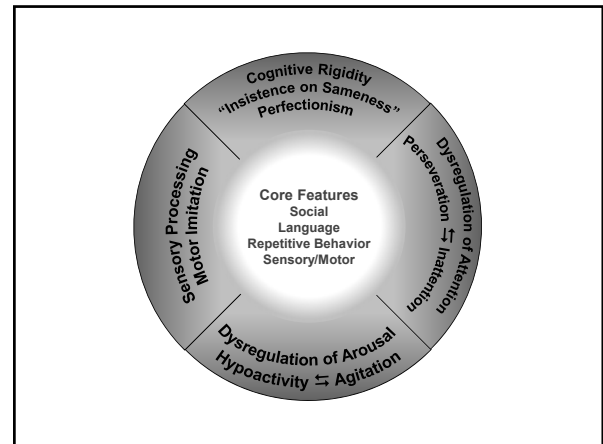
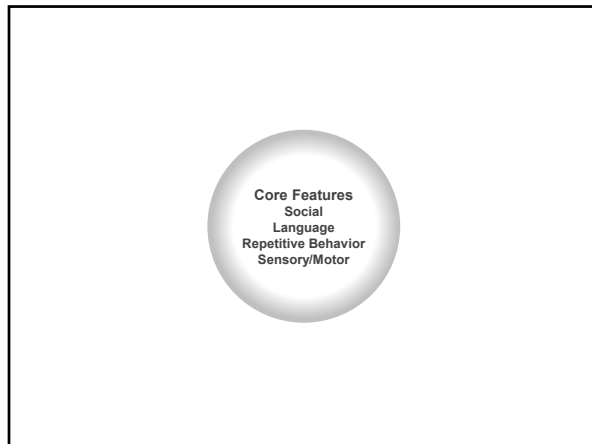
*Frequency in individuals referred for chromosomal microarray testing. Common indications for testing include neurodevelopmental disorders and multiple congenital anomalies.¹⁰

Table 1: Variable expressivity in selected microdeletion syndromes. *Lancet Neurology* 2013; 12: 406-414



deLacy & King 2013

There appears to be no question that a phenotypic continuum links the SCZ and autism spectra; moreover, it incorporates neuropsychiatric deficits associated with all of the classic neurodevelopmental disorders [ID...DD... ASD...ADHD, and SCZ]. Affected persons display some subset of symptoms from this neurodevelopmental superset, in individually varying phenotypes likely molded by pleiotropy, different types of genetic defects, and epigenetic mechanisms.



A New Care Model

- **Need for Adult Services**
 - Clinics for “Long-Term Survivors of Childhood ASD” patterned after Long-Term Survivors of Childhood Cancer
 - Mental Health
 - Job coaching
 - Social contact
 - Family / Caregiver support (parents, partners)
 - Developmental screening of offspring

www.drcoplan.com

Systems Change

- **ASD community needs to make common cause with MH community in advocating for child and adult MH services**
 - Old division between DD and MH not scientifically tenable
 - Not financially viable
 - Not in the best interests of children and families

Obstacles

- **Lack of data**
 - Adult prevalence data
 - Privacy issues
 - Longitudinal outcome data
- **Cross-Disciplinary collaboration / “Turf”**
 - Child / Adult / Family
 - DD / Mental Health / Education / Law Enforcement
- **Long-term funding**
- **Stigma**

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Summary

- **DSM5:**
 - Oversimplifies and restricts Dx
 - Is still symptom-based
 - Takes a small step toward acknowledging change over time (prior H/O repetitive behavior counts towards a dx), but negates the concept of “well-compensated” ASD
 - Will probably result in excluding some persons with mild ASD from medical funding
 - May have less impact in schools?

Summary

- **The most common known causes of ASD are genetic, and the list keeps growing**
- **Pleiotropy: ASD and Mental Illness are interwoven; no “bright line” of separation**

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Summary

- **Mental Illness is not “a separate problem.”** Rather, impaired MH is another expression of shared neurobiology
 - Not “co-morbidity,” but continuum and metamorphosis
- **Over time, mental health issues present a progressively greater challenge, that may supersede the ASD**

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Summary


- **Need for Adult Services**

- Clinics for “Long-Term Survivors of Childhood ASD” patterned after Long-Term Survivors of Childhood Cancer
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Thank you