Autism: What have we learned in the past 125 years?
James Coplan, MD
June 25, 2015

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 may include a discussion of off-label drug use**

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Time-ordered agenda

- **8:30-10:00 Patting the elephant – The history of a syndrome**
- **10:00-10:15 BREAK**
- **10:15-12:00 Under the hood: The neurobiology of ASD**
- **12:00-1:15 LUNCH**
- **1:15-3:00 It takes a village: Primary, secondary, and tertiary intervention; next steps**

Outline

- **Patting the elephant (The history of a syndrome)**
  - **Down, Kanner, Asperger**
  - **DSM: "Are we there yet?"**
  - **3D model**
    - **The Natural History of ASD**
    - **Where did all these kids come from?**
- **Under the hood**
- **It takes a village**

Outline

- **Patting the elephant**
- **Under the hood**
  - **Neurobiology and Neuropsychology of ASD**
    - **Cognitive Rigidity**
    - **Dysregulation of attention**
    - **Dysregulation of arousal and mood**
    - **Dysregulation of sensory processing**
      - **Mirror Neurons: Motor imitation, empathy, and reality testing**
    - **Theory of Mind & Introspection**
    - **Central Coherence**
  - **Genetics (and other causes)**
  - **The expanded autism syndrome**
    - **Not "comorbidity," but continuum and metamorphosis**
      - **"Is schizophrenia on the autism spectrum?"***
  - **All in the family**
    - **Broad Autism Phenotype and Non-ASD MH disorders**
- **It takes a village**

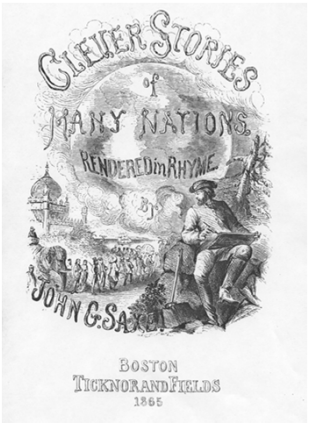
* King & Lord

Outline

- **Patting the elephant**
- **Under the hood**
- **It takes a village**
  - **Treatment:**
    - **Primary prevention** – *Brave new world*?
      - **CNVs – carrier screening for ASD and MH risk**
      - **Pre / Perinatal intervention: Oxytocin and the GABA switch**
    - **Secondary intervention (symptom-oriented)**
      - **Child-Centered**
        - **At home: self-awareness, self-esteem**
        - **Mental Health services & Psychopharmacology**
      - **Parent and Family Centered: Nature *and* Nurture**
        - **Intro to Family Systems Theory**
    - **Tertiary intervention (system-oriented)**
      - **At school: Reclaiming IDEA: Positive Behavior Support for Internalizing Behavior**
      - **Routine MH screening of children w. ASD, and routine screening of *family health***
      - **Adult services for "survivors" of childhood autism**
      - **ASD and MH communities need to unite**
      - **Reunify behaviorism, classical psychology, neuropsychology, & psychiatry**

Outline

- **Patting the elephant (The history of a syndrome)**
  - **Down, Kanner, Asperger**
  - **DSM: "Are we there yet?"**
  - **3D model**
    - **The Natural History of ASD**
    - **Where did all these kids come from?**



THE BLIND MEN AND THE ELEPHANT.

A HINDOO FABLE.

It was six men of Indostan,
To learning much inclined
Who went to see the Elephant,
(Though all of them were blind,)
That each by observation
Might satisfy his mind.

The **First** *approached the Elephant,*
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! – but the Elephant
Is very like a wall!"

The **Second**, *feeling of the tusk,*
Cried "Ho! What have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"

The **Third** *approached the animal,*
And, happening to take
The squirming trunk within his hands,
Thus boldly up and spake: -
"I see," quoth he, "the Elephant
Is very like a snake!"

The **Fourth** *reached out his eager hand,*
And felt about the knee;
"What most this wondrous beast is like
Is mighty plain," quoth he;
" 'Tis clear enough the Elephant
Is very like a tree!"

The **Fifth**, *who chanced to touch the ear,*
Said, "E'en the blindest man
Can tell what this resembles most:
Deny the fact who can,
This marvel of an Elephant
Is very like a fan!"

The **Sixth** *no sooner had begun*
About the beast to grope,
Than, seizing on the swinging tail
That fell within his scope,
"I see," quoth he, "the Elephant
Is very like a rope!"

And so these men of Indostan,
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!

http://upload.wikimedia.org/wikipedia/commons/e/e1/Blind.JPG

Is autism…

- ***A behavioral disorder***
- ***A cognitive disorder***
- ***A sensory processing disorder***
- ***An emotional disorder***
- ***etc.***

- **Answer: All of the above, and more**

VICTORIA REGINA ET IMPERATRIX

b. 1819 – d. 1901
r. 1837-1901

The Royal Earlswood Asylum for Idiots (est. 1854)

http://en.wikipedia.org/wiki/Royal_Earlswood_Hospital
http://langdondownmuseum.org.uk/dr-john-langdon-down-and-normansfield/the-earlswood-asylum-for-idiots/

ETHNIC CLASSIFICATION OF IDIOTS.

'London Hospital Reports', 1866.

"Mongolian Idiocy" ➔ Down Syndrome ➔ Trisomy 21

ON SOME OF THE

MENTAL AFFECTIONS

OF

CHILDHOOD AND YOUTH

BEING

THE LETTSOMIAN LECTURES

DELIVERED BEFORE THE MEDICAL SOCIETY OF LONDON IN 1887

TOGETHER WITH OTHER PAPERS

BY

J. LANGDON DOWN, M.D.LOND.

FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON; SENIOR PHYSICIAN TO, AND LECTURER ON CLINICAL MEDICINE AT, THE LONDON HOSPITAL; FORMERLY LECTURER ON MEDICINE, MATERIA MEDICA, AND COMPARATIVE ANATOMY AT THE LONDON HOSPITAL; AND PHYSICIAN TO THE EARLSWOOD ASYLUM

Langdon Down, 1887

I have alluded already to a group which I have ventured to describe as "accidental"…. They are children who are born, or ready to be born, with all the potentiality of intelligence, but whose brain becomes damaged…. In these cases there is no outward sign of mental vacuity… no hereditary taint to mar the beauty of his visage…

14-16

Langdon Down, 1887

They are bright in their expression, often active in their movements, agile to a degree, mobile in their temperament, fearless as to danger, persevering in mischief, petulant to have their own way. Their language is one of gesture only; living in a world of their own they are regardless of the ordinary circumstances around them, and yield only to the counter-fascination with music…

14-16

Langdon Down, 1887

These are the cases in which mothers entertain the strongest hope… I cannot enforce too strongly grave caution in the prognosis which should be given in such cases…

I know nothing more painful than the long motherly expectancy of speech; how, month after month, the hopes are kept at high tension, waiting for the prattle which never comes. How the self-contained and self-absorbed little one cares not to be entertained other than in his own dreamland, and by automatic movements of his fingers or rhythmical movements of his body….

15-16

Langdon Down, 1887

Even when speech does exist it is often echo-like… To my question "How are you today?" came the immediate reply "Today." I ask another "Are you a good girl?" the response is simply "Girl."….

Sometimes the whole question is repeated, and the echo is not simply that of the last word.

72

Langdon Down, 1887

… [T]hey live entirely in a world of their own; they do not listen with a childlike curiosity to the conversation which is going on in their presence…. They hear what is said, but they do not attend, nor can their attention be arrested, except by diverting them into new channels by a more attractive trail. They usually have great intensity of purpose, and succeed in having their own way, the mothers giving up the contest for the sake of peace…

Automatic movements are also very common… these may include rhythmical movements of the fingers before the eyes

Pp 70-71

Langdon Down, 1887

This is a convenient place to treat of an interesting class of cases for which the term "idiots savants' has been given… This name has been applied to children who, while feeble-minded, exhibit special faculties which are capable of being cultivated to a very great extend. One youth who was under my care who could build exquisite model ships from drawings, and carve with a great deal of skill, who yet could not understand a sentence… Another … who can draw in crayons with marvelous skill and feeling, in whom nevertheless there was a comparative blank in all higher faculties of mind.

58-59

Langdon Down, 1887

Extraordinary memory is often met with associated very great defect of reasoning power. A boy came under my observation who, having once read a book, could ever more remember it…. I discovered, however, that it was simple a process of verbal adhesion. I once gave him Gibbon's "Rise and Fall of the Roman Empire" to read. This he did, and on reading the third page he skipped a line, found out his mistake and retraced his steps; ever after, when reciting from memory the stately periods of Gibbon, he would, on coming to the third page, skip the line and go back and correct the error with as much regularity as if it had been part of the regular text….

58-60

Langdon Down, 1887

Often the memory takes the form of remembering dates and past events… One boy never fails to be able to tell the name and address of every confectioner's shop he has visited in London – and they have been numerous – and can as readily tell the date of every visit.

58-60

Why have we forgotten Langdon Down?

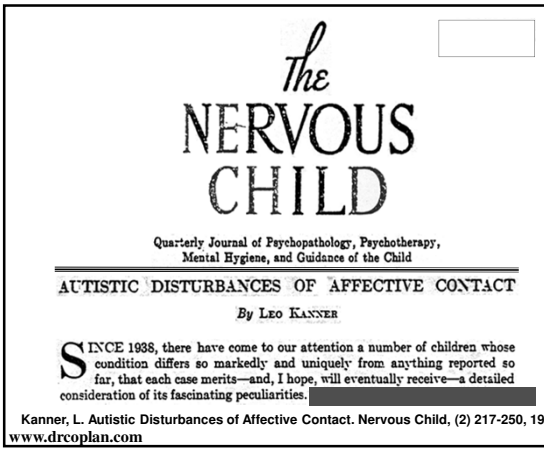
- **Association with Eugenics?**
  - **"Mongolism" / Social Darwinism**
- **WWI – Social disruption / loss of continuity**
- **He didn't give it a name**
- **Ahead of his time?**

Time Passes……

1887 ➔➔➔ 1943

Leo Kanner
1894-1981

Johns Hopkins Hospital



The NERVOUS CHILD

Quarterly Journal of Psychopathology, Psychotherapy, Mental Hygiene, and Guidance of the Child

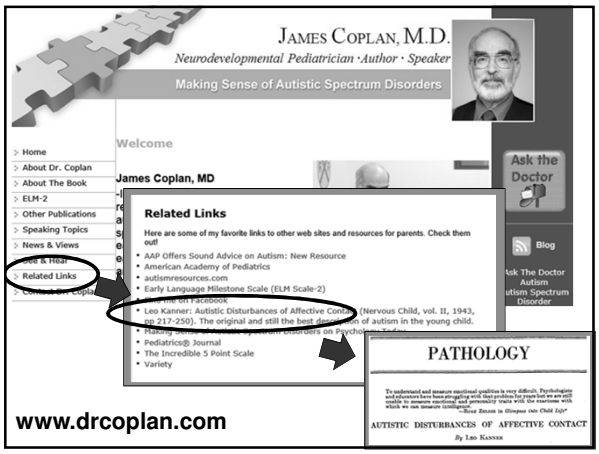
AUTISTIC DISTURBANCES OF AFFECTIVE CONTACT

By Leo Kanner

SINCE 1938, there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits—and, I hope, will eventually receive—a detailed consideration of its fascinating peculiarities.

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

www.drcoplan.com



Kanner, 1943

- **N = 11 (M 8; F 3)**
- **Age: 2 to 8 yr.**
- **Symptoms in 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**

www.drcoplan.com

Idiosyncratic Language

- **Echolalia**
- **Delayed Echolalia**
- **Pronoun Reversal**
- **Odd inflection**

www.drcoplan.com

Repetitious Behaviors

- **Rigid Routines**
- **Stereotypies**
- **Lining up / spinning objects**

www.drcoplan.com

Unusual sensory responses

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

www.drcoplan.com

Kanner, 1938 → 1943

- Gradual improvement in early childhood
  - ↑Social skills
  - ↑Language
  - ↓Cognitive rigidity
  - ↓Sensory Aversions

www.drcoplan.com

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

www.drcoplan.com

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

www.drcoplan.com

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": the ability to see the big picture

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

www.drcoplan.com

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

www.drcoplan.com

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

It is not easy to evaluate the fact that all of our patients have come of highly intelligent parents.

This much is certain, that there 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, 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. Even some of the happiest marriages are rather cold and formal affairs. Three of the marriages were dismal failures.

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

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.

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]

Follow-up Study of Eleven Autistic Children
Originally Reported in 1943

LEO KANNER[1]
John Hopkins University School of Medicine
Copyright © 1971 by Scripta Publishing Corporation.

- 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

Kanner's contributions

- Clinical Description
  - Social
  - Language
  - Repetitious behavior
  - Sensory aversions / attractions
- Described the *Natural History* of improvement over time (irrespective of treatment)
- Attribution
  - An "inborn disturbance of affective contact"

www.drcoplan.com

"Autism's first child"
***The Atlantic*, 2010**

http://www.theatlantic.com/magazine/archive/2010/10/autism-8217-s-first-child/8227/

Archiv für Psychiatrie und Nervenkrankheiten
3. Juni 1944, Volume 117, Issue 1, pp 76-136

Die „Autistischen Psychopathen" im Kindesalter

Doz. Dr. Hans Asperger

- lack of empathy
- little ability to form friendships
- one-sided conversations
- special interests
- "little professors"
- clumsy movements

http://autismus-kultur.de/wp-content/uploads/2006/06/asperger-syndrom.jpg
http://en.wikipedia.org/wiki/Hans_Asperger
http://www.icn.ucl.ac.uk/dev_group/ufrith/documents/Ch%201,%20Asperger%20and%20his%20syndrome%20copy.pdf

Lorna Wing

7 October 1928 – 6 June 2014

"Asperger Syndrome" - 1981

Image © Tina Norris, www.tinanorris.co.uk

Lorna Wing: "Asperger syndrome: a clinical account" (1981)

http://www.mugsy.org/wing2.htm

- **Articulate yet strangely ineloquent**
- **Active but odd**
- **Specialists in unusual fields**
- **Speech is pedantic and often consisting of lengthy disquisitions on favourite subjects**

Uta Frith: "Asperger and his syndrome"

http://www.icn.ucl.ac.uk/dev_group/ufrith/documents/Ch%201,%20Asperger%20and%20his%20syndrome%20copy.pdf

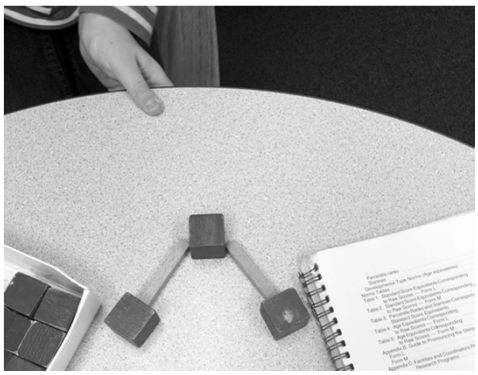
"….clever-sounding language, invented words and spoke more like grown-ups than children… There was something not quite right in the way they used language…

….socially inept but often socially interested…."

http://www.icn.ucl.ac.uk/dev_group/ufrith/documents/Ch%201,%20Asperger%20and%20his%20syndrome%20copy.pdf

Kanner & Asperger

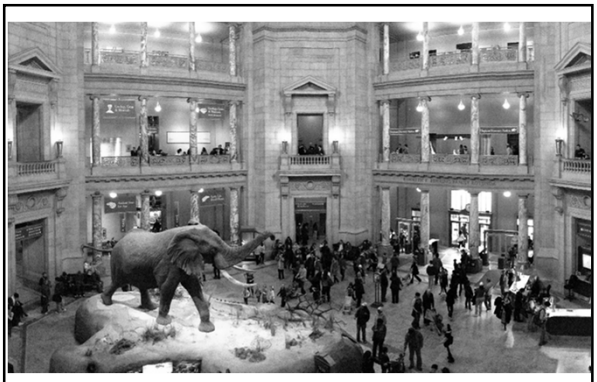
- **Similarities**
  - **Impaired socialization**
  - **Impaired pragmatics**
  - **Impaired prosody & nonverbal cues**
  - **Repetitive behavior and mentation**
  - **Clumsiness, sensory issues**
  - **Often a positive Fam Hx for odd or obsessive behavior**
- **Differences**
  - **Hypoverbal (Kanner) vs. Hyperverbal & pedantic (AS)**
  - **"Aloof & withdrawn" (Kanner) vs. "Active but odd" (AS)**



"I made water"

MRN 13-0829

Natural History



National Museum of Natural History

Natural History: "The temporal course a disease from onset to resolution"

Center for Disease Control & Prevention

ASD has a *Natural History*

www.drcoplan.com

1 - Social Interaction

"Our child is *among* us, but not *with* us."

Parent of a 4 year old with ASD

www.drcoplan.com

Clinical Domain ⇓	Decreasing Atypicality / Increasing Age ⇒		
	Severe / Youngest	Moderate / Older	Mild / Older
1. Social Interaction	•No eye contact •No physical affection •Cannot be engaged in imitative tasks	•Intermittent eye contact •Seeks affection "on his own terms" •May invade personal space of others (not true affection) •Engageable in imitative tasks, although with difficulty	•Good eye contact •Shows interest in others, but often does not know how to join in •Easily engaged in imitative activities •Rigid; has difficulty if perceives that rules have been broken •Difficulty with "Theory of Mind" tasks

www.drcoplan.com

Clinical Domain ⇓	Decreasing Atypicality / Increasing Age ⇒		
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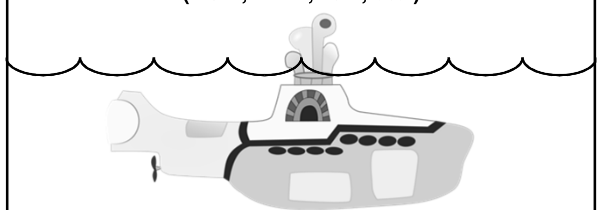
www.drcoplan.com

**Visible features
(DSM, IDEA, ICD, etc.)**



Underlying Neuropsychological Traits
- ↓ Theory of Mind

Theory of Mind (ToM)

- Realization that other people have an internal mental & emotional state, different from one's own
- Ability to gauge the internal mental & emotional state of others
  - Able to infer motives & predict behavior of others
  - Empathy
  - Humor

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Theory of Mind (ToM)

*How does the boy feel?
Why?*

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Theory of Mind (ToM)

Q: How does the boy feel?
A: "I don't know, because I can't see his mouth."

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Theory of Mind (ToM)

Muff

Muff is a little yellow kitten.
She drinks milk.
She sleeps on a chair.
She does not like to get wet.

Q: How would Muff feel, if you gave her a bath?

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Theory of Mind (ToM)

Muff

Muff is a little yellow kitten.
She drinks milk.
She sleeps on a chair.
She does not like to get wet.

Q: How would Muff feel, if you gave her a bath?
A: Clean!

www.drcoplan.com

Theory of Mind (ToM)

Muff

Muff is a little yellow kitten.
She drinks milk.
She sleeps on a chair.
She does not like to get wet.

Q: How would Muff feel, if you gave her a bath?
A: I don't know. We haven't come to that part of the story yet.

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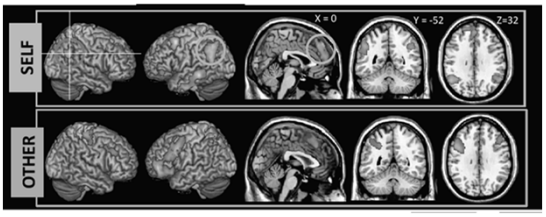
Introspection

Awareness of *one's own* thoughts & feelings

ToM and Introspection



Theory of Mind for you, and for me: behavioral and **neural similarities** and **differences in thinking about beliefs of the self and other**
Gweon H, Young L and , Saxe R, Dept of Brain and Cognitive Sciences, MIT

http://www.mit.edu/~hyora/Hyo/CV_files/xplane_revision_final.pdf

THE LANCET Psychiatry

Suicidal ideation and suicide plans or attempts in adults with Asperger's syndrome attending a specialist diagnostic clinic: a clinical cohort study 25 June 2014

Dr Sarah Cassidy PhD a, Paul Bradley MRCPsych b, Janine Robinson DClinPsy b, Carrie Allison PhD a, Meghan McHugh BSc b, Prof Simon Baron-Cohen PhD a b

Subjects

- 374 adults newly diagnosed with Asperger Syndrome
  - Men: 256
  - Women: 118
- Mean age at Dx: 31.5 yr (range 17-67 yr)
- 87 (23%) in full-time education at the time of study

Methods:

- Self-Report Questionnaire, lifetime experience of:
  - Suicidal thoughts
  - Suicidal plans or attempts
  - Depression

http://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(14)70248-2/fulltext

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Results:

- Suicidal ideation: 66%
- Plans or attempts at suicide: 35%
- Depression: 31%

➢ Delayed Dx: Lack of treatment → Poor outcome?
➢ ↓ Introspection?

http://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(14)70248-2/fulltext

2 - Language

"My child talks, but he doesn't communicate."

Mother of a 3 year old with autism

www.drcoplan.com

Clinical Domain ⇓	Decreasing Atypicality / Increasing Age ⇒		
	Severe / Youngest	Moderate / Older	Mild / Older
2. Language •Pragmatics •Prosody	•Nonverbal •No response to voice; may "act deaf" •No use of gestures as a means of compensating for absence of spoken language •May use "hand-over-hand" to guide caregiver to desired objects	•Echolalia, Delayed echolalia •Verbal Perseveration •Odd Inflection (stilted, sing-song, ↑↓ volume) •May use stock phrases in an attempt to communicate •Makes use of visual communication modalities (symbol cards; sign language)	•Speaks fluently, but literal; lacks understanding of verbal nuance •Difficulty with Pragmatics (framing, turn-taking, topic maintenance; conversational repair; talks "at" rather than "with" others) and Theory of Mind language tasks (fibbing; humor, verbal make-believe)

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www.drcoplan.com

Clinical Domain ⇓	Decreasing Atypicality / Increasing Age ⇒		
	Severe / Youngest	Moderate / Older	Mild / Older
2. Language •Pragmatics •Prosody	•Nonverbal •No response to voice; may "act deaf" •No use of gestures as a means of compensating for absence of spoken language •May use "hand-over-hand" to guide caregiver to desired objects	•Echolalia, Delayed echolalia •Verbal Perseveration •Odd Inflection (stilted, sing-song, ↑↓ volume) •May use stock phrases in an attempt to communicate •Makes use of visual communication modalities (symbol cards; sign language)	•Speaks fluently, but literal; lacks understanding of verbal nuance •Difficulty with Pragmatics (framing, turn-taking, topic maintenance; conversational repair; talks "at" rather than "with" others) and Theory of Mind language tasks (fibbing; humor, verbal make-believe)

www.drcoplan.com

Language Deficits in ASD: Literal Thinking

- **5 ½ year old boy with ASD and Superior IQ (Verbal Comprehension Index: 146)**

Q: "Which is bigger, 9 or 6?"

A: "They are both the same size, but 9 has a loop at the top, and 6 has a loop at the bottom."

www.drcoplan.com MRN 10-0681

Literal

Q: Who lives in a tree?
A: Nobody lives in a tree!
Q: What *animals* live in a tree?
A: Birds, squirrels….

3 - Repetitious Behavior with Insistence on Sameness

"Our son experiences extreme anxiety when what he anticipates isn't what happens…When we know a change is coming we can prepare him, but those we can't anticipate are still very upsetting for *him…The switch flips in his mind, and it's out of his control.*"

6 y.o. boy with ASD, anxiety, and normal nonverbal IQ

MRN 12-0782

Clinical Domain ⇓	Decreasing Atypicality / Increasing Age ⇒		
	Severe / Youngest	Moderate / Older	Mild / Older
3. Repetitious Behaviors *Cognitive*	•Extreme distress if *routines* are changed or when required to *transition* from one task to another •Fascination with odd objects (tags, wheels, fans, etc.)	• Same, but with diminishing level of distress; able to accept verbal preparation for changes in routine • Complex repetitious play (lining up objects, memorizes numbers, letters, etc)	• May demonstrate conscious awareness of preference for routines; easier to self-modulate •Play remains repetitious, but repetitive quality is more subtle; "obsessive preoccupations" •Problems with Central Coherence
Motoric	•Frequent, intense stereotypical movements (flapping, spinning, toe-walking, finger twiddling)	• Motor stereotypies occasional; may re-emerge when excited	• Motor stereotypies rare or absent

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Clinical Domain ⇓	Decreasing Atypicality / Increasing Age ⇒		
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Clinical Domain ⇓	Decreasing Atypicality / Increasing Age ⇒		
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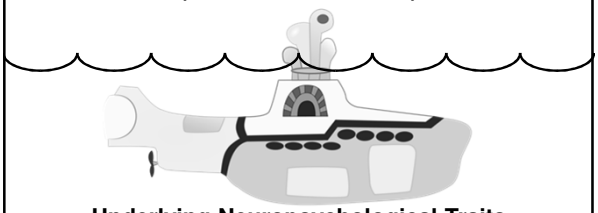
Visible features
(DSM, IDEA, ICD, etc.)



Underlying Neuropsychological Traits

- ↓ Theory of Mind
- ↓ Central Coherence

Persons with ASD:
Great at seeing details…

Persons with ASD:
Great at seeing details…

"?"

Persons with ASD:
Great at seeing details…

"Where are 8, 9, and 10?"

Not so good at seeing the big picture

What's happening in this picture?

"The man is drowning."

"The man is swimming, and the car is about to fall on him."

A: ***The man took off his clothes and jumped in the water.***
Q: Why did he do that?
A: ***Because the car was about to crash?***

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.***

Visible features
(DSM, IDEA, ICD, etc.)

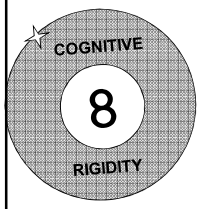
Underlying Neuropsychological Traits

- **Theory of Mind**
- **Central Coherence**
- **Cognitive Rigidity**

- Without a doubt
- Reply hazy, try again
- Signs point to NO
- Better not tell you now…

Cognitive Rigidity

(Difficulty shifting mental sets)



"Externalizing Behaviors"

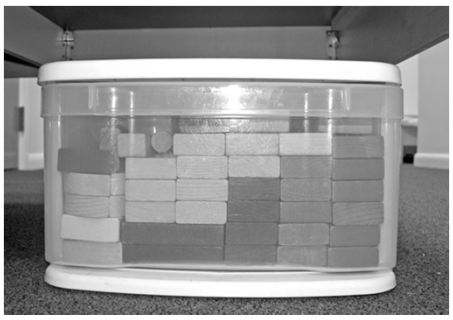
- ***Insistently*** **repetitious behavior**
- **Difficulty w. unmet expectations**
- **Perfectionism**
- **Compulsions**
- **Perseveration**
- **(Aggression, SIB)**

- **Perfectionism**
- **Obsessions**
- **(Anxiety / Depression)**

"Internalizing Behaviors"

Perfectionism

Perfectionism



Perfectionism

Tony

8 y.o. boy with HFA, Anxiety, and Perfectionism

Teacher's Report: "Tony tries to exclude himself from any 'competition' types of games or activities, as he really dislikes being 'wrong,' 'out,' or to lose. On the times he has had tantrums after being 'out' or when his team has lost, the other children have been very empathetic towards him and he has not lashed out at them. *His frustration appears to be with himself.*"

8 yr old boy with AS
MRN: 14-0916

Tony

8 y.o. boy with HFA, Anxiety, and Perfectionism

Office Visit

Examiner: "Sometimes you just need to do your best, and then move on," we stated in an encouraging tone of voice, then asked him "What do you think of that?"

Pt: "Not much," he replied bluntly.

8 yr old boy with AS
MRN: 14-0916

Sam

10 y.o. boy with AS, OCD, & perfectionism

- **Exam**
  - **Friendly & cooperative**
  - **"My brain makes me worry about stupid stuff, like 'Did I touch something?'"**
  - **Pedantic tone**
  - **Private monologues: "Pluto is the equality of Hades in Greek mythology…. Ares is the Greek god of war…. Cupid is the son of Aphrodite and Zeus…."**

MRN 14-0933

Sam

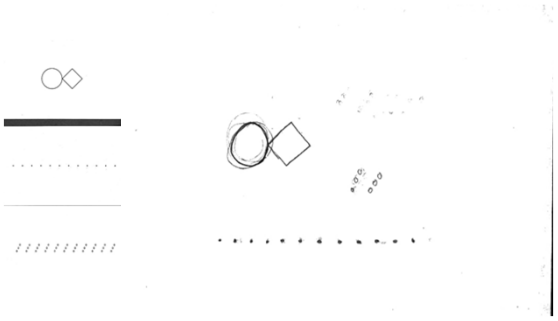
10 y.o. boy with AS, OCD, & perfectionism

Exam: Perfectionism

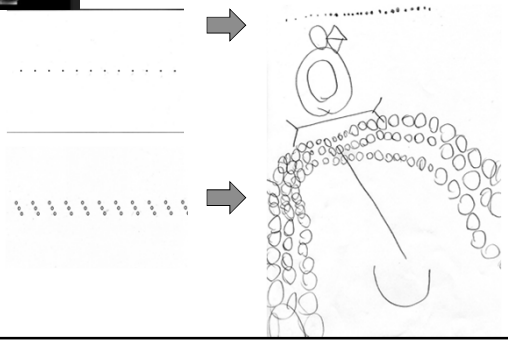
"Sam earnestly attempted the Bender-Gestalt figures, but became overwhelmed, repeatedly erasing and re-erasing. He went so far as to measure the distance between the dots on one of the stimulus cards with his finger, trying to replicate the spacing exactly. *'If I can't get something right I get angry with myself… Sometimes I take it out on other people,'* he confided. After he had labored mightily over the first few cards, he sighed *'This is torture…'* After he had manfully struggled over a single card for several minutes, we opted to move on to another task."

Perfectionism: "This is torture"

MRN 14-0933



Perseveration



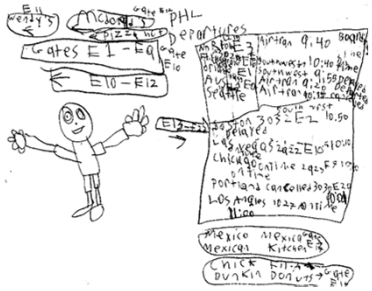
P.

Obsessive Interests & Perseveration

"We went to Washington and stayed at a hotel."

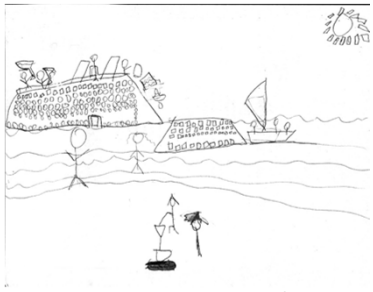
WW. 9 y.o. boy w. AS
MRN: 12-0827

Obsessive Interests & Perseveration



"We are at the Philadelphia airport waiting for our flight. Can I draw just me? My family already went ahead to the gate." WW. 11 y.o. boy w. AS
MRN: 12-0827

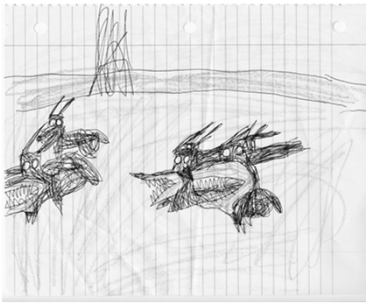
Obsessive Interests & Perseveration



"We went to the Jersey Shore."

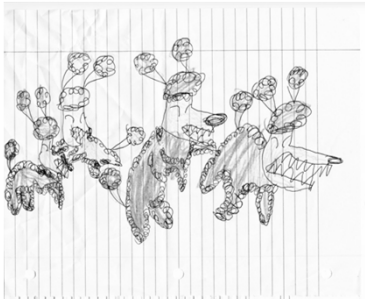
WW. 12 y.o. boy w. AS
MRN: 12-0827

Anxiety



RD. 7 y.o. F, nl IQ, PDD-NOS & Anxiety. Father: GAD
www.drcoplan.com
MRN: 07-0427

Anxiety



RD. 7 y.o. F, nl IQ, PDD-NOS & Anxiety. Father: GAD
www.drcoplan.com
MRN: 07-0427

Anxiety

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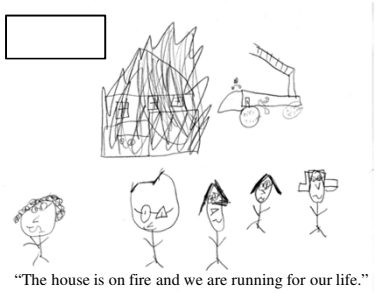
Anxiety



"The house is on fire and we are running for our life."

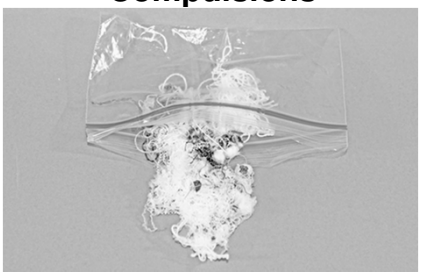
A.W.: 9 year old boy with PDD-NOS and normal IQ (MRN 11-07710

Anxiety

"Standing in the Atlantic Ocean. The ocean has a very high surface, up to their mouth, so they can't breathe." Six year old boy with ASD and Anxiety.

BK;MRN 09-0605

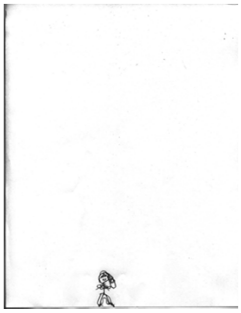
Anxiety + Perseveration = Compulsions



JF: 15 y.o. boy Asperger Syndrome

MRN: 05-0096

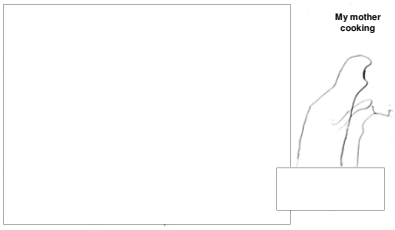
Depression



www.drcoplan.com KO; 10 yr old female, PDD-NOS, normal IQ

Depression

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

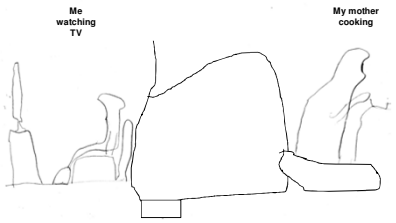


IB; 12 yr old male, Mild ASD, Superior IQ

I. B. MRN 06-0256

Depression

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

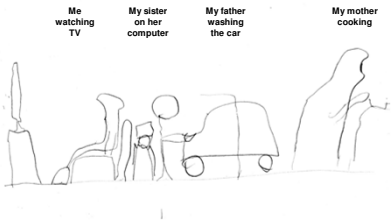


IB; 12 yr old male, Mild ASD, Superior IQ

I. B. MRN 06-0256

Depression

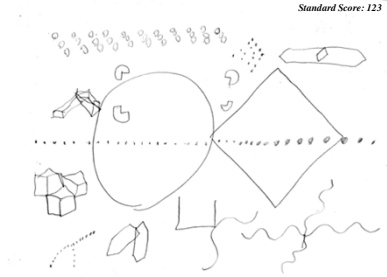
"Draw a picture of your family, with everybody in the picture doing something."



IB; 12 yr old male, Mild ASD, normal IQ

I. B. MRN 06-0256

Depression & Perseveration



IB; 12 yr old male, Mild ASD, normal IQ

I. B. MRN 06-0256

Repetitious behavior in ASD

- A direct expression of the underlying biology
  - Perseveration
  - Stereotypies
- Stress relief
  - SIB / Endorphin release
- A coping mechanism, to offset deficits in Theory of Mind & Central Coherence
  - "Better the devil you know…"

4 - Sensory & Motor Processing

Quantifying severity of ASD - 4

Clinical Domain ⇓	Decreasing Atypicality / Increasing Age ⇒		
	Severe / Youngest	Moderate / Older	Mild / Older
4.Sensorimotor: •*Intense aversion or attraction to specific classes of stimuli* •*Clumsiness*	•*Auditory*: Hyperacusis, covers ears, acts deaf •*Visual*: self-stimulation (lights/patterns); looks at objects from odd angles •*Tactile*: rubbing, licking, mouthing, deep pressure; averse to light touch •*Olfactory*: Sniffing •Extreme food selectivity •♠ ♦Pain threshold •Fears: Heightened / blunted	Same, but diminishing intensity	Same, but diminishing intensity

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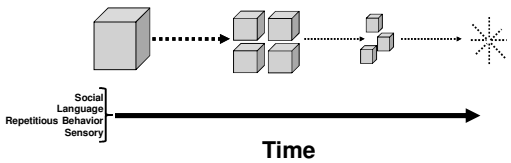
"Over time, the ice melts"



ASD has a natural history of improvement over time, even without treatment.

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Time Passes……

1943 ➔➔➔ 1980

Outline

- Patting the elephant (The history of a syndrome)
  - Down, Kanner, Asperger
  - DSM: "Are we there yet?"
  - 3D model
    - The Natural History of ASD
    - Where did all these kids come from?
- Under the hood
- It takes a village

DSM III

Yr	Event	Criteria / 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, severe criteria for Dx of autism, including: •Pervasive lack of responsiveness to other people •Gross deficits in language development •Bizarre responses to various aspects of the environment

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DSM III-R

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

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DSM IV

Year	Event	Criteria / Comment
1994	DSM-IV: •Broader menu for diagnosis •Asperger's Disorder first appears (but poorly defined)	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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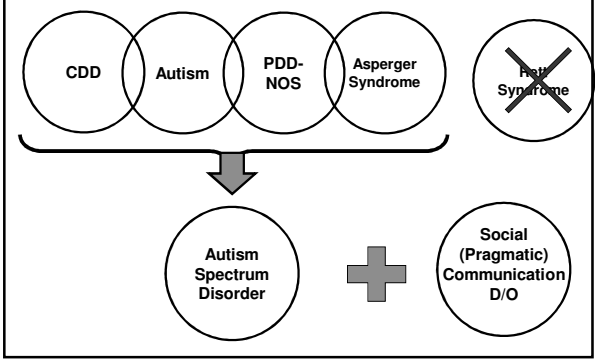
2013: DSM5



Autism Spectrum Disorder

Two Clinical Domains (vs. 3 in DSMIV, and 4 in Kanner)

A. **Deficits in Social Communication and Interaction**
B. **Restricted, Repetitive, Behaviors, Interests, and Activities**

DSM-5

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).

DSM 5

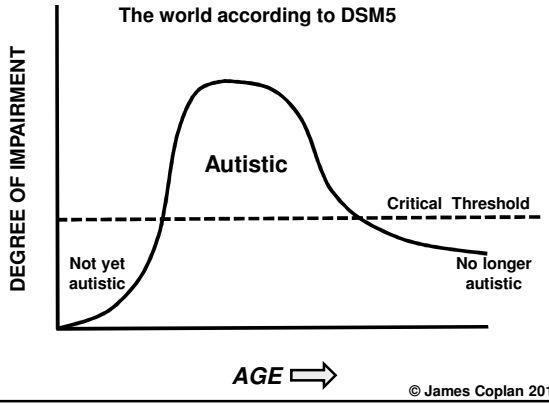
Symptom Domain*	Autism Spectrum D/O	Social (Pragmatic) Communication D/O
Social and Language	Persistent deficits in social communication & social interaction across multiple contexts: ✓deficits in *social-emotional reciprocity* ✓*nonverbal communication*, and ✓*maintaining / understanding relationships* (all 3)	"Deficits in social communication result[ing] 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	✓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 hyporeactivity to sensory input (at least 2 out of 4)	NO

* Presently, or remotely by Hx

Sensory (listed under repetitive behavior)

- **"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)"**

- **"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.**



DSM 5

DSM5

- The Good
  - Abnormal sensory processing is now a scorable criterion that counts towards the dx
  - Qualifiers for severity
  - Greater emphasis on developmental differences over time and the need to review early developmental Hx

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

DSM5

- The Bad
  - Locating Social Pragmatic Language Disorder outside the realm of ASD
  - Combining Language & Social into 1 domain
  - Placing sensory issues under "Repetitive Behavior" instead of as a primary domain

DSM5

- The Ugly
  - In order to get a Dx, one must be impaired. "Compensated" ASD is not recognized
  - Rejects "subclinical" diagnosis

Outline

- Patting the elephant (The history of a syndrome)
  - Down, Kanner, Asperger
  - DSM: "Are we there yet?"
  - 3D model
    - The Natural History of ASD
    - Where did all these kids come from?
- Under the hood
- It takes a village

Influence of IQ on Prognosis

- "In terms of scholastic progress, social competence, and work opportunities, the child's IQ level is as influential as the presence of autism."*
- 1973-2005: > 10 studies; >1000 subjects
  - Reviewed in Coplan, 2010, Appendix II

* Bartak, L. and M. Rutter, Differences between mentally retarded and normally intelligent autistic children. Journal of Autism & Childhood Schizophrenia, 1976. 6(2): p. 109-20

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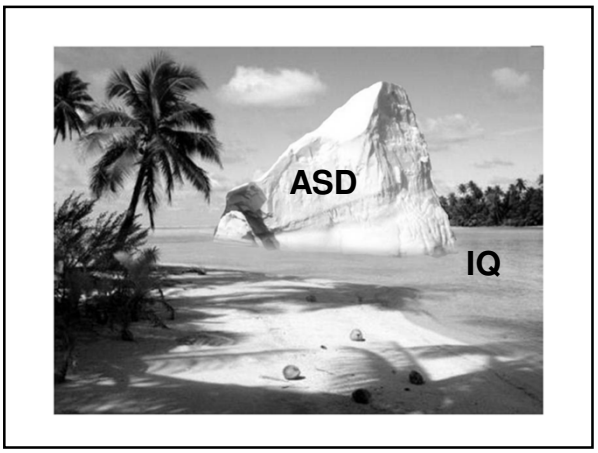
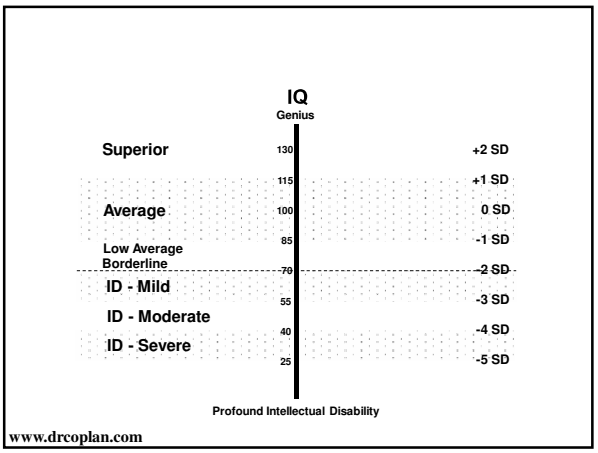
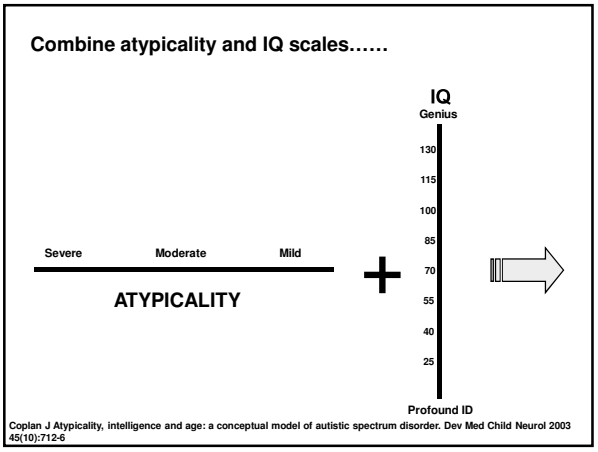
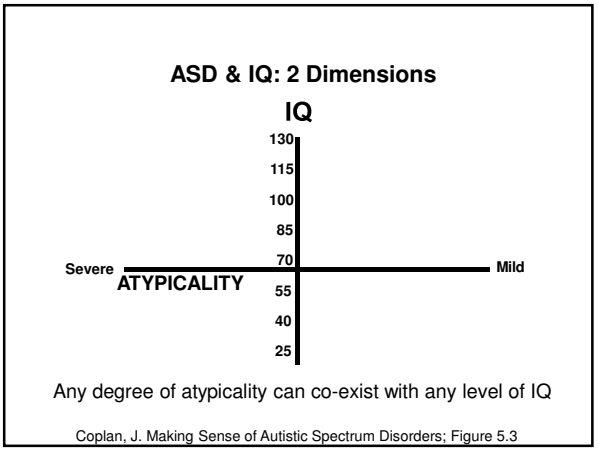
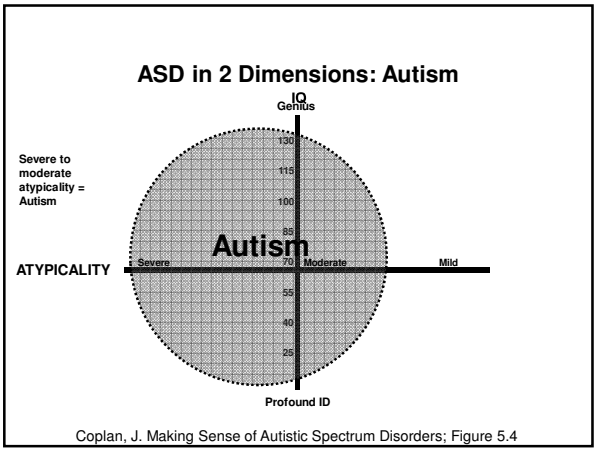
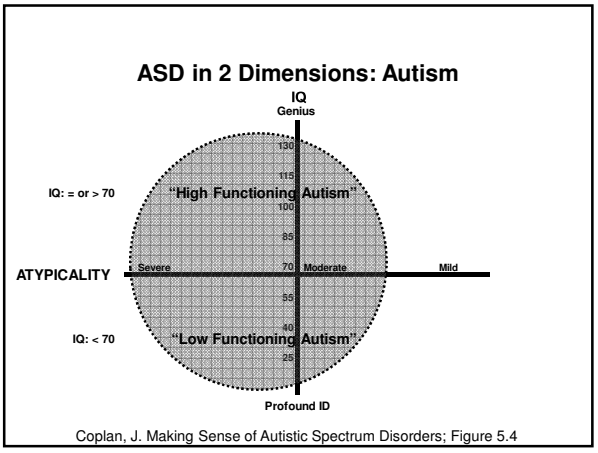

ASD
IQ

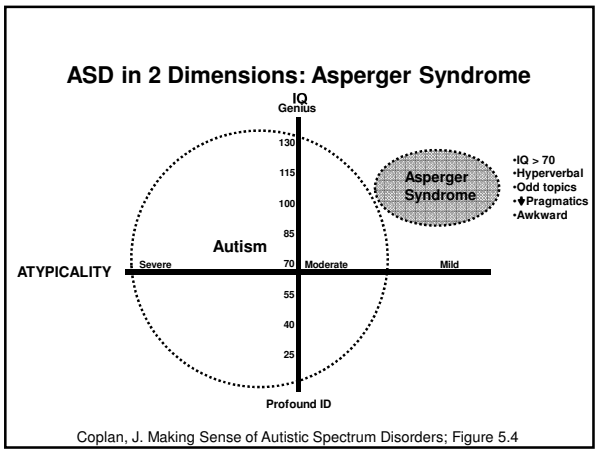

IQ
Genius
Superior
Average
Low Average
Borderline
ID - Mild
ID - Moderate
ID - Severe
130
115
100
85
70
55
40
25
+2 SD
+1 SD
0 SD
-1 SD
-2 SD
-3 SD
-4 SD
-5 SD
Profound Intellectual Disability
www.drcoplan.com

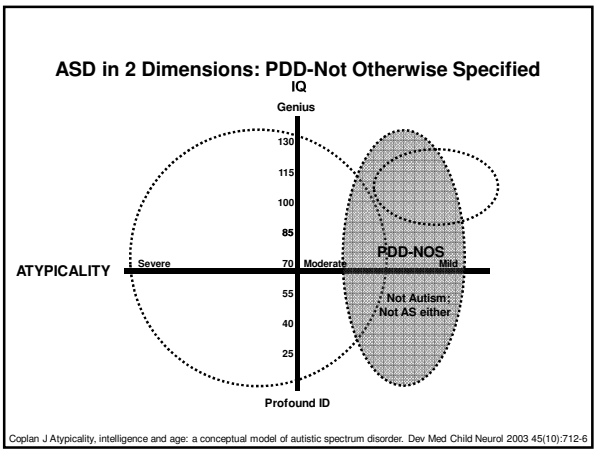

Combine atypicality and IQ scales……
Severe
Moderate
Mild
ATYPICALITY
IQ
Genius
130
115
100
85
70
55
40
25
Profound ID
Coplan J Atypicality, intelligence and age: a conceptual model of autistic spectrum disorder. Dev Med Child Neurol 2003 45(10):712-6

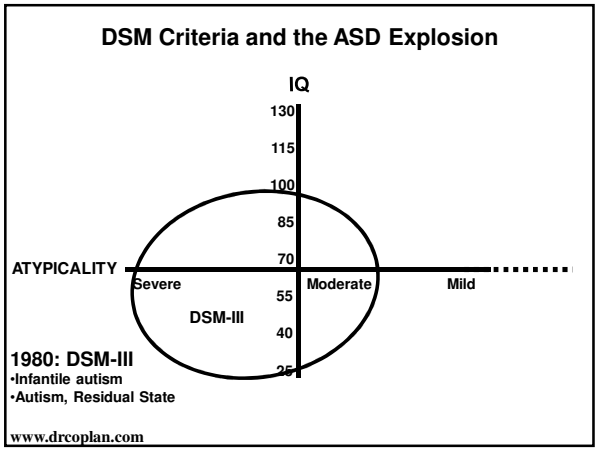

ASD & IQ: 2 Dimensions
IQ
130
115
100
85
70
55
40
25
Severe
Mild
ATYPICALITY
Any degree of atypicality can co-exist with any level of IQ
Coplan, J. Making Sense of Autistic Spectrum Disorders; Figure 5.3

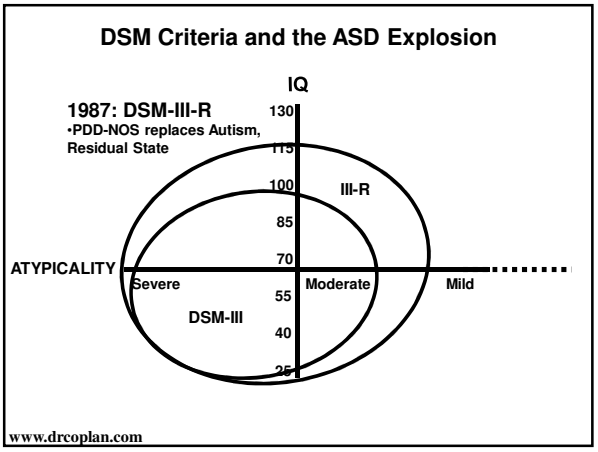

ASD in 2 Dimensions: Autism
IQ
Genius
Severe to moderate atypicality = Autism
Autism
ATYPICALITY
Severe
Moderate
Mild
130
115
100
85
70
55
40
25
Profound ID
Coplan, J. Making Sense of Autistic Spectrum Disorders; Figure 5.4

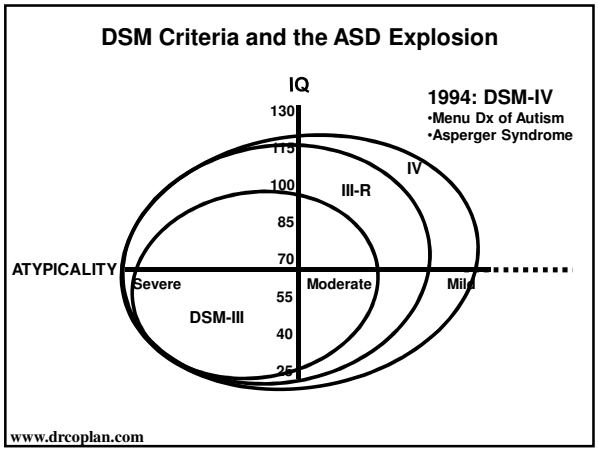

ASD in 2 Dimensions: Autism
IQ
Genius
IQ: = or > 70
"High Functioning Autism"
ATYPICALITY
Severe
Moderate
Mild
IQ: < 70
"Low Functioning Autism"
130
115
100
85
70
55
40
25
Profound ID
Coplan, J. Making Sense of Autistic Spectrum Disorders; Figure 5.4

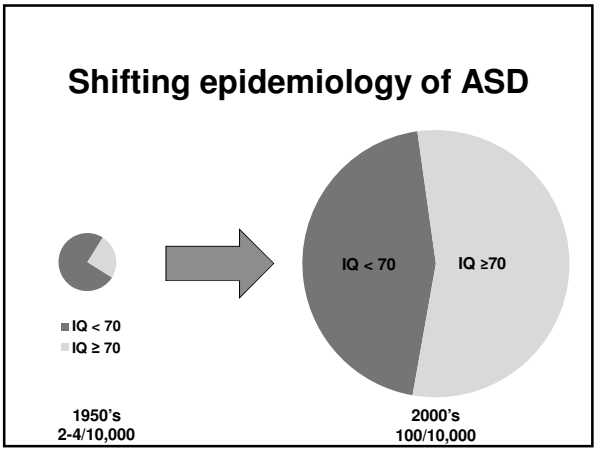

ASD in 2 Dimensions: Asperger Syndrome
IQ
Genius
130
115
100
85
70
55
40
25
Profound ID
ATYPICALITY
Severe
Moderate
Mild
Autism
Asperger Syndrome
•IQ > 70
•Hyperverbal
•Odd topics
•Pragmatics
•Awkward
Coplan, J. Making Sense of Autistic Spectrum Disorders; Figure 5.4

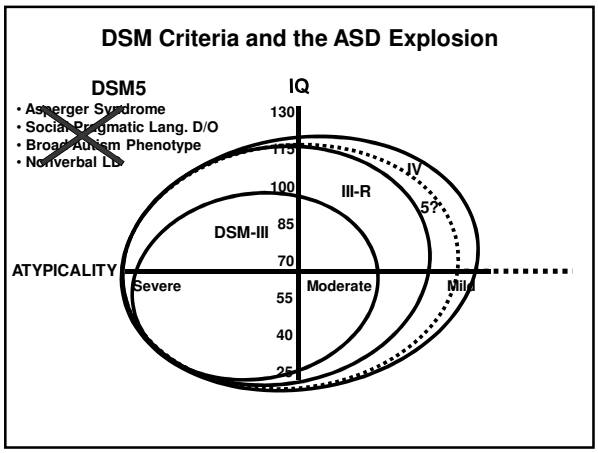

ASD in 2 Dimensions: PDD-Not Otherwise Specified
IQ
Genius
130
115
100
85
70
55
40
25
Profound ID
ATYPICALITY
Severe
Moderate
Mild
PDD-NOS
Not Autism;
Not AS either
Coplan J Atypicality, intelligence and age: a conceptual model of autistic spectrum disorder. Dev Med Child Neurol 2003 45(10):712-6

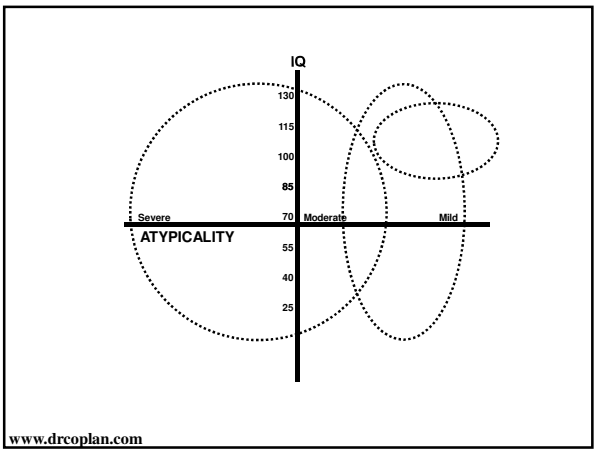

DSM Criteria and the ASD Explosion
IQ
130
115
100
85
70
55
40
25
ATYPICALITY
Severe
Moderate
Mild
DSM-III
1980: DSM-III
•Infantile autism
•Autism, Residual State
www.drcoplan.com

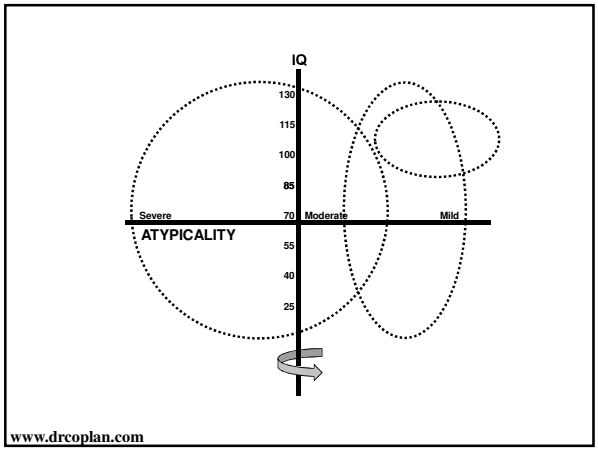

DSM Criteria and the ASD Explosion
IQ
1987: DSM-III-R
•PDD-NOS replaces Autism,
Residual State
130
115
100
85
70
55
40
25
III-R
ATYPICALITY
Severe
Moderate
Mild
DSM-III
www.drcoplan.com

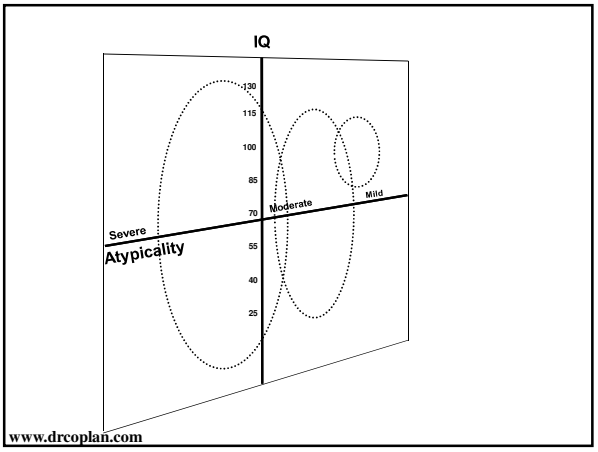

DSM Criteria and the ASD Explosion
IQ
1994: DSM-IV
•Menu Dx of Autism
•Asperger Syndrome
130
115
100
85
70
55
40
25
IV
III-R
ATYPICALITY
Severe
Moderate
Mild
DSM-III
www.drcoplan.com

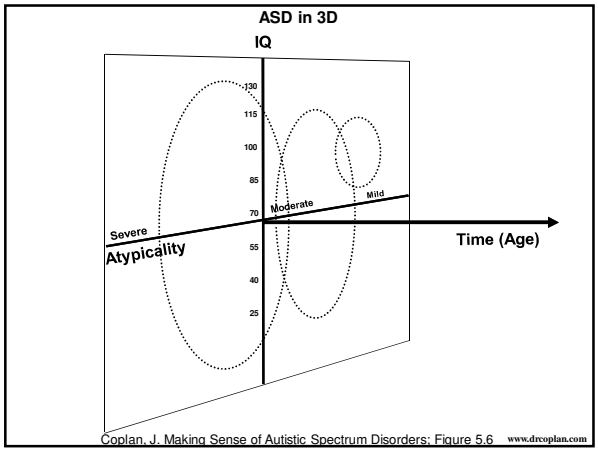

Shifting epidemiology of ASD
IQ < 70
IQ ≥ 70
IQ < 70
IQ ≥70
1950's
2-4/10,000
2000's
100/10,000

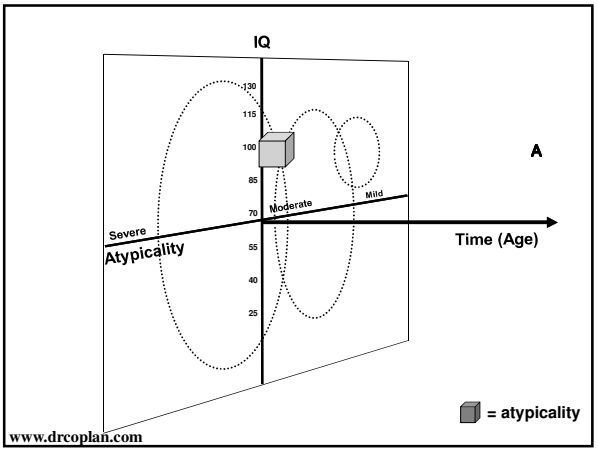

DSM Criteria and the ASD Explosion
DSM5
• Asperger Syndrome
• Social Pragmatic Lang. D/O
• Broad Autism Phenotype
• Nonverbal LD
IQ
130
115
100
85
70
55
40
25
JV
III-R
5?
DSM-III
ATYPICALITY
Severe
Moderate
Mild

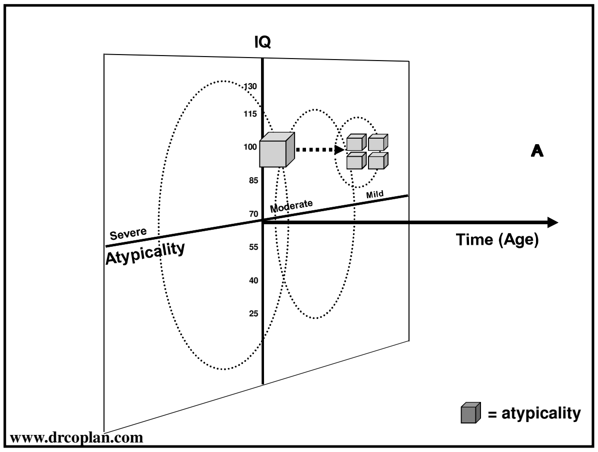

IQ
130
115
100
85
70
55
40
25
Severe
Moderate
Mild
ATYPICALITY
www.drcoplan.com

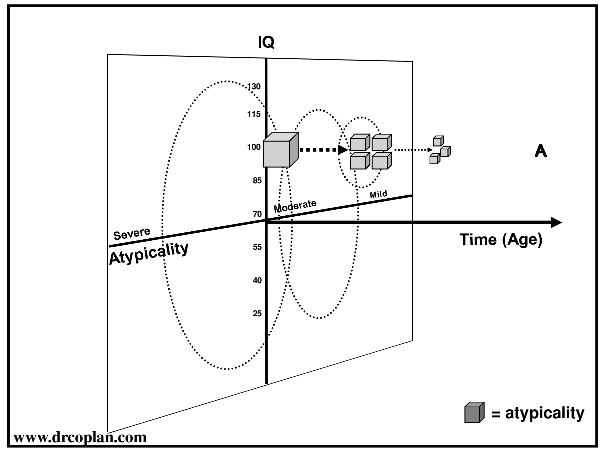

IQ
130
115
100
85
70
55
40
25
Severe
Moderate
Mild
ATYPICALITY
www.drcoplan.com

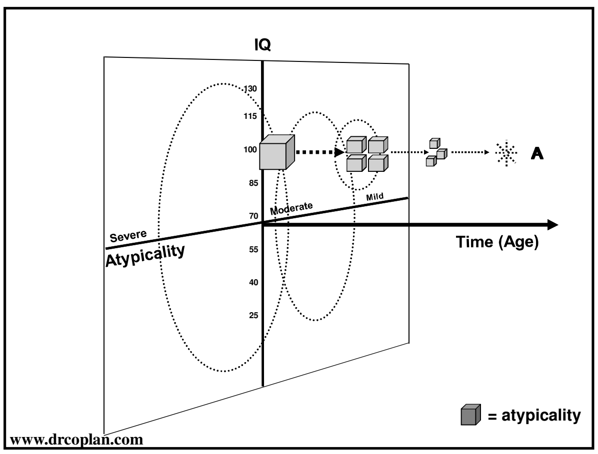

IQ
130
115
100
85
70
55
40
25
Moderate
Mild
Severe
Atypicality
www.drcoplan.com

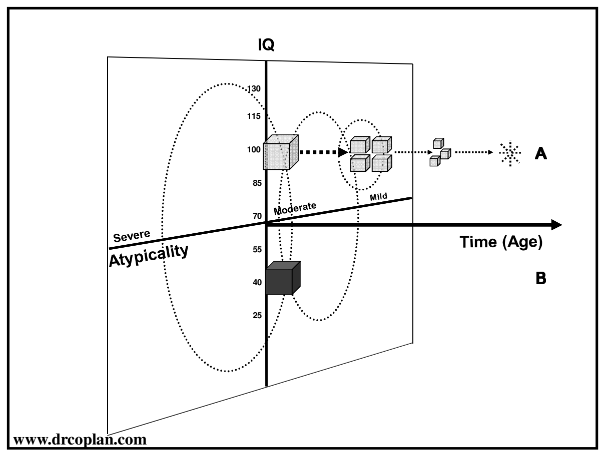

ASD in 3D
IQ
130
115
100
85
70
55
40
25
Moderate
Mild
Severe
Atypicality
Time (Age)
Coplan, J. Making Sense of Autistic Spectrum Disorders: Figure 5.6 www.drcoplan.com

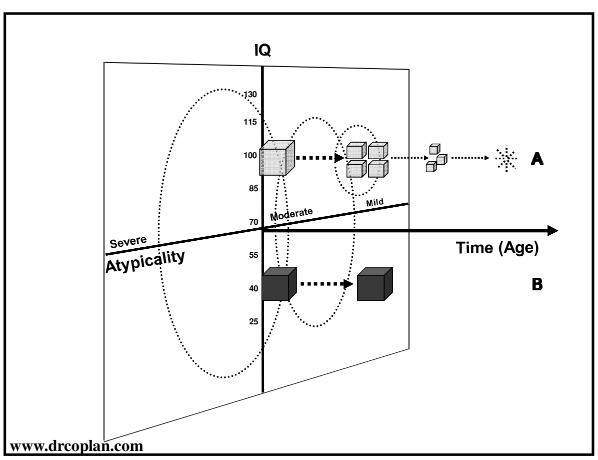

IQ
130
115
100
85
70
55
40
25
A
Moderate
Mild
Severe
Atypicality
Time (Age)
= atypicality
www.drcoplan.com

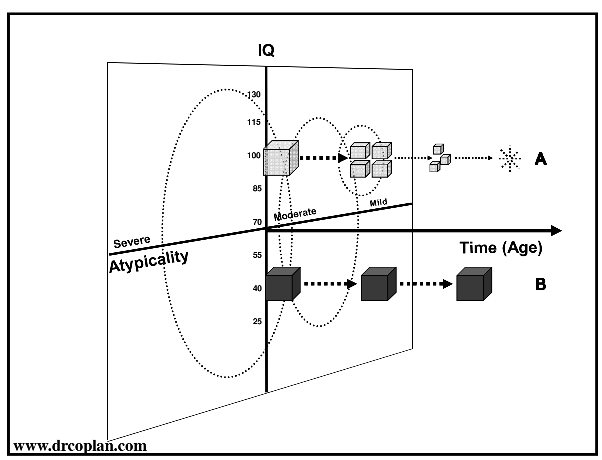

IQ
130
115
100
85
70
55
40
25
Moderate
Mild
Severe
Atypicality
Time (Age)
A
= atypicality
www.drcoplan.com

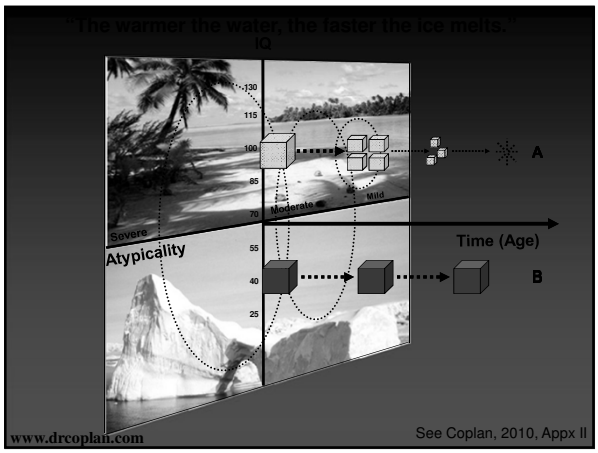

IQ
130
115
100
85
70
55
40
25
Moderate
Mild
Severe
Atypicality
Time (Age)
A
= atypicality
www.drcoplan.com


IQ
130
115
100
85
70
55
40
25
Moderate
Mild
Severe
Atypicality
Time (Age)
A
= atypicality
www.drcoplan.com


IQ
130
115
100
85
70
55
40
25
Moderate
Mild
Severe
Atypicality
Time (Age)
A
B
www.drcoplan.com


IQ
130
115
100
85
70
55
40
25
Moderate
Mild
Severe
Atypicality
Time (Age)
A
B
www.drcoplan.com


IQ
130
115
100
85
70
55
40
25
Moderate
Mild
Severe
Atypicality
Time (Age)
A
B
www.drcoplan.com



Therapies for ASD: A Modest Proposal

- **Therapies for ASD should be matched to the natural history of ASD itself**
  - ***As the child's symptoms evolve, so should the forms of therapy***
  - ***It's not a matter of right vs wrong; It's a matter of what & when***

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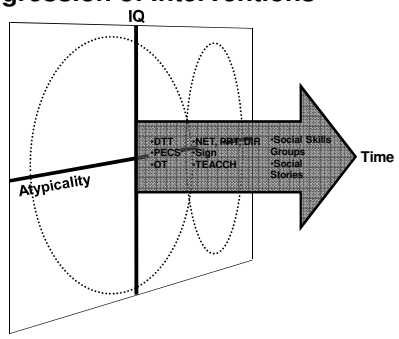
Natural History of ASD, and the Progression of Interventions



Coplan, 2009, in press

Outline

- Patting the elephant
- ➢ Under the hood
  - Neurobiology and Neuropsychology of ASD
    - Cognitive Rigidity
    - Dysregulation of attention
    - Dysregulation of arousal and mood
    - Dysregulation of sensory processing
      - Mirror Neurons: Motor imitation, empathy, and reality testing
    - Theory of Mind & Introspection
    - Central Coherence
  - Genetics (and other causes)
  - The expanded autism syndrome
    - Not "comorbidity," but continuum and metamorphosis
      - "Is schizophrenia on the autism spectrum?"*
  - All in the family
    - Broad Autism Phenotype and Non-ASD MH disorders
- It takes a village

* King & Lord

The History of Science in 1 Slide

Description* & *Classification*

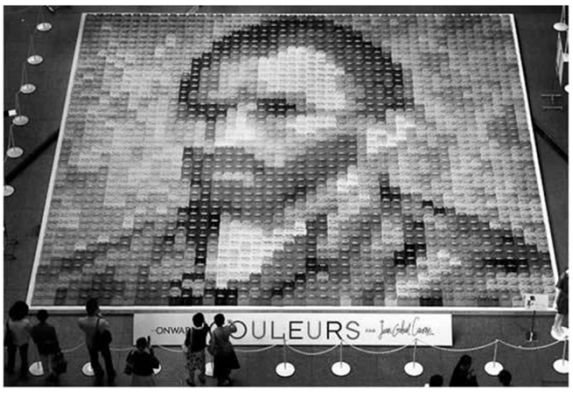
(Group items into categories, based on externally visible characteristics)

⬇

Analysis

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

** 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 categori*es, eventually the big picture will emerge.**



Taxonomy of animals

Description* & *Classification
(based on externally visible characteristics)

↓

Analysis
(based on an understanding of fundamental mechanisms)

Aristotle (384-322 BCE)
to Linneaus
(*Systema Naturae, 1758*)

↓

Cuvier
Darwin
Mendel
Watson & Crick

Biology circa 1758

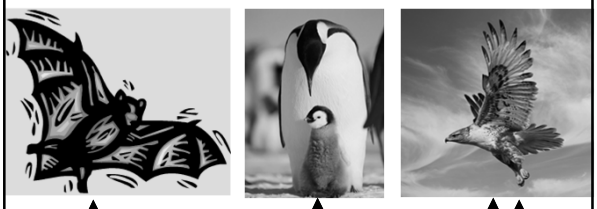

SYSTEMA NATURÆ
REGNA TRIA NATURÆ,
CLASSES, ORDINES, GENERA, SPECIES,
TOMUS I.

I. QUADRUPEDIA (animals with 4 legs) | II. AVES (birds) | III. AMPHIBIA (amphibians) | IV. PISCES (fish) | V. VERMES (worms)

Problems with classification schemes based on appearance

- Different underlying mechanisms can produce similar-appearing results
- Same underlying mechanism can produce different-appearing results

Which 2 belong together?



Pleitropy

Phenocopy

Scientific Advances in Biology

Description* & *Classification
(based on externally visible characteristics)

↓

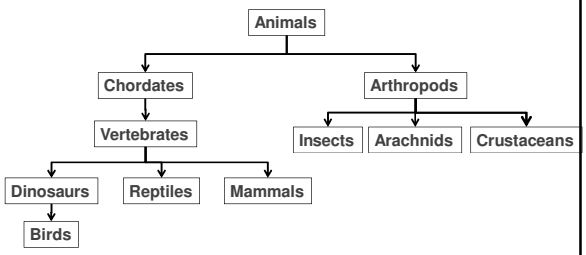
Analysis
(based on an understanding of fundamental mechanisms)

Linneaus (1758)
(Systema Naturae)

↓

Cuvier
(Extinction – 1813)
Darwin
(Natural Selection - 1859);
Mendel
(Dominant & recessive inheritance - 1866);
Watson & Crick
(DNA - 1953)

Modern Taxonomy of Animals



Categories *emerge and disappear*, and *boundaries between categories change*, as our understanding of underlying mechanisms increases

Psychiatry: Where we are today

Description* & *Classification
(based on externally visible characteristics)

↓

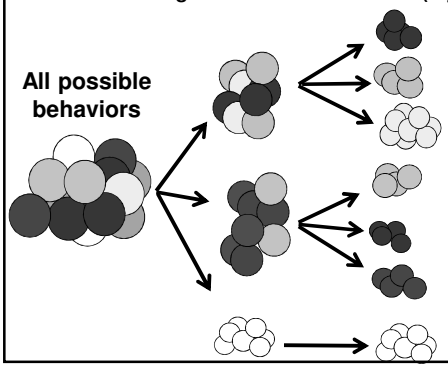
Analysis
(based on an understanding of fundamental mechanisms)

DSM5:
Categories based on symptoms → quest for *symptom homogeneity within categories*

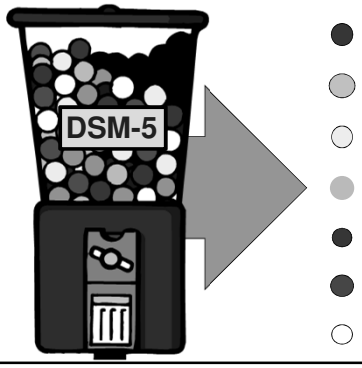
↓

DSM 6
(classification based on causation and brain systems)

Keep sub-dividing until homogeneity within categories has been achieved (myth #1)



Make Diagnoses



Comorbidity:

A, B, C…. etc. are completely different entities, that sometimes just happen to co-exist (myth #2)

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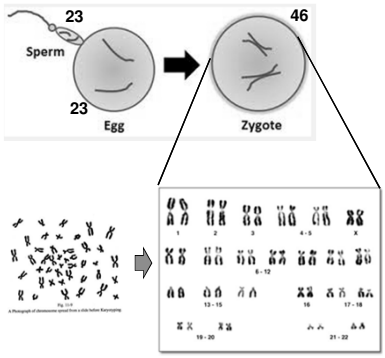
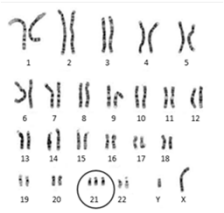
A quick review

Discovery of Cell Division ("mitosis"), nuclear division, and Chromosomes (1882)

Human Genome = 46 Chromosomes (Tjio & Levan, 1955)



Chromosomal Basis for Down Syndrome
Jerome Lejeune, 1959

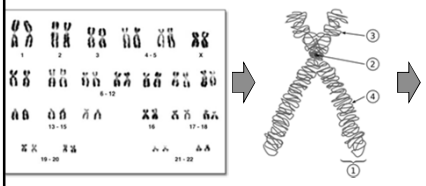


Trisomy 21

Double Helix: Rosalind Franklin, Watson & Crick, 1950s

46 Chromosomes

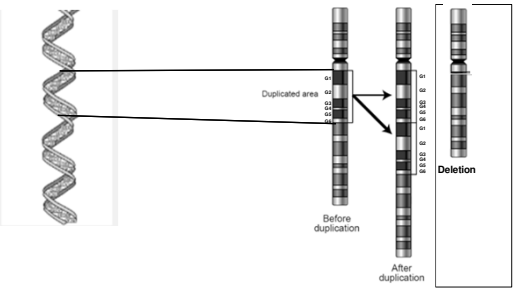
Each chromosome is composed of tightly wound DNA*



Genes = Segments of DNA (humans: ~24,000 genes)

*6 feet of DNA per cell; 10 billion miles of DNA in the human body

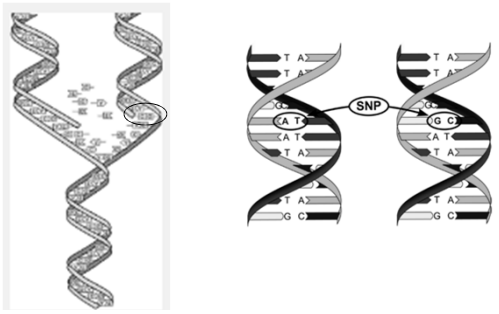
Copy Number Variations (CNVs)



- **Duplications or deletions in segments of DNA**
- **~1KB to several MB (within or spanning several genes)**

- **Human genome: ~ 24,000 genes**
- **Includes 1,447 copy number variable regions (CNVRs), which can encompass overlapping or adjacent gains or losses, and comprise 12% of the genome**
- **CNVRs contain hundreds of genes, disease loci, and functional elements**

Single Nucleotide Polymorphisms (SNIPs)



- **Substitution of individual nucleotides (A, T, G, C)**
  - Adenine:Thymine; Guanadine:Cytosine

Traditional Medical Practice

("What's the matter with my patient?")

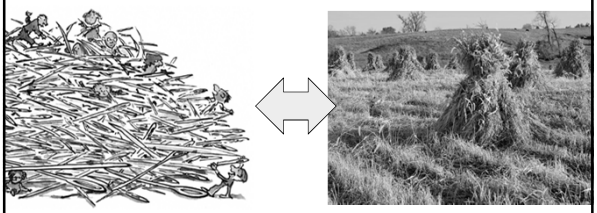
Down Syndrome: 1866 ➔ 1959

New Way:

What does this particular genetic variation do (if anything)?

New Way

(Many needles, many haystacks)



Neuron

NeuroView

Simons Variation in Individuals Project (Simons VIP): A Genetics-First Approach to Studying Autism Spectrum and Related Neurodevelopmental Disorders

The Simons VIP Consortium[1,*,**]
[1]Membership of the Consortium is provided in Table S5
*Correspondence: jspiro@simonsfoundation.org (J.E. Spiro)
**Correspondence: wkc15@columbia.edu (W.K. Chung)
DOI 10.1016/j.neuron.2012.02.014

"Clinical phenotyping… for …neuropsychiatric disorders such as ASD, bipolar disorder, and schizophrenia…. can be a particular challenge given the heterogeneity and complexity of the symptomatology for these disorders, which are diagnosed using inherently subjective behavioral criteria"

Neuron
NeuroView

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DOI 10.1016/j.neuron.2012.02.014

"Diagnosis-First" data sets (i.e., enrollment is limited to subjects meeting strict clinical criteria for ASD):

- **Autism Genetic Resource Exchange (AGRE)**
- **Simons Simplex Collection (SSC)**
- **Autism Genome Project**
- **NIMH repository**

Neuron
NeuroView

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DOI 10.1016/j.neuron.2012.02.014

We describe a project aimed at studying a large number of individuals (>200) with specific recurrent genetic variations (deletion or duplication of segment 16p11.2) that increase the risk of developing autism spectrum (ASD) and other developmental disorders

Neuron
NeuroView

Simons Variation in Individuals Project (Simons VIP): A Genetics-First Approach to Studying Autism Spectrum and Related Neurodevelopmental Disorders

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DOI 10.1016/j.neuron.2012.02.014

"By recruiting and studying large numbers of families with deletions or duplications of 16p11.2, without regard to clinical diagnosis or age, we aim to address this question by studying the cross sectional diversity and early longitudinal course of this genetically well-defined group of individuals at the behavioral and neurocognitive level.

Neuron
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Simons Variation in Individuals Project (Simons VIP): A Genetics-First Approach to Studying Autism Spectrum and Related Neurodevelopmental Disorders

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DOI 10.1016/j.neuron.2012.02.014

16p11.2 has been associated with

- **ASD**
- **Schizophrenia**
- **Bipolar disorder**
- **Developmental Delay**
- **Body weight regulation**

How and why does this variation occur?

Genetic changes we study:

Researchers are collecting information on the following genetic changes associated with developmental delay and features of autism.

Copy Number Variants:	
16p11.2 Deletions	16p11.2 Duplications
1q21.1 Deletions	1q21.1 Duplications

Genes Associated with Features of Autism			
ACTL6B	*BCL11A*	*KATNAL2*	*REST*
ADNP	*CHD2*	*KDM5B*	*SCN2A*
ANK2	*CHD8*	*KDM6B*	*SETD5*
ANKRD11	*CTNNB1*	*KMT2C*	*SMARCC1*
ARID1B	*CUL3*	*KMT2E*	*SMARCC2*
ASH1L	*DSCAM*	*MBD5*	*SUV420H1*
ASXL3	*DST*	*MED13L*	*SYNGAP1*
BAF105	*DYRK1A*	*PBRM1*	*TBR1*
BAF190	*FOXP1*	*POGZ*	*PTEN*
BAF35	*GRIN2B*	*PTCHD1*	

https://simonsvipconnect.org/

https://simonsvipconnect.org/

Neuron
NeuroView

Cell PRESS

Simons Variation in Individuals Project (Simons VIP): A Genetics-First Approach to Studying Autism Spectrum and Related Neurodevelopmental Disorders

"Although the Simons VIP project is initially focused on 16p11.2, the structure of the project should have broader applications for other complex genetic disorders."

A Genotype-First Approach to Defining the Subtypes of a Complex Disease Stessman et al 2014

Cell

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The Autism Spectrum/Intellectual Disability network (ASID): 21 basic research and clinical laboratories, >15,000 patients with ASD, ID, epilepsy, or DD. It emphasizes collections where parental DNA is available and where patient recontact is possible to accurately resolve phenotype-genotype correlations.

A Genotype-First Approach to Defining the Subtypes of a Complex Disease

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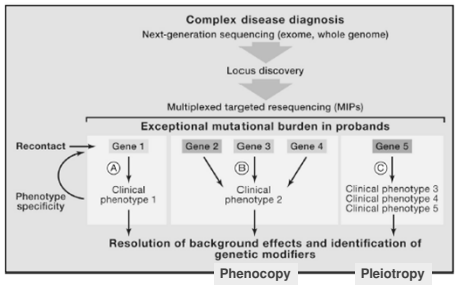

Figure 1. Schematic of Genotype-First Approach for ASD

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

Andres Moreno-De-Luca*, Scott M Myers*, Thomas D Challman, Daniel Moreno-De-Luca, David W Evans, David H Ledbetter

Deletion	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.[3]

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

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Phenocopy

Deletion	Frequency in clinical cohorts*	Intellectual disability or developmental delay	Autism spectrum disorder	Schizophrenia	Epilepsy
22q11.2	1 in 167	√	√	√	√
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Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence

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Pleiotropy

Deletion	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	√	√	--	√
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17p11.2	1 in 985	√	√	--	√
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*Frequency in individuals referred for chromosomal microarray testing. Common indications for testing include neurodevelopmental disorders and multiple congenital anomalies.[3]

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

Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs

Cross-Disorder Group of the Psychiatric Genomics Consortium
Nature Genetics: v. 45, pp 984–994(2013)

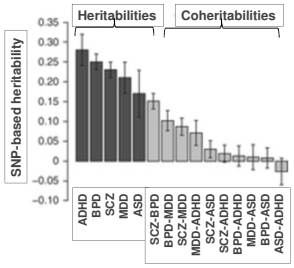

Fig. 1. Evidence for genome-wide pleiotropy between psychiatric d/o.

Review

Cell
2013

Feature Review

A *de novo* convergence of autism genetics and molecular neuroscience

Niklas Krumm[1], Brian J. O'Roak[1], Jay Shendure[1], and Evan E. Eichler[1,2]

[1] Department of Genome Sciences, University of Washington, Seattle, WA, USA
[2] Howard Hughes Medical Institute, University of Washington School of Medicine, Seattle, WA, USA

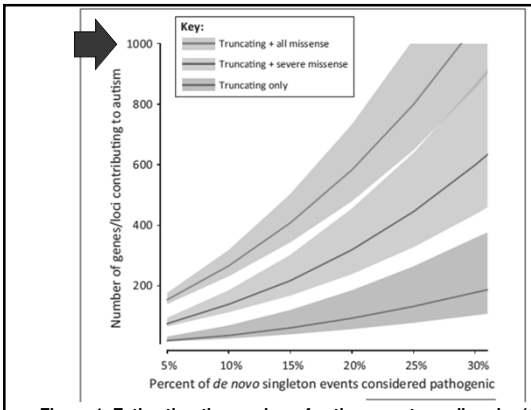

Figure 1. Estimating the number of autism spectrum disorder (ASD) / intellectual disability (ID) risk genes. Krumm, 2013

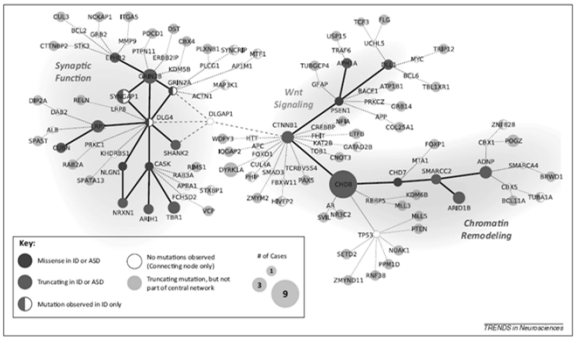

Figure 3. Predicted proteins disrupted by genic de novo mutations in autism spectrum disorder (ASD) and intellectual disability (ID) form a central connected network. Krumm 2013

Krumm 2013

- **Which mutations are necessary and sufficient for, as opposed to simply increasing the risk of, developing ID or ASD? What constitutes proof of a genetic cause of autism/ID?**
- **To what extent does the impact of de novo variants depend on the underlying genetic background of the individuals?**
- **What is the relative contribution of rare variants, syndromic causes, and common variants to the overall gestalt of ASD? Is there a fraction of the heritable risk that will never be explained?**
- **What role does epigenetics and environment play? Will the identification of hundreds of ASD genes help to identify new environmental or gene-by-environment components?**

Krumm 2013

- **Will the definition of specific subtypes lead to clinically distinguishable forms of autism? How will these data inform future molecular therapies?**
- **How will clinical cohorts of tens to hundreds of thousands of patients be amassed and research studies coordinated to resolve the heterogeneity of these disorders?**

J Dev Behav Pediatr. 2015 Feb-Mar;36(2):61-7. doi: 10.1097/DBP.0000000000000126.

Epigenetics of autism-related impairment: copy number variation and maternal infection.

Mazina V[1], Gerdts J, Trinh S, Ankenman K, Ward T, Dennis MY, Girirajan S, Eichler EE, Bernier R.

- **Goal: To explore the impact of ASD-associated CNVs and prenatal maternal infection on clinical severity of ASD**
- **Subjects & Methods: Simons Simplex Collection sample: 1,971 children w. ASD, age 4 - 18 yr**
  - **Array comparative genomic hybridization screening**
  - **Information on infection and febrile episodes during pregnancy was collected through parent interview**
  - **ASD severity was clinically measured through parent-reported interview and questionnaires.**

J Dev Behav Pediatr. 2015 Feb-Mar;36(2):61-7. doi: 10.1097/DBP.0000000000000126.

Epigenetics of autism-related impairment: copy number variation and maternal infection.

Mazina V[1], Gerdts J, Trinh S, Ankenman K, Ward T, Dennis MY, Girirajan S, Eichler EE, Bernier R.

RESULTS

- **Individuals with ASD-associated CNVs plus a history of maternal infection demonstrated increased rates of social communicative impairments and repetitive/restricted behaviors**
- **Our findings support a gene-environment interaction model of autism impairment, in that individuals with ASD-associated CNVs are more susceptible to the effects of maternal infection and febrile episodes in pregnancy on behavioral outcomes**

J Dev Behav Pediatr. 2015 Feb-Mar;36(2):61-7. doi: 10.1097/DBP.0000000000000126.

Epigenetics of autism-related impairment: copy number variation and maternal infection.

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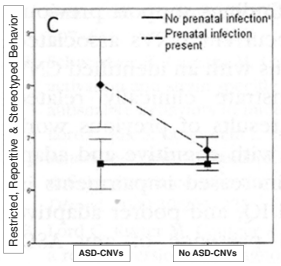

ARTICLE

doi:10.1038/nature12818

CNVs conferring risk of autism or schizophrenia affect cognition in controls

Hreinn Stefansson[1*], Andreas Meyer-Lindenberg[2*], Stacy Steinberg[1], Brynja Magnusdottir[3], Katrin Morgen[2], Sunna Arnarsdottir[1,3], Gyda Bjornsdottir[1], G. Bragi Walters[1], Gudrun A. Jonsdottir[1], Orla M. Doyle[4], Heike Tost[2], Oliver Grimm[2], Solveig Kristjansdottir[1], Heimir Snorrason[5], Solveig R. Davidsdottir[1], Larus J. Gudmundsson[5], Gudbjorn F. Jonsson[1], Berglind Stefansdottir[1], Isafold Helgadottir[1], Magnus Haraldsson[3,5], Birna Jonsdottir[6], Johan H. Thygesen[7], Adam J. Schwarz[8], Michael Didriksen[9], Tine B. Stensbol[9], Michael Brammer[4], Shitij Kapur[4], Jonas G. Halldorsson[3], Stefan Hreidarsson[10], Evald Saemundsen[5,10], Engilbert Sigurdsson[3,5] & Kari Stefansson[1]

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Stefansson et al 2014

"Little information is available on whether or how rare CNVs conferring high risk of schizophrenia and/or autism affect physiologic function of otherwise normal brains. …. We aimed to examine the possibility that the CNVs affect cognition in control carriers, those who do not suffer either disease or intellectual disability."

Stefansson et al 2014

"We based our selection of CNVs on a literature search for CNVs associated with schizophrenia and/or autism ('neuropsychiatric CNVs'); this search produced 26 CNV alleles. These CNV alleles are rare, found in 0.002% to 0.2% frequency, and cumulatively in 1.16% of our sample of 101,655 genotyped subjects, representing approximately one-third of the Icelandic population."

Stefansson et al 2014

- **Subjects carrying neuropsychiatric CNVs performed worse than population controls on cognitive tests (Verbal & Performance IQ, reading, math), GAF,* and history of learning difficulties**
- **Subjects carrying neuropsychiatric CNVs also showed structural changes in the brain**

*GAF = Global Assessment of Functioning Scale

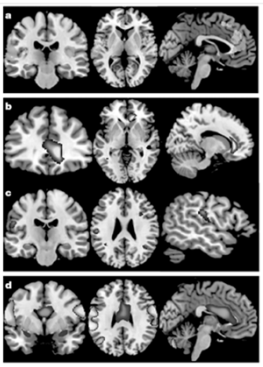
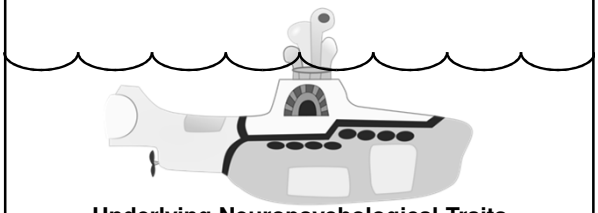


Figure 3. Dose-dependent alterations in brain structure in 15q11.2 (BP1-BP2) CNV carriers. Stefansson 2014

Food for thought

- **Since nominally "asymptomatic" carriers of specific CNVs (which are known to be associated w. SCZ & ASD) have demonstrable cognitive and neuroanatomic changes, where is the real boundary between "normal" and "abnormal"?**
  - **DSM's rejection of "subclinical" disorders?**
  - **An opportunity to practice preventive care?**
  - **Ethical issues of identification in "normal" individuals?**

Visible features
(DSM, IDEA, ICD, etc.)



Underlying Neuropsychological Traits

- **↓ Central Coherence**
- **↓ Theory of Mind**
- **Cognitive Rigidity**
  - **Impaired regulation of arousal & mood**

Severe mood problems in adolescents with autism spectrum disorder

Simonoff, E., et al., Journal of Child Psychology and Psychiatry, 2012. 53(11): p. 1157-1166

- **91 adolescents w. ASD (M: 83)**
- **Methods:**
  - **IQ, Adaptive function, neuropsych measures**
  - **"Severe Mood Problems (SMP) Scale"**
    - **Explosive rage**
    - **Low mood**
    - **Depressive thoughts**
    - **Labile mood**
  - **Maternal self-report (GHQ)**
    - **maternal mood, anxiety and somatic difficulties**

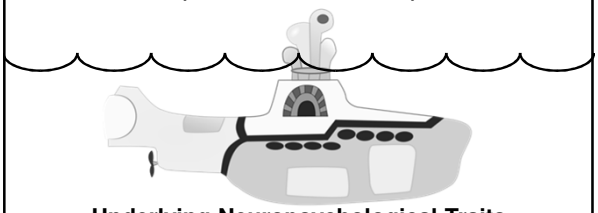
Severe mood problems in adolescents with autism spectrum disorder

Simonoff, E., et al., Journal of Child Psychology and Psychiatry, 2012. 53(11): p. 1157-1166

Results

- **High SMP: 24 (26%)**
  - **Predictors of severe mood problems:**
    - **Emotional & behavioral problems at age 12**
    - **Autism severity (by parent report)**
    - **Maternal GHQ: "*The current analyses suggest a specific relationship between maternal affective symptoms and SMP in offspring*"**
  - **Not predictors:**
    - **Full Scale IQ**
    - **Adaptive function**

Visible features
(DSM, IDEA, ICD, etc.)

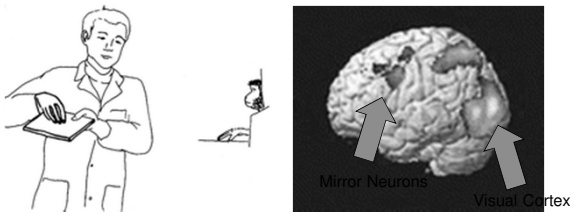


Underlying Neuropsychological Traits

- ↓ Central Coherence
- ↓ Theory of Mind
- Cognitive Rigidity
- Impaired regulation of arousal & mood
- ➢ Impaired Mirror Neuron Functioning

Mirror Neuron System

The neuroanatomic basis for motor imitation, sense of "self," and empathy?



"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

Figure 2.5. Stimulus faces of Andrew Meltzoff and a young mimic.

Meltzoff, Andrew N. and Moore, M. K. Imitation of facial and manual gestures by human neonates. Science 198:75-78, 1977

http://en.wikipedia.org/wiki/File:Makak_neonatal_imitation.png

Altered Connectivity and Action Model Formation in Autism Is Autism

The Neuroscientist
17(4) 437–448
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DOI: 10.1177/1073858410392381
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Stewart H. Mostofsky[1] and Joshua B. Ewen[2]

MNS

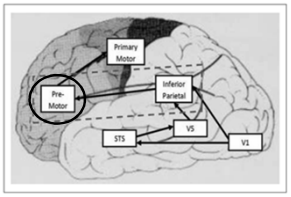

Figure 1. Brain regions associated with praxis and imitative function

"Children with autism place a greater than normal reliance during motor learning on their own proprioception while discounting visual consequences in the extrinsic world"

doi:10.1093/scan/nss106 SCAN (2014) 9, 98–105

Functional Brain Networks and White Matter Underlying Theory-of-Mind in Autism

Rajesh K. Kana, Lauren E. Libero, Christi P. Hu, Hrishikesh D. Deshpande, and Jeffrey S. Colburn
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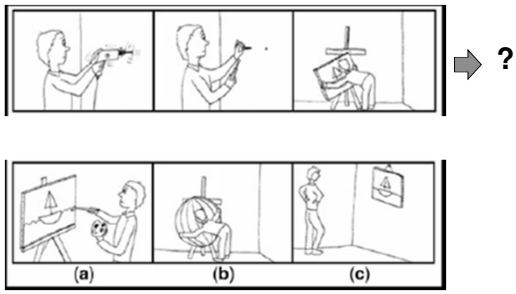

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Department of Psychology, University of Alabama at Birmingham, Birmingham, AL 35294-0021, USA

In typically developing controls, Theory of Mind tasks activated the Medial Prefrontal Cortex (MPFC) and the posterior superior temporal sulcus (pSTS) at the Tempero-Parietal Junction (TPJ), as well as the portions of the Mirror Neuron System (ventral premotor region).

In subjects with ASD, there was decreased activation of the Mirror Neuron System, and decreased connectivity between Medial Prefrontal Cortex (MPFC) and Tempero-Parietal Junction (TPJ)

doi:10.1093/scan/nss106 SCAN (2014) 9, 98–105

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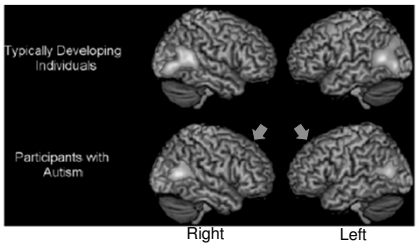

Fig. 2 Within-group brain activation patterns for the contrast intentional causality > physical causality in three different groups. Recruitment of posterior superior temporal sulci and TPJ in all participant groups. In addition, while the whole group and control participants recruited ventral premotor regions, it is missing in the autism group ($P < 0.001$ uncorrected; $k = 80$ voxels).

doi:10.1093/scan/nss106 SCAN (2014) 9, 98–105

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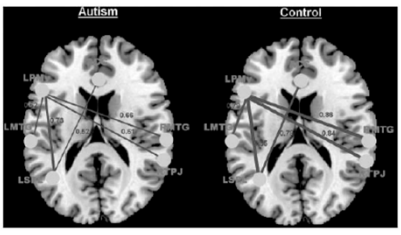

Fig. 3 Significantly weaker functional connectivity in participants with autism, relative to controls, in ToM-related areas and ventral premotor areas during intentional causal attribution.

doi:10.1093/scan/nss106 SCAN (2014) 9, 98–105

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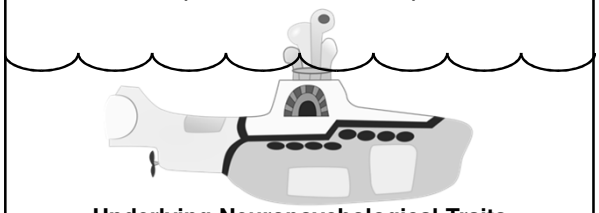
"The simulation theory of mindreading suggests that others' actions are understood by 'putting ourselves in their shoes'. At the neural level, this may be accomplished by a mirror mechanism…. The functional underconnectivity found in participants with ASD between the mirroring and mentalizing systems may be vital in understanding the deficits in social cognition in autism at the neural level."

Visible features
(DSM, IDEA, ICD, etc.)



Underlying Neuropsychological Traits

- ↓ Central Coherence
- ↓ Theory of Mind

⇨ Psychosis / SCZ ?

- Cognitive Rigidity
- Impaired regulation of arousal & mood
- Impaired mirror neuron function

"Is Schizophrenia on the Autism Spectrum?"

King & Lord, 2011

- **"Schizotypal Personality" is distinguished by "unusual preoccupations, unusual perceptual experiences, odd thinking and speech (e.g., overelaborate, or stereotyped), inappropriate or constricted affect, behavior or appearance that is odd, eccentric, or peculiar; lack of close friends or confidants other than first-degree relatives, and social anxiety…"**

"Is Schizophrenia on the Autism Spectrum?"

King & Lord, 2011

- **"What arguably distinguishes schizophrenia spectrum from autism spectrum in two individuals who otherwise share all of these symptoms is the presence of paranoid ideation…**

"Is Schizophrenia on the Autism Spectrum?"

King & Lord, 2011

- **"Given the degree of overlap [of symptoms], one might reasonably ask if paranoid thinking could be a logical downstream consequence of a common underlying difficulty in the perception of social communication"**

What's happening in this picture?

What's happening in this picture?

Two strangers got into the house and are handing out newspapers.

What's happening in this picture?

"They are stealing the children."

Possible Relationship Between ASD and SCZ

How would your behavior change, if you suddenly lost Theory of Mind and Central Coherence?

Primary failure to develop ToM & CC → ***Autism Spectrum Disorder***

Loss of previously acquired ToM & CC → ***Schizophrenia Spectrum Disorder***

BIRTH — **ADOLESCENCE**

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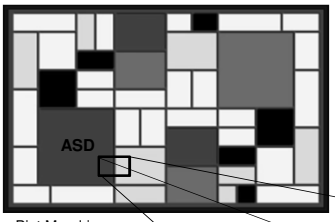
Psychatric Symptoms in ASD: Paradigm Shift

- **Not "Comorbidity," but**
- **Continuum, and**
- **Metamorphosis**

Not this…..



Piet Mondrian
Line over Form

Comorbidity

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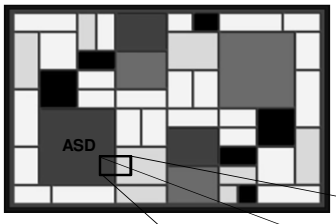
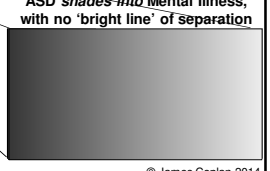
but this…..



Continuum:
ASD *shades into* Mental Illness, with no 'bright line' of separation



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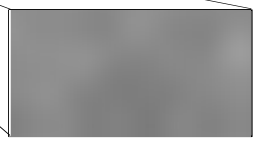
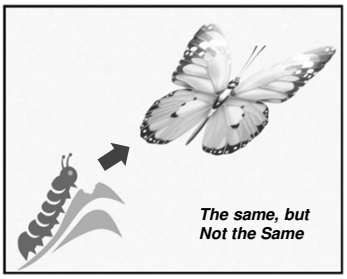
Claude Monet
Water Lillies

Continuum



Not Piet Mondrian, but Claude Monet…

and this…



Metamorphosis:

Over time, symptoms of ASD *evolve into, or are overshadowed by,* symptoms of Mental Illness.

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In the world of Metamorphosis…

"Losing the diagnosis" does not mean "cured"

- **Persistence of**
  - **Cognitive patterns**
  - **Behavioral patterns**
  - **Emotional patterns**
- **Emergence of Non-ASD psychiatric disorders**
  - **Anxiety**
  - **Depression**
  - **Mood Disorders**
  - **Schizophrenia**

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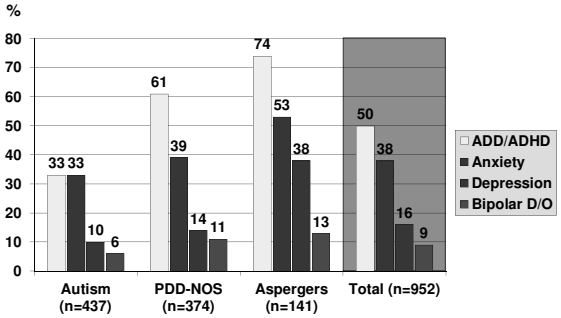
Children with ASDs, age 10+: Neuropsychiatric Co-Morbidity



IAN Research Report #1 - May 2007
http://www.iancommunity.org/cs/ian_research_reports

Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample

Simonoff, E., et al. J Am Acad Child & Adolescent Psychiatry, 2008. 47(8):921-929

- **112 children with ASD, age 10-14**
  - **Assessed using the parent-report Strengths and Difficulties Questionnaire (SDQ)**
  - **70% had at least one comorbid disorder**
  - **41% had two or more**

Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample

Simonoff, E., et al. J Am Acad Child & Adolescent Psychiatry, 2008. 47(8):921-929

Disorder	Prevalence (%)
Anxiety Disorder (any)	41.9
• *Social anxiety disorder*	• 29.2
• *Generalized anxiety disorder*	• 13.4
• *Panic disorder*	• 10.1
• *Simple phobia*	• 8.5
• *Obsessive-compulsive disorder*	• 8.2
• *Agoraphobia*	• 7.9
• *Separation anxiety disorder*	• 0.5
Any depressive disorder *	1.4
ODD or Conduct Disorder	30.0
ADHD	28.2
Other disorders	24.7
• *Enuresis, Encopresis*	• 11.0, 6.6
• *Tic D/O, Tourette syndrome*	• 9.0, 4.8
• *Trichotillomania*	• 3.9
Any comorbid disorder	**70%**

*An additional 10.9% had irritability / depression not meeting DSM criteria

Psychiatric Symptom Impairment in Children with Autism Spectrum Disorders

Kaat, A.J., et al. Journal of Abnormal Child Psychology, 2013

- **115 pts w. ASD at University Hosp. Child Devel. Clinic**
  - **Age 6–12 yr; Male : 86 %; White: 91 %**
  - **Mean IQ : 85**
    - **≥70: 91 (77%)**
    - **<70: 24 (23 %)**
  - **Spectrum Dx:**
    - **Autistic Disorder: 31 %**
    - **Asperger's Disorder: 19 %**
    - **PDD-NOS: 50%**
- **Child and Adolescent Symptom Inventory-4R**
  - **Parent & teacher ratings**

Psychiatric Symptom Impairment in Children with Autism Spectrum Disorders

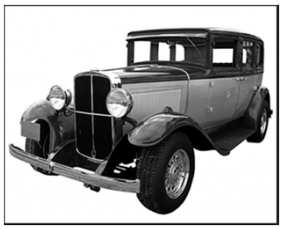
Kaat, A.J., et al. Journal of Abnormal Child Psychology, 2013

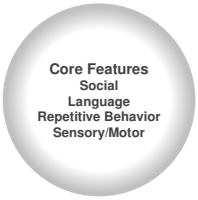
Disorder	Prevalence (%)*	
	Impairment**	DSM-IV criteria
ADHD (any type)	83%	82%
Oppositional defiant disorder	53%	34%
Conduct disorder	23%	9%
Anxiety disorders	70%	47%
• *Generalized anxiety disorder*	• *48%*	• *32%*
• *Social phobia*	• *51%*	• *23%*
Major Depressive D/O, Dysthymia	45%	19%
Manic episode	53%	18%
Schizophrenia	48%	10%
Any disorder	94%	84%

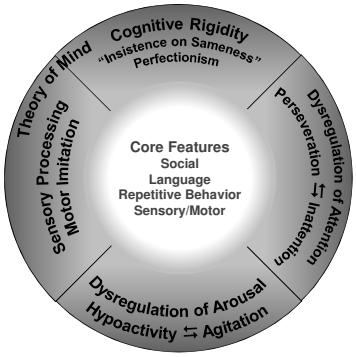
* Combined Parent & Teacher ratings
** "Impairment" = Symptoms "Often or Very Often"

Question

- **When comorbidity approaches 100%, is it really "co" morbidity, or is it part of the base package (pleiotropy)?**







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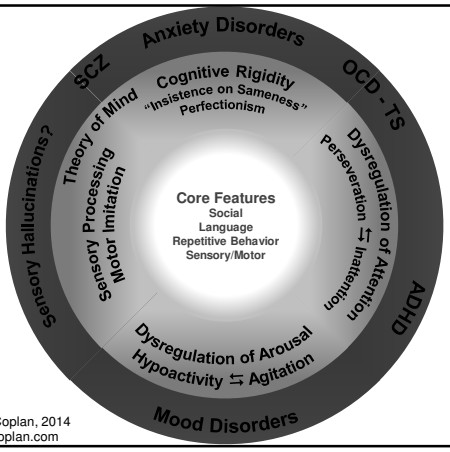

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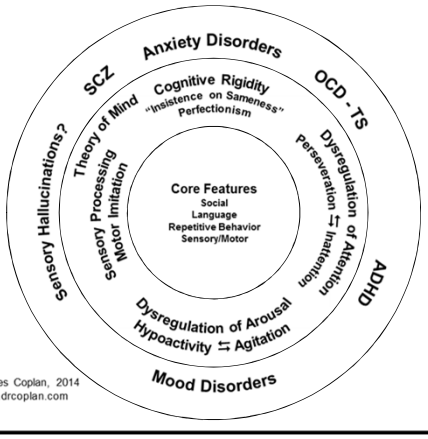

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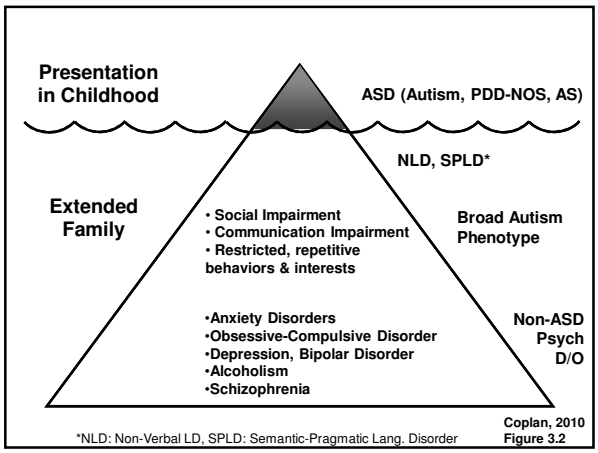
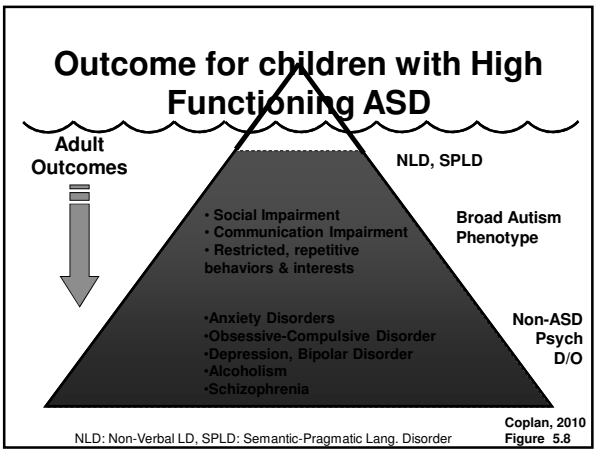
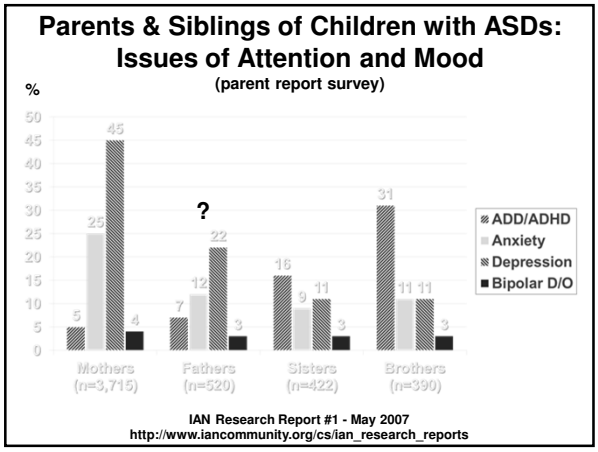
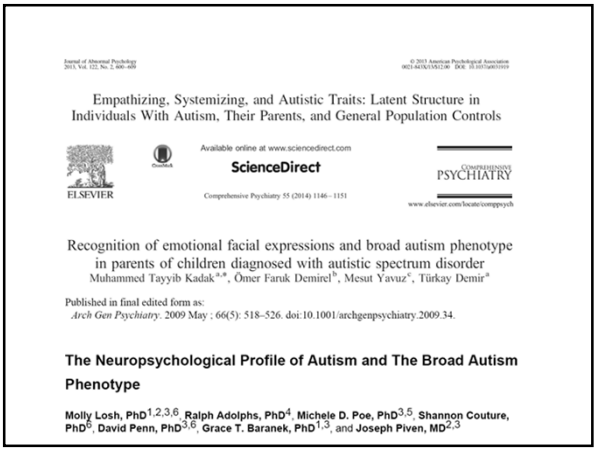







Empathizing, Systemizing, and Autistic Traits: Latent Structure in Individuals With Autism, Their Parents, and General Population Controls

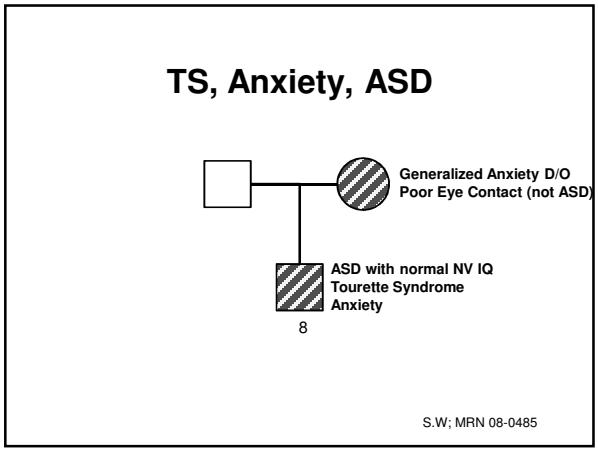
Recognition of emotional facial expressions and broad autism phenotype in parents of children diagnosed with autistic spectrum disorder

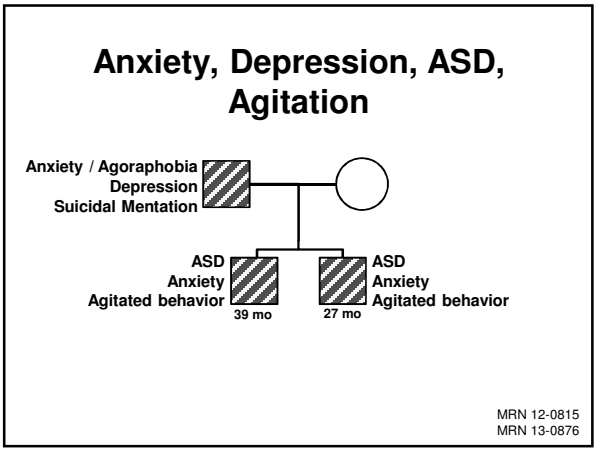
Muhammed Tayyib Kadak, Ömer Faruk Demirel, Mesut Yavuz, Türkay Demir

Published in final edited form as:
Arch Gen Psychiatry. 2009 May ; 66(5): 518–526. doi:10.1001/archgenpsychiatry.2009.34.

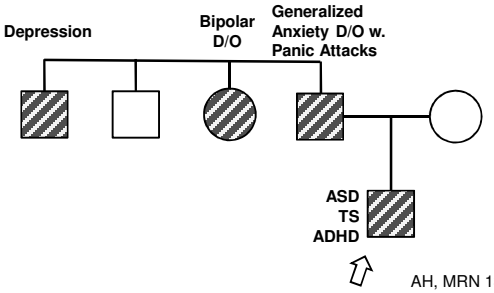
The Neuropsychological Profile of Autism and The Broad Autism Phenotype

Molly Losh, PhD, Ralph Adolphs, PhD, Michele D. Poe, PhD, Shannon Couture, PhD, David Penn, PhD, Grace T. Baranek, PhD, and Joseph Piven, MD

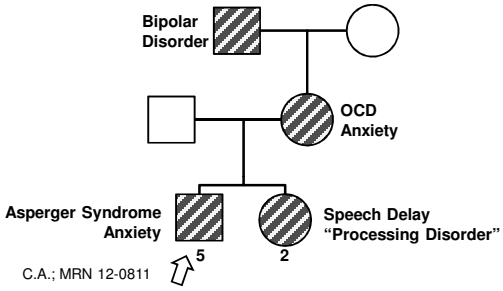




TS, Anxiety, Depression, Bipolar D/O, ASD, ADHD



BPD, OCD, Anxiety, AS



Bullying Experiences Among Children and Youth with Autism Spectrum Disorders.
Cappadocia, M.C., J.A. Weiss, and D. Pepler, JADD, 2011

Subjects

- **192 children / young adults w. ASD age 5–21**
  - **HFA (14%)**
  - **AS (54%)**
  - **PDD-NOS (13%)**
  - **Autism (19%)**

Results

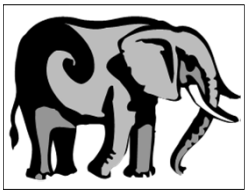
- **Bullied (physical, verbal, social, cyber) within the past month: 77%**
  - **1 time: 11%; 2-3 times: 23%; ≥ 4 times: 43%**

Cappadocia, M.C., J.A. Weiss, and D. Pepler, *Bullying Experiences Among Children and Youth with Autism Spectrum Disorders.* JADD, 2011

Risk factors for being bullied	*p**
Child - Gender	NS
Child - Age (being younger)	< .05
Child - Social skills deficit	NS
Child - Communication difficulties	< .05
Child - Internalizing mental health problems	< .001
Child - Externalizing mental health problems	NS
Parent - Mental health problems	< .01
Child - Fewer friends at school	< .05

***Smaller p = less likely to occur by chance.**
NS = Not statistically significant.

The Real Elephant in the Room



Child w. ASD (± MH D/O) + Parent w. MH D/O =

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Other factors to be considered

- **Prenatal**
  - **Maternal infection / inflammation**
  - **Other teratogens?**
- **Perinatal**
  - **Hazards of premature birth**
- **Postnatal?**
  - **No clear evidence**

Molecular Psychiatry (2014) 19, 259–264
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www.nature.com/mp

ORIGINAL ARTICLE

Elevated maternal C-reactive protein*and autism in a national birth cohort

AS Brown[1,2], A Sourander[1,3,4], S Hinkka-Yli-Salomäki[3,4], IW McKeague[5], J Sundvall[6] and H-M Surcel[7]

- **Finnish Prenatal Study of Autism: case-control design**
  - **Children with ASD (National Register): 1132 born between 1987-2003. 677 were enrolled**
  - **677 non-ASD controls**
- **Banked 1st or 2nd trimester maternal CRP levels**

* C-Reactive Protein (CRP): Elevated in inflammation / infection

Elevated maternal C-reactive protein and autism in a national birth cohort

AS Brown[1,2], A Sourander[1,3,4], S Hinkka-Yli-Salomäki[3,4], IW McKeague[5], J Sundvall[6] and H-M Surcel[7]

*

Table 3. Maternal early gestational C-reactive protein (CRP) levels by decile in childhood autism cases and matched controls

CRP by decile (%) [Range (mg dl^{-1})]	Cases, N (%)	Controls, N (%)	OR (95% CI)	P
⩽10 (0.10–0.57)	45 (6.5)	71 (10.5)	1	NA
11–20 (0.58–0.92)	74 (10.9)	66 (9.7)	1.76 (1.06–2.92)	0.03
21–30 (0.93–1.31)	51 (7.5)	68 (10.0)	1.15 (0.70–1.89)	0.58
31–40 (1.32–1.77)	61 (9.0)	66 (9.7)	1.51 (0.89–2.57)	0.13
41–50 (1.78–2.42)	69 (10.2)	69 (10.2)	1.62 (0.98–2.66)	0.06
51–60 (2.43–3.18)	73 (10.8)	68 (10.0)	1.68 (1.02–2.78)	0.04
61–70 (3.19–4.33)	80 (11.8)	66 (9.7)	1.92 (1.17–3.14)	0.01
71–80 (4.34–5.83)	60 (8.9)	69 (10.2)	1.37 (0.83–2.26)	0.22
81–90 (5.84–9.54)	89 (13.1)	67 (9.9)	2.08 (1.28–3.40)	0.003
91–100 (9.55–88.90)	75 (11.1)	67 (9.9)	1.80 (1.09–2.97)	0.02

Abbreviations: CRP, C-reactive protein; CI, confidence interval; OR, odds ratio.

"Cases" were 1.8 to 2x more likely than non-ASD controls to have been exposed to CRP levels >80

Journal of Neuroimmunology 272 (2014) 94–98

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short communication

Systemic auto-antibodies in children with autism ☆,☆☆,★

Gehan A. Mostafa [a,b,*], Dalia F. El-Sherif[a], Laila Y. Al-Ayadhi[b]

[a] Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[b] Autism Research and Treatment Center, Al-Amodi Autism Research Chair, Department of Physiology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia

- **Cases: 100 children with autism (74 male; age 4-11)**
- **Controls: 100 age- and sex-matched apparently healthy children**
- **Seropositivity of Anti-nuclear antibodies (ANA)**
  - **Children with ASD: 25%**
  - **Children with normaldevelopment: 4%**
- **Significant difference ($p < 0.001$).**

Behavioural Brain Research 266 (2014) 46–51

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Embryonic intraventricular exposure to autism-specific maternal autoantibodies produces alterations in autistic-like stereotypical behaviors in offspring mice

Jasmin Camacho[a,b,1], Karen Jones[c,d,1], Elaine Miller[a,b], Jeanelle Ariza[a,b], Stephen Noctor[c,e], Judy Van de Water[c,d], Verónica Martínez-Cerdeño[a,b,c,*]

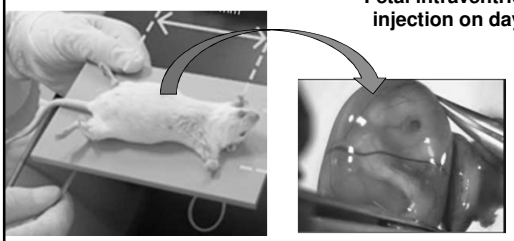
[a] Department of Pathology and Laboratory Medicine, UC Davis, 95817 Sacramento, CA, United States
[b] Institute for Pediatric Regenerative Medicine and Shriners Hospitals for Children Northern California, 95817 Sacramento, CA, United States
[c] M.I.N.D. Institute, UC Davis, 95817 Sacramento, CA, United States
[d] Department of Rheumatology/Allergy and Clinical Immunology, UC Davis, 95616 Davis, CA, United States
[e] Department of Psychiatry and Behavioral Sciences, UC Davis, 95817 Sacramento, CA, United States

Embryonic intraventricular exposure to autism-specific maternal autoantibodies produces alterations in autistic-like stereotypical behaviors in offspring mice

- **Mothers of children with ASD harbor specific antibodies reactive to fetal brain proteins, which are absent in mothers of children w/o ASD**
- **IgG from blood plasma of 2 mothers of children with autistic disorder (MAU) and from 3 mothers of children with typical development (MTD)**
  - **MAU samples possess IgG antibody against 37kDa and 73kDa fetal brain proteins**
  - **MTD samples possess no anti-fetal brain IgG**

Embryonic intraventricular exposure to autism-specific maternal autoantibodies produces alterations in autistic-like stereotypical behaviors in offspring mice

Fetal intraventricular injection on day 14



Embryonic intraventricular exposure to autism-specific maternal autoantibodies produces alterations in autistic-like stereotypical behaviors in offspring mice

Behavioral testing on postnatal day 25

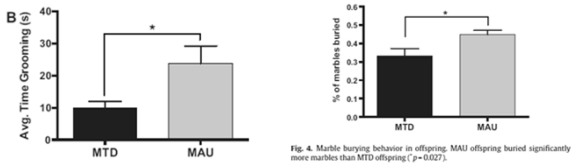


Fig. 4. Marble burying behavior in offspring. MAU offspring buried significantly more marbles than MTD offspring ($^*p = 0.027$).

Time spent grooming (left) and marble-burying (right): Mouse equivalents of human repetitive behavior?

JAMA. 2013 February 13; 309(6): 570–577. doi:10.1001/jama.2012.155925.

ASSOCIATION BETWEEN MATERNAL USE OF FOLIC ACID SUPPLEMENTS AND RISK OF AUTISM IN CHILDREN

Pål Surén, MD, MPH[a,b], Christine Roth, MSc[a,c], Michaeline Bresnahan, PhD[c,d], Margaretha Haugen, PhD[a], Mady Hornig, MD[c], Deborah Hirtz, MD[e], Kari Kveim Lie, MD[a], W. Ian Lipkin, MD[c], Per Magnus, MD, PhD[a], Ted Reichborn-Kjennerud, MD, PhD[a,f], Synnve Schjølberg, MSc[a], George Davey Smith, MD, DSc[g], Anne-Siri Øyen, PhD[a,h], Ezra Susser, MD, DrPH[(*),c,d], and Camilla Stoltenberg, MD, PhD[a,i,(*)]
[a]The Norwegian Institute of Public Health, Oslo, Norway

- **85,176 mother-infant pairs (Norwegian Mother and Child Cohort Study)**
- **Child age range was 3.3–10.2 yr (mean age 6.4 yr)**
- **Exposure of interest: folic acid from 4 weeks before to 8 weeks after the start of pregnancy**

JAMA. 2013 February 13; 309(6): 570–577. doi:10.1001/jama.2012.155925.

ASSOCIATION BETWEEN MATERNAL USE OF FOLIC ACID SUPPLEMENTS AND RISK OF AUTISM IN CHILDREN

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[a]The Norwegian Institute of Public Health, Oslo, Norway

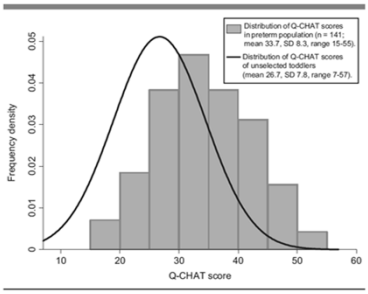
In children whose mothers took folic acid, 0.10% (64/61,042) had autistic disorder, compared with 0.21% (50/24,134) in those unexposed to folic acid. The adjusted ODDS RATIO for autistic disorder in children of folic acid users was 0.61 (95% CI, 0.41–0.90).

ORIGINAL ARTICLES
www.jpeds.com • The Journal of Pediatrics

Evaluation of Early Childhood Social-Communication Difficulties in Children Born Preterm Using the Quantitative Checklist for Autism in Toddlers

Hilary S. Wong, MRCPCH, MSc[1], Angela Huertas-Ceballos, MSc, FRCPCH[2], Frances M. Cowan, PhD, FRCPCH[1], and Neena Modi, MD, FRCPCH[1], on behalf of the Medicines for Neonates Investigator Group*

Subjects:
- **141 infants born < 30 wk; mean age at testing 24 mo**



Wong J Peds 2014

Figure. Histogram of Q-CHAT scores of preterm population with superimposed distribution of published Q-CHAT scores of unselected toddlers.

"The Quantitative Checklist for Autism in Toddlers (Q-CHAT) is a recent revision of the M-CHAT… a parent-completed questionnaire consisting of updated items, with each item having a 5-point rating scale instead of a binary scoring system. Assessments of the test properties and clinical validity of the Q-CHAT are ongoing.

ORIGINAL ARTICLES www.jpeds.com • THE JOURNAL OF PEDIATRICS

J Pediatr 2014;164:20-5

Prevalence and Neonatal Factors Associated with Autism Spectrum Disorders in Preterm Infants

Michael W. Kuzniewicz, MD, MPH[1,2], Soora Wi, MPH[1], Yinge Qian, MS[1], Eileen M. Walsh, RN, MPH[1], Mary Anne Armstrong, MA[1], and Lisa A. Croen, PhD[1]

Retrospective cohort of infants born at ≥24 weeks 1/1/00 – 12/31/07 at 11 Kaiser Permanente Northern California hospitals (n = 195,021). ASD cases were defined by a diagnosis made at a Kaiser Permanente ASD evaluation center, by a clinical specialist, or by a pediatrician ("KP ASD")

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J Pediatr 2014;164:20-5

Prevalence and Neonatal Factors Associated with Autism Spectrum Disorders in Preterm Infants

Michael W. Kuzniewicz, MD, MPH[1,2], Soora Wi, MPH[1], Yinge Qian, MS[1], Eileen M. Walsh, RN, MPH[1], Mary Anne Armstrong, MA[1], and Lisa A. Croen, PhD[1]

- **Prevalence of ASD in infants <37 weeks was 1.78%, *vs* 1.22% in infants born ≥37 weeks (P < .001)**
- **Adjusted Hazard Ratio (HR) for a Dx of ASD *vs* ≥37 wk:**
  - **34-36 wk: adjusted HR 1.3 (95%CI 1.1-1.4)**
  - **27-33 wk: adjusted HR 1.4 (95% CI 1.1-1.8)**
  - **24-26 wk: adjusted HR 2.7 (95% CI 1.5-5.0)**
- **High frequency ventilation and intracranial hemorrhage**
- **were associated with ASD among infants <34 weeks**

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J Pediatr 2014;164:20-5

Prevalence and Neonatal Factors Associated with Autism Spectrum Disorders in Preterm Infants

Michael W. Kuzniewicz, MD, MPH[1,2], Soora Wi, MPH[1], Yinge Qian, MS[1], Eileen M. Walsh, RN, MPH[1], Mary Anne Armstrong, MA[1], and Lisa A. Croen, PhD[1]

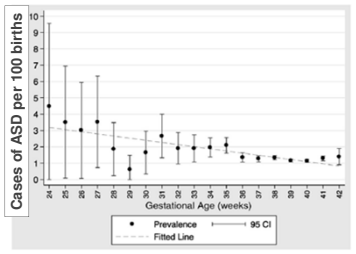

Figure. Prevalence of KP ASD by gestational age.

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J Pediatr 2014;164:20-5

Prevalence and Neonatal Factors Associated with Autism Spectrum Disorders in Preterm Infants

Table III. Association between KP ASD and neonatal risk factors in infants <34 wk gestational age, KPNC births from 2000-2007

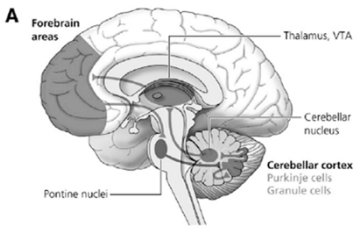
Variable	KP ASD	No ASD	HR*	95% CI
NEC	0%†	1.4%	n/a	-
Bacteremia	14%	7%	1.6	0.8-3.4
Inotropic support	21%	13%	1.4	0.7-2.8
Transfusion	38%	27%	1.4	0.7-2.7
Mechanical ventilation	49%	41%	1.2	0.7-2.0
High frequency ventilation	19%	7%	2.2	1.1-4.6
ICH				
None or U/S not done	71%	86%	Reference	
Grade 1/2	21%	12%	1.9	1.1-3.4
Grade 3/4	8%	2%	3.4	1.4-8.6
Cystic PVL	1%	1%	1.7	0.2-12.4
Delivery room: epinephrine or chest compressions	5%	4%	1.1	0.4-3.1

NEC, necrotizing enterocolitis; *PVL*, periventricular leukomalacia.
*Adjusted for gestational age (continuous), sex, maternal age (continuous), maternal education (categorical), SGA.
†Column percentages.

CellPress Neuron Perspective

The Cerebellum, Sensitive Periods, and Autism

Samuel S.-H. Wang,[1,*] Alexander D. Kloth,[1] and Aleksandra Badura[1]
[1]Princeton Neuroscience Institute and Department of Molecular Biology, Princeton University, Princeton, NJ 08544, USA
*Correspondence: sswang@princeton.edu



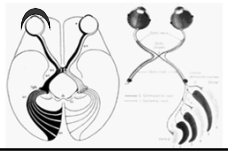
The Cerebellum, Sensitive Periods, and Autism

Samuel S.-H. Wang,[1,*] Alexander D. Kloth,[1] and Aleksandra Badura[1]
[1]Princeton Neuroscience Institute and Department of Molecular Biology, Princeton University, Princeton, NJ 08544, USA
*Correspondence: sswang@princeton.edu

- **In addition to its role in the mature brain, the cerebellum acts in early life to shape the function of other brain regions, especially those relating to cognition and affect**
- **We propose that the cerebellum takes an early role in processing external sensory and internally generated information to influence neocortical circuit refinement during developmental sensitive periods.**
- **As part of this framework, we propose that cerebellar dysfunction may disrupt the maturation of distant neocortical circuits ("developmental diaschisis")**

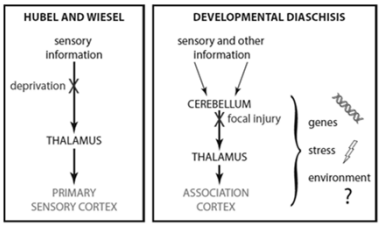
Diaschisis

- **Injury to one part of the brain produces remote / delayed effects**
  - **Ex: Occlusion of one eye during infancy → die-off of target neurons in the lateral geniculate**



The Cerebellum, Sensitive Periods, and Autism

Samuel S.-H. Wang,[1,*] Alexander D. Kloth,[1] and Aleksandra Badura[1]
[1]Princeton Neuroscience Institute and Department of Molecular Biology, Princeton University, Princeton, NJ 08544, USA
*Correspondence: sswang@princeton.edu



TSC1, Fra-X, MECP2, many others

Maternal Infection / Immune response
Stress hormones

Perinatal cerebellar injury
Surgical lesions

Figure 2. A Developmental Diaschisis Model for Neurodevelopmental Disorders
Left: a diagram of activity-dependent influences on neural circuit refinement in primary sensory neocortex during sensitive periods of development, as articulated by Hubel and Wiesel. Right: a proposed generalization for the influence of cerebellar processing of multisensory information on neocortical areas essential for social and cognitive processing.

Vaccine 32 (2014) 3623–3629
Contents lists available at ScienceDirect
Vaccine
journal homepage: www.elsevier.com/locate/vaccine

Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies

Luke E. Taylor, Amy L. Swerdfeger, Guy D. Eslick*

- **All retrospective and prospective cohort studies and case-control studies published in any language looking at the relationship between vaccination and disorders on the autistic spectrum.**
- **A systematic search of the databases Medline (from 1950), PubMed (from 1946), Embase (from 1949), and GoogleScholar (from 1990) through to April 2014, to identify relevant articles**

Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies

Luke E. Taylor, Amy L. Swerdfeger, Guy D. Eslick*

Vaccine 2014

- **Five retrospective cohort studies (1,256,407 children)**
  - **Combining the data for a summary odds ratio found no increased risk of developing autism or ASD following MMR, Hg, or thimerosal exposure**
- **Five case-control studies (9,920 children)**
  - **The overall odds ratio for risk of developing autism or ASD following MMR, Hg, or thimerosal exposure was non-significant**

Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies

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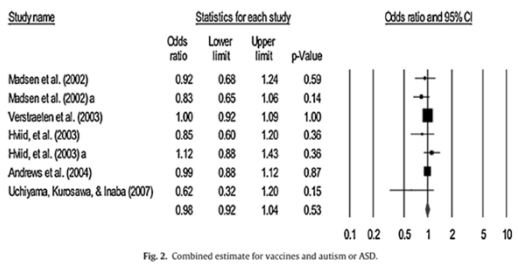

Fig. 2. Combined estimate for vaccines and autism or ASD.

It is better to light one candle than to curse the darkness.

LUNCH !

Outline

- **Patting the elephant**
- **Under the hood**
- **It takes a village**
  - **Treatment:**
    - **Primary prevention** – *Brave new world*?
      - **CNVs – carrier screening for ASD and MH risk**
      - **Pre / Perinatal intervention: Oxytocin and the GABA switch**
    - **Secondary intervention (symptom-oriented)**
      - **Child-Centered**
        - **At home: Self-esteem; knowledge is power**
        - **Mental Health services & Psychopharmacology**
      - **Parent and Family Centered: Nature *and* Nurture**
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      - **ASD and MH communities need to unite**
      - **Reunify behaviorism, classical psychology, neuropsychology, & psychiatry**

Risk Reduction & Primary Prevention

- **Fetal sexing?**
- **CNV screening; then what?**
- **Oxytocin and the GABA switch**

J Autism Dev Disord (2014) 44:521–531
DOI 10.1007/s10803-013-1899-3

ORIGINAL PAPER

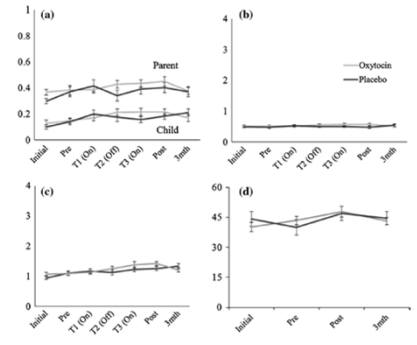
Nasal Oxytocin for Social Deficits in Childhood Autism: A Randomized Controlled Trial

Mark R. Dadds · Elayne MacDonald · Avril Cauchi · Katrina Williams · Florence Levy · John Brennan

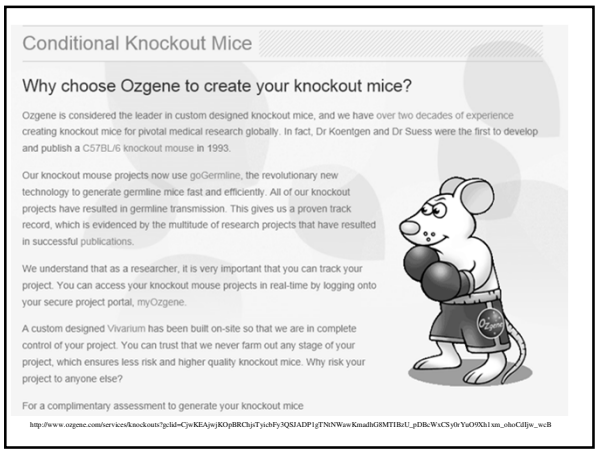
These results show no benefit of oxytocin for young individuals with ASDs, and suggest some caution in recommending nasal oxytocin as a general treatment for young people with autism

Nasal Oxytocin for Social Deficits in Childhood Autism: A Randomized Controlled Trial

- **54 male children recruited between January 2010 and January 2012 (mean age = 11 yr, range 7-16 yr). All met DSM-IV criteria for Autistic disorder, Asperger's disorder or PDD-NOS. Exluded: 16; studied: 38**
- **Comorbid diagnoses: ADHD (20); 13 had a diagnosis of Oppositional Defiant Disorder (13), anxiety disorders (6).**
- **Psychotropic medication for ≥ 8 wk: 17**
- **Exclusion criteria: Female gender, allergy to preservatives, major comorbid illness (e.g. epilepsy, heart disease)**



Oxytocin and placebo group means: (a) eye contact, (b) child verbal content, (c) nonverbal behaviours, (d) global parent ratings on the Social Skills Rating Scale



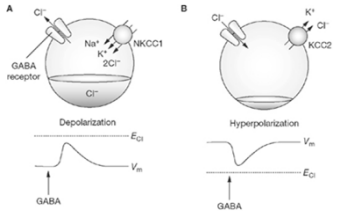
Sci Transl Med. 2015 Jan 21;7(271):271ra8. doi: 10.1126/scitranslmed.3010257.

Exogenous and evoked oxytocin restores social behavior in the Cntnap2 mouse model of autism.

Peñagarikano O[1], Lázaro MT[2], Lu XH[3], Gordon A[4], Dong H[2], Lam HA[5], Peles E[4], Maidment NT[5], Murphy NP[5], Yang XW[3], Golshani P[6], Geschwind DH[7].

- **Knockout mouse homolog of CNTNAP2 (contactin-associated protein-like 2)**
  - **Decrease in the number of oxytocin immunoreactive neurons in the paraventricular nucleus (PVN) of the hypothalamus in mutant mice, decrease in brain oxytocin levels, and abnormal social behavior**
- **Administration of a selective melanocortin receptor 4 agonist caused endogenous oxytocin release and acutely rescued the social deficits, an effect blocked by an oxytocin antagonist.**

The GABA Switch



Oxytocin Surge (Birth)

Excitatory (depolarization) ⇨ **Inhibitory (hyperpolarization)**

446 • The Journal of Neuroscience, January 8, 2014 • 34(2):446 – 450

The Developmental Switch in GABA Polarity Is Delayed in Fragile X Mice

Qionger He,[1] Toshihiro Nomura,[1,2] Jian Xu,[1] and Anis Contractor[1,3]
[1]Department of Physiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611, [2]Department of Pediatrics and Department of Physiology, School of Medicine, Keio University, Shinjuku-ku, Tokyo 160-8582, and [3]Department of Neurobiology, Weinberg College of Arts and Sciences, Northwestern University, Evanston, Illinois 60208

The GABA Switch

Fra-X & Valproic Acid (VPA) rodent models: do not respond to OXT surge, but can be "rescued" with maternal prepartum treatment

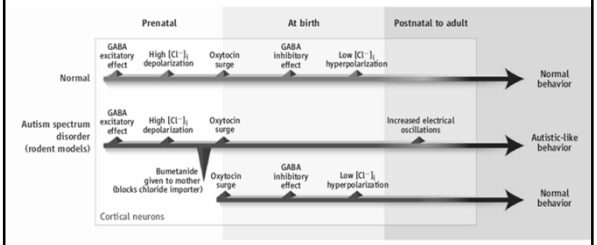
Oxytocin Surge (Birth)

Excitatory (depolarization) ⇨ **Inhibitory (hyperpolarization)**

Could Autism Be Treated Prenatally?

Treatment of rodent models of autism spectrum disorder with a drug that alters the function of a neurotransmitter ameliorates autistic-like behavior in offspring.

Andrew W. Zimmerman[1] and Susan L. Connors[2]



Treat and switch. The switch from excitatory to inhibitory GABAergic signaling in rodent cortical neurons is mediated by oxytocin during the transition from prenatal to postnatal life. In rodent models of ASD (the FRX mouse and VPA rat), the normal shift from high to low intracellular chloride concentration does not take place but can be restored to normal in both cases by prenatal maternal oral administration of bumetanide.

7 FEBRUARY 2014 VOL 343 SCIENCE www.sciencemag.org
Published by AAAS

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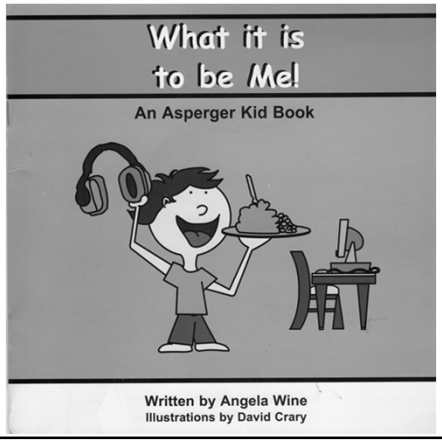
Self-Awareness

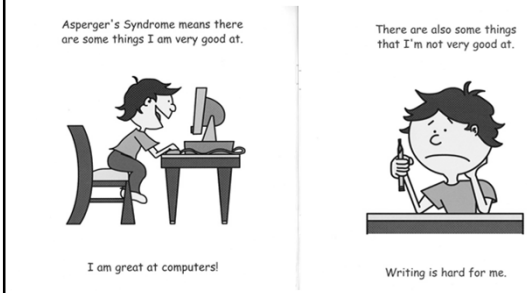
- **Knowledge is Power**
  Sir Francis Bacon

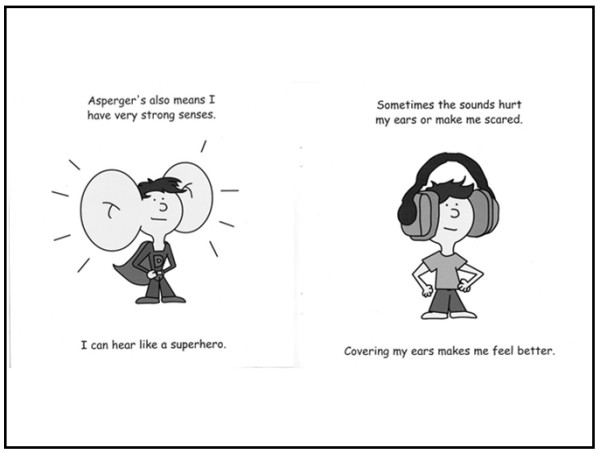
Self-Awareness

Know your enemy and know yourself, and in 100 battles you will never be defeated

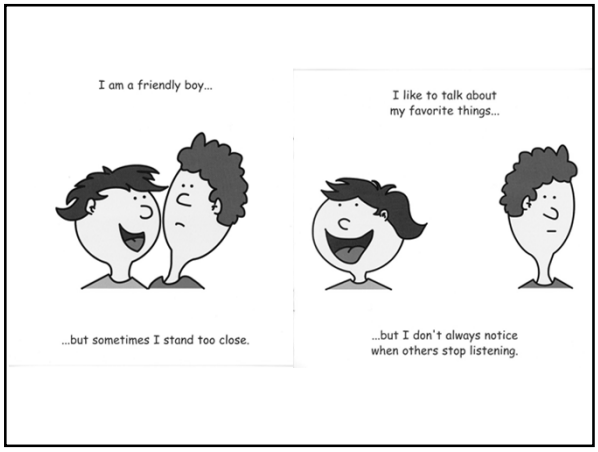
The Art of War
Sun Tsu

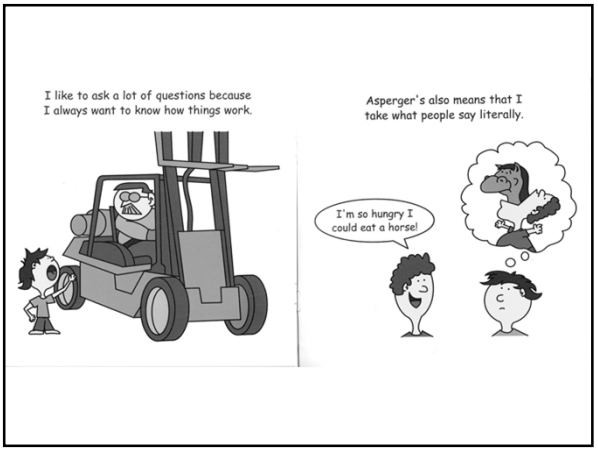


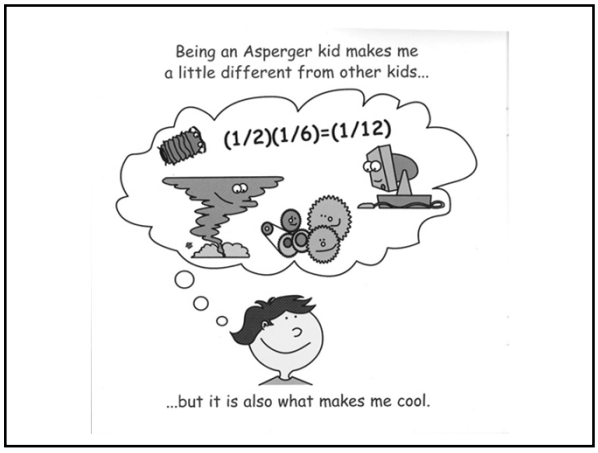


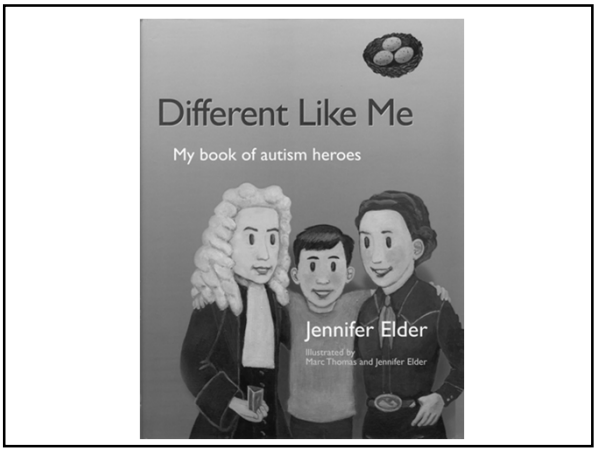

Asperger's also means I have very strong senses.
I can hear like a superhero.
Sometimes the sounds hurt my ears or make me scared.
Covering my ears makes me feel better.


My tastes are powerful.
I always know when Mommy tries to sneak different stuff into my food.
Sometimes I don't want to be touched.
Sometimes I like to be wrapped up tight.


I am a friendly boy...
...but sometimes I stand too close.
I like to talk about my favorite things...
...but I don't always notice when others stop listening.


I like to ask a lot of questions because I always want to know how things work.
Asperger's also means that I take what people say literally.
I'm so hungry I could eat a horse!


Being an Asperger kid makes me a little different from other kids...
(1/2)(1/6)=(1/12)
...but it is also what makes me cool.


Different Like Me
My book of autism heroes
Jennifer Elder
Illustrated by Marc Thomas and Jennifer Elder

About Me

Hello! My name is Quinn. I'm eight and three-quarters years old. My favorite things are baseball, dolphins, and ancient Egypt. Oh yeah, and I'm autistic. Sometimes I don't understand people, and sometimes they don't understand me. Little things get on my nerves, like too many people talking at once. It can be hard to fit in. But when the other kids see how good I am at drawing, they are interested. This is how I make my place in the world. I just concentrate on what I do best.

Albert Einstein

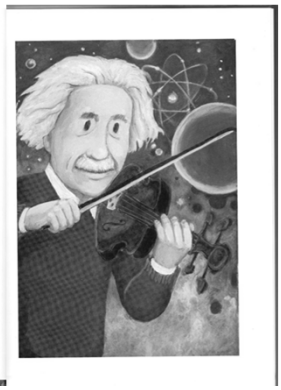
Albert Einstein was not a boy genius—at least, not as far as anyone knew. Most people thought that he wasn't very smart. He didn't talk at all until the age of three, and still didn't speak well when he reached the age of nine. About the only thing he was good at was playing the violin. Albert didn't do well in school, and his teachers were often irritated with him. One school even threw him out. They thought he was hopeless.

They were wrong.

There was something going on inside Albert's head, something wonderful. The first time Albert saw a compass, when he was around age five, he was fascinated. What made the needle move? How did it know which way to point? These questions, along with his love of math, would eventually lead young Albert to the science of physics.

After college, Albert took a job in a patent office. He never stopped thinking about physics, though, and began to write his ideas about time and space. Then, in 1905, he published a paper that shook the world. When people read what he wrote, they were amazed. Some of it was hard to understand; he predicted that time could slow as you approached the speed of light and that space itself could be pulled out of shape. He even showed that anything—a jellybean, a lump of metal, a drop of water—held immense energy inside of it. His ideas took years for other scientists to prove, but one thing was always certain: Einstein's work would change everything. Albert became very famous. He traveled all over, lecturing and teaching—even at the college where he had been a poor student.

Some of Albert's ideas were used to build the atomic bomb, the biggest weapon ever made. This made Albert sad, because he was a pacifist—someone who is against war. He spent the rest of his life trying to convince countries not to use the bomb. For this reason, he is remembered not just as a great scientist, but as a great man as well.



Benjamin Banneker

Benjamin Banneker's grandmother was from England, and his grandfather was from Africa. In the 1700s in America, there were laws against people of different colors getting married. They got married anyway, though, and lived out in the country where nobody would bother them.

The Banneker family farm was far from town, so Benjamin's grandmother taught the children at home. Then, when Benjamin was 12, a school for boys opened nearby. Benjamin was excited about going to school, and he was a brilliant student. In fact, he learned so fast that soon he knew more about math than the teacher did!

When Benjamin was 21, he was given a pocket watch. After taking the watch apart and putting it back together, Benjamin decided to make his own clock out of wood. The wooden clock kept good time for 40 years. It is said to be the first clock made in America.

Later, after reading a book on astronomy, Benjamin built a "work cabin" on his land. Neighbors were used to seeing him lying on his back, looking at the stars. Now he had a skylight to look through and a telescope. He used his math skills to predict many events, including a solar eclipse. Other astronomers thought it would be on a different day, but Benjamin saw that they had made a mistake. The eclipse took place on April 14 1789, just as Benjamin had predicted.

Benjamin loved science and math, but he realized that other things were important, too. The books that he wrote included ideas about peace and freedom. He was proud to be an American, and proud of his African heritage. The fight against slavery was very important to him. Benjamin was a free man, but his father and grandfather had both been slaves. He had learned from them what a terrible thing slavery was. Benjamin even exchanged letters with Thomas Jefferson on the subject, hoping to change the future president's mind.

Today, we know Benjamin Banneker as the first African-American scientist. In his own time, though, he was known by a more colorful name: The Sable Genius.

Julia Bowman Robinson

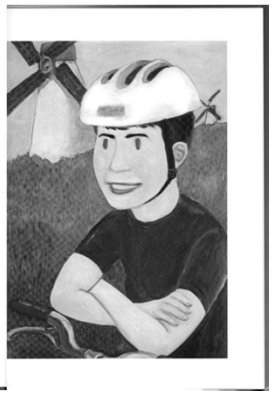
The first thing Julia Bowman could remember doing was sitting on the ground, lining up pebbles. To Julia, they were more than pretty patterns. They were the beginnings of her lifelong love of numbers. Julia was slow to speak and very shy. When she came down with a terrible fever and had to stay home from school, her parents worried that she would fall behind. Instead, over the two years she missed, Julia completed almost four years of class work.

When she went back to school, Julia was the only 12-year-old in the ninth grade. This made her even more timid. She ate lunch in a corner as fast as she could. Then, one day, a girl named Virginia invited Julia to eat lunch with her. Virginia was as good at art as Julia was at math. The two girls became best friends, and Julia came out of her shell. It didn't matter anymore that she was the only girl in her math class, the only girl in physics. Julia didn't pay any attention to what girls were or weren't supposed to do. In the 1930s baseball was for boys, but Julia was an avid fan. She spent all her money on sports magazines, went to baseball games, and kept detailed records of the scores.

In college, Julia took a class in a branch of mathematics called number theory. It was a hard class; by the end of the year there were only four students left. But Julia was hooked. Number theory reminded her of the pebbles from her childhood. She felt that this was what she was always meant to do.

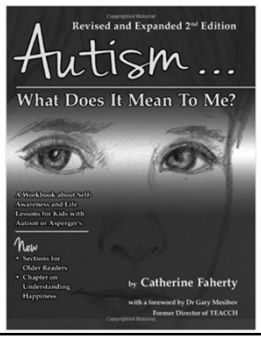
Julia became a very successful mathematician. She worked for large companies and taught college classes. She was honored with many awards. Still, one thing made Julia sad. She loved bicycles, but her childhood illness had left her too weak to ride. Then, when she was 41, Julia had an operation on her heart. After that, she could ride as much as she wanted. Julia was overjoyed. She took long trips across America and Holland. Julia felt free.

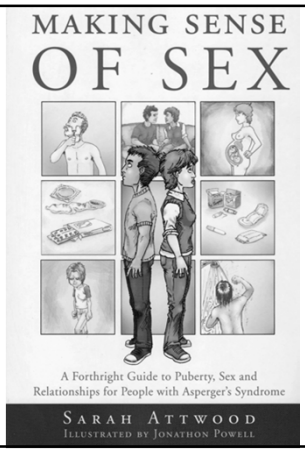
Over the years, there was one math problem Julia could not solve. It was called "Hilbert's Tenth." Of course, nobody else could solve it either, but Julia knew it was possible. Julia thought about it for 20 years. She thought about it while she worked. She thought about it while she rode her bike. She thought about it while she ate her lunch. Julia had solved the whole thing, except for one little piece. Then, one day, she heard that a young man in Russia had found the missing piece. "Hilbert's Tenth" was solved. You might think that after working on the problem for so long, Julia would be upset that she couldn't solve it on her own. But she was happy. Julia said that for all those years, she was just waiting for that young man to grow, so he could help her.



Wow, those people did a lot of great things! And they didn't let anybody else make them feel bad for not fitting in. They just turned what they did best into great art, or great inventions, or important new ideas. I still haven't decided what to do with my life—there's plenty of time for that! But whatever it is, I'm going to do it my own way, just like all the great people before me…only different.

Self-Awareness

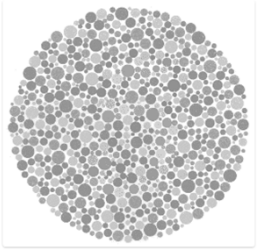




The alternative….

Know what you don't know

Ishihara Color Blindness Test Plate 4



Know what you don't know

- **"I was in High School before I realized that my classmates couldn't do computer assisted design in their head the way I can. But I was also in High School before I realized that they were capable of passing invisible messages back and forth that I can't see." (Paraphrase of Temple Grandin; *Thinking In Pictures*)**

Self-Confidence

$$\text{Self-Confidence} = \sum \left(\begin{array}{l} \text{All the setbacks you survived} + \\ \text{All the hurdles you overcame} \end{array} \right)$$

Mistakes are OK
I made a mistake – I will not die
I can try again
Mistakes are how I learn new things
- ***Michelangelo & the angel***

Self-Confidence

Self-Confidence = $\sum$ (All the setbacks you survived + All the hurdles you overcame)

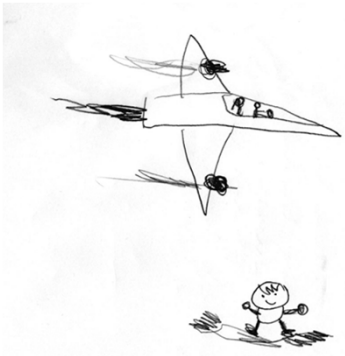
Parents:
It's OK to let my child struggle a little bit.
My job is to set goals so my child can succeed most of the time.
(It's OK if I make a few mistakes too.)

Mistakes are OK
I made a mistake – I will not die
I can try again
Mistakes are how I learn new things
- ***Michelangelo & the angel***

Angel with Candlestick, 1494-95

"I saw the angel in the marble and carved until I set him free." Michelangelo

"Draw a picture of your family, with everybody doing something."



RB

"Draw a picture of your family, with everybody doing something."

MW

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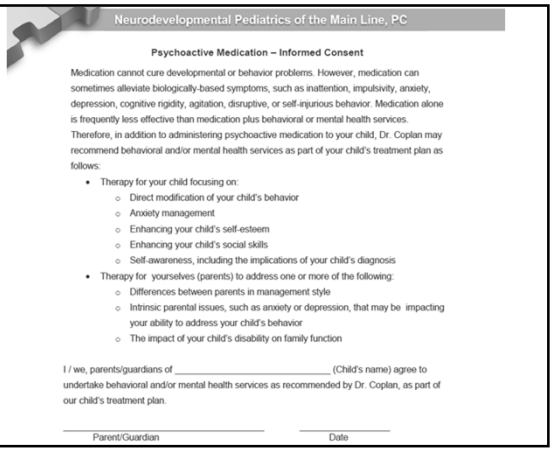


Neurodevelopmental Pediatrics of the Main Line, PC

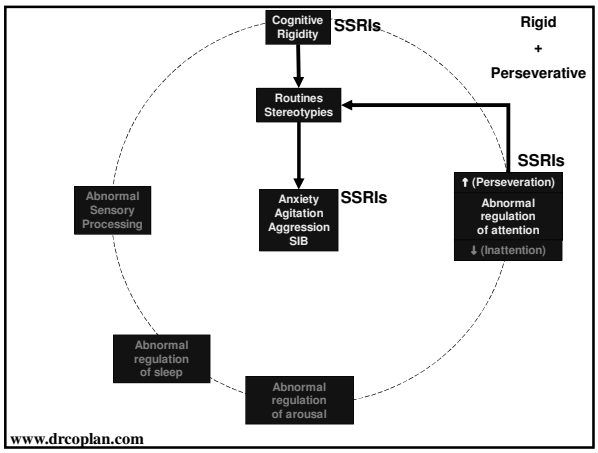
Psychoactive Medication – Informed Consent

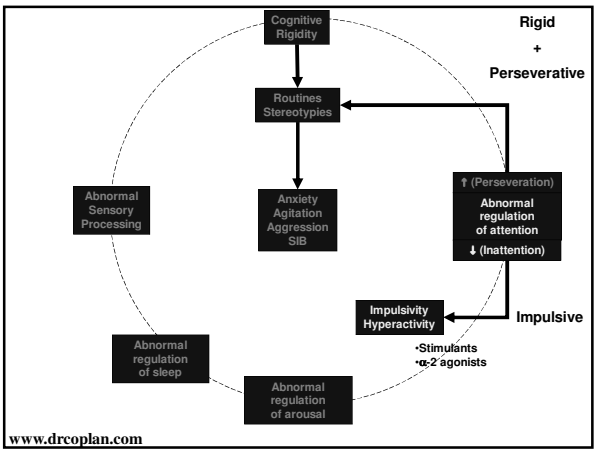
Medication cannot cure developmental or behavior problems. However, medication can sometimes alleviate biologically-based symptoms, such as inattention, impulsivity, anxiety, depression, cognitive rigidity, agitation, disruptive, or self-injurious behavior. Medication alone is frequently less effective than medication plus behavioral or mental health services. Therefore, in addition to administering psychoactive medication to your child, Dr. Coplan may recommend behavioral and/or mental health services as part of your child's treatment plan as follows:

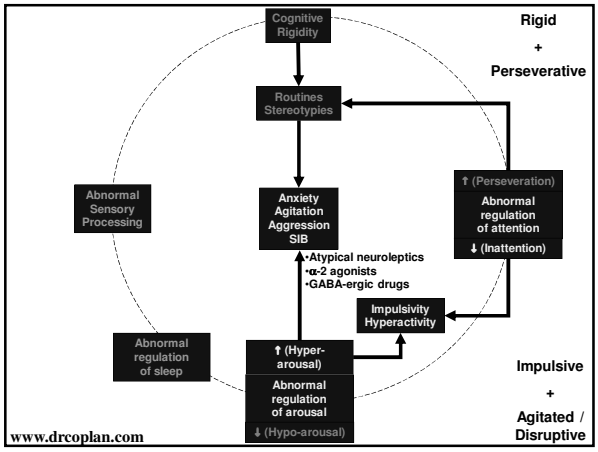
- Therapy for your child focusing on:
  - Direct modification of your child's behavior
  - Anxiety management
  - Enhancing your child's self-esteem
  - Enhancing your child's social skills
  - Self-awareness, including the implications of your child's diagnosis
- Therapy for yourselves (parents) to address one or more of the following:
  - Differences between parents in management style
  - Intrinsic parental issues, such as anxiety or depression, that may be impacting your ability to address your child's behavior
  - The impact of your child's disability on family function

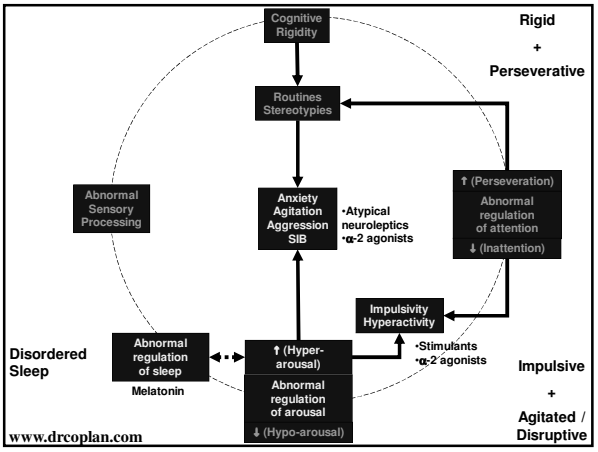
I / we, parents/guardians of _____ (Child's name) agree to undertake behavioral and/or mental health services as recommended by Dr. Coplan, as part of our child's treatment plan.

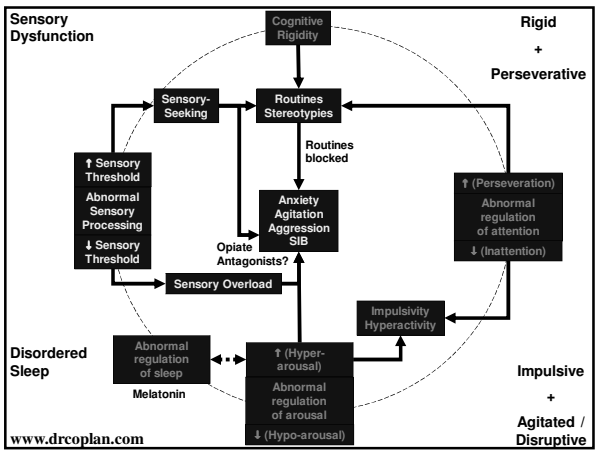
_____ _____
Parent/Guardian Date

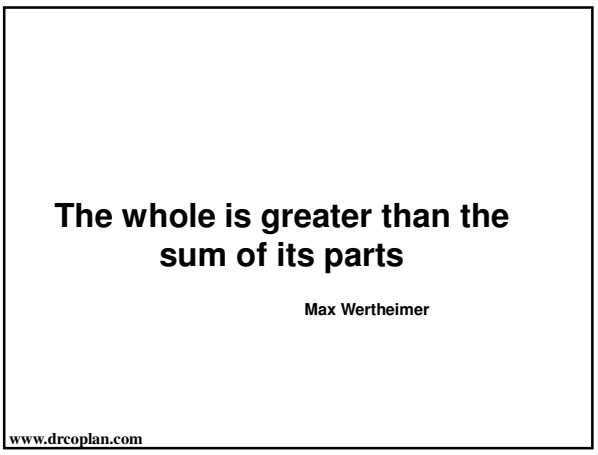

Cognitive Rigidity
SSRIs
Rigid
+
Perseverative
Routines Stereotypies
SSRIs
Abnormal Sensory Processing
Anxiety Agitation Aggression SIB
SSRIs
↑ (Perseveration)
Abnormal regulation of attention
↓ (Inattention)
Abnormal regulation of sleep
Abnormal regulation of arousal
www.drcoplan.com

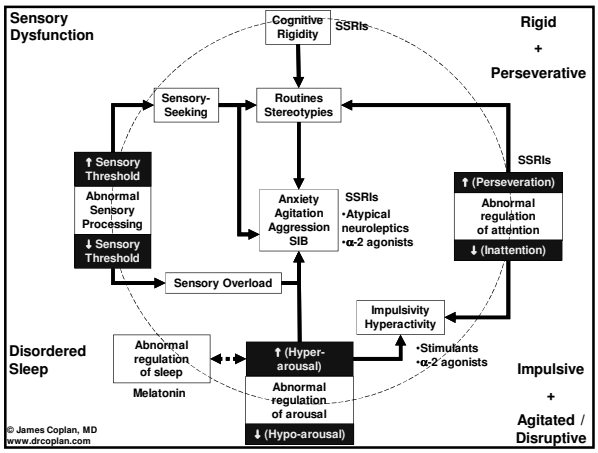

Cognitive Rigidity
Rigid
+
Perseverative
Routines Stereotypies
Abnormal Sensory Processing
Anxiety Agitation Aggression SIB
↑ (Perseveration)
Abnormal regulation of attention
↓ (Inattention)
Impulsivity Hyperactivity
Impulsive
•Stimulants
•α-2 agonists
Abnormal regulation of sleep
Abnormal regulation of arousal
www.drcoplan.com


Cognitive Rigidity
Rigid
+
Perseverative
Routines Stereotypies
Abnormal Sensory Processing
Anxiety Agitation Aggression SIB
•Atypical neuroleptics
•α-2 agonists
•GABA-ergic drugs
↑ (Perseveration)
Abnormal regulation of attention
↓ (Inattention)
Impulsivity Hyperactivity
Abnormal regulation of sleep
↑ (Hyper-arousal)
Abnormal regulation of arousal
↓ (Hypo-arousal)
Impulsive
+
Agitated / Disruptive
www.drcoplan.com


Cognitive Rigidity
Rigid
+
Perseverative
Routines Stereotypies
Abnormal Sensory Processing
Anxiety Agitation Aggression SIB
•Atypical neuroleptics
•α-2 agonists
↑ (Perseveration)
Abnormal regulation of attention
↓ (Inattention)
Impulsivity Hyperactivity
Disordered Sleep
Abnormal regulation of sleep
Melatonin
↑ (Hyper-arousal)
•Stimulants
•α-2 agonists
Abnormal regulation of arousal
↓ (Hypo-arousal)
Impulsive
+
Agitated / Disruptive
www.drcoplan.com


Sensory Dysfunction
Cognitive Rigidity
Rigid
+
Perseverative
Sensory-Seeking
Routines Stereotypies
Routines blocked
↑ Sensory Threshold
Abnormal Sensory Processing
↓ Sensory Threshold
Anxiety Agitation Aggression SIB
Opiate Antagonists?
↑ (Perseveration)
Abnormal regulation of attention
↓ (Inattention)
Sensory Overload
Impulsivity Hyperactivity
Disordered Sleep
Abnormal regulation of sleep
Melatonin
↑ (Hyper-arousal)
Abnormal regulation of arousal
↓ (Hypo-arousal)
Impulsive
+
Agitated / Disruptive
www.drcoplan.com


The whole is greater than the sum of its parts
Max Wertheimer
www.drcoplan.com



Outline

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      - Adult services for "survivors" of childhood autism
      - ASD and MH communities need to unite
      - Reunify behaviorism, classical psychology, neuropsychology, & psychiatry

Family Health

("We give our children roots and wings" – Hodding Carter)

Family Health is a key ingredient in outcome for *all* children, but especially for children with developmental disabilities, who are less able to work around obstacles arising from family dysfunction than children with normal development.

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Signs of Family Health

- **Systemic support for emotional growth of all members as they are able**
- **Flexibility**
  - **Shifting alliances (adults vs. kids, "boys vs. girls," etc.)**
  - **Shifting roles (role of "hero" or "in the doghouse")**
  - **Shifting solutions (one size does not fit all; "equitable" vs. "equal")**
  - **Shifting combinations for activities. All legitimate combinations should come up once in a while.**
- **Sense of humor / playfulness / resiliency**

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Danger Signs

- **Inflexibility**
  - **Fixed roles**
  - **Fixed solutions**
- **Hypervigilance**
  - **Lack of trust in care providers**
- **Social Isolation**

Family Systems Theory

Murray Bowen, 1913-1990

- **"A theory of human behavior that views the family as an emotional unit and uses systems thinking to describe the complex interactions in the unit"**

http://www.thebowencenter.org/

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Family Systems Theory

- Differentiation of Self
- Triangles
- Nuclear Family Emotional System
- Family Projection Process
- Multigenerational Transmission Process
- Emotional Cutoff
- Sibling Position
- Societal Emotional Process

http://www.thebowencenter.org/pages/theory.html

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Family Systems Theory

- "Emotional interdependence presumably evolved to promote the cohesiveness and cooperation families require to protect, shelter, and feed their members"
- People have a 'thinking brain,' language, a complex psychology and culture, but… the emotional system affects most human activity and is the principal driving force in the development of clinical problems."

http://www.thebowencenter.org/pages/theory.html

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Nuclear Family Emotional Systems

- "The basic relationship patterns result in family tensions coming to rest in certain parts of the family
- The more anxiety one person or one relationship absorbs, the less other people must absorb. This means that some family members maintain their functioning at the expense of others."
- Triangles can lead to *dysfunctional* but *stable* interrelationships that work to the detriment of one or more family members

http://www.thebowencenter.org/pages/theory.html

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Where is the problem?

- The person with the identified "problem" may not be the actual source of the difficulty
- The family system itself is often out of balance

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You, Me, and US

I + I = WE
(You & Me) = US

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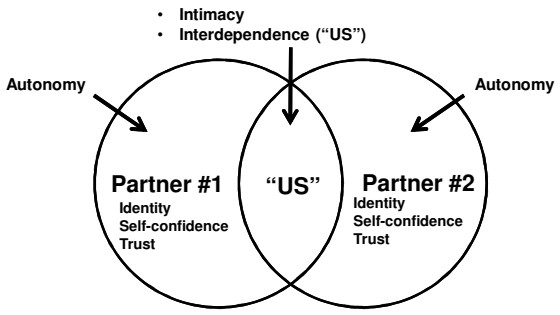

"US" = *The relationship* (ex: " 'US' needs a vacation)

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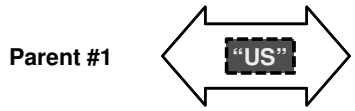
B.C. (Before Children)



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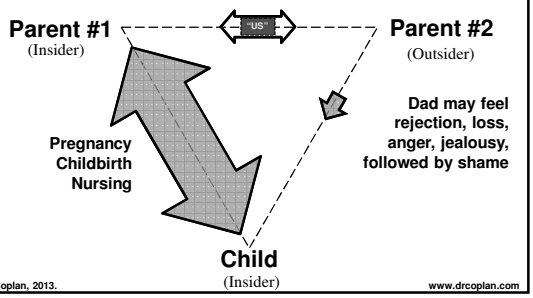
Pregnancy through infancy



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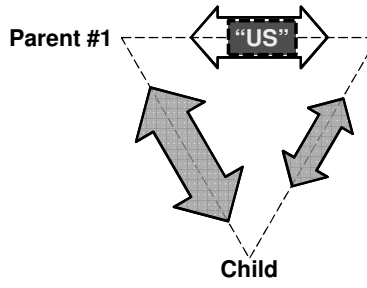
Re-adjustment



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A parent reflects…

"I would compare the experience of having a disabled child to the experience of parenting during the first eight weeks of an infant's life – intense, exhausting, you are always on duty (vigilant). All other aspects of your life fade into the background…. It's that intense, and the difference goes on for years"

Marshak, LE and Prezant, FP:
Married with special needs children
[A couples' guide to keeping connected]
Woodbine House, 2007

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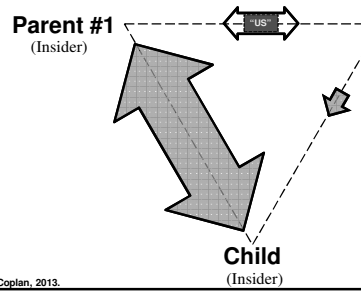
Child with a disability



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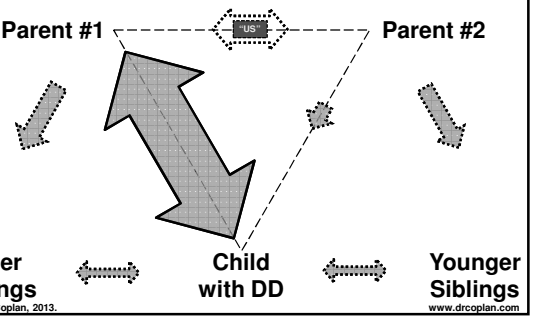
Imbalanced Family System



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Dysfunctional (but common) coping responses

- **Utilitarian Model**
- **Enmeshment**

Marshak, LE and Prezant, FP:
Married with special needs children
Woodbine House, 2007

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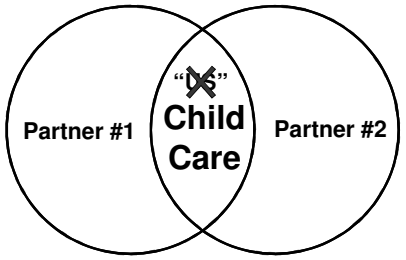
Utilitarian Relationship:

Love Child care is what holds us together



Marshak, LE and Prezant, FP:
Married with special needs children
Woodbine House, 2007

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Utilitarian Relationship

(Child care is what holds us together)

" 'Us' is always at the bottom of the list of things that need to be done."

Mother of an 8 year old boy with severe ASD, ID, and SIB.
Child is in 40 hr/wk home-based therapy program.
Mom has become certified therapy instructor.

DC. MRN 13-0837

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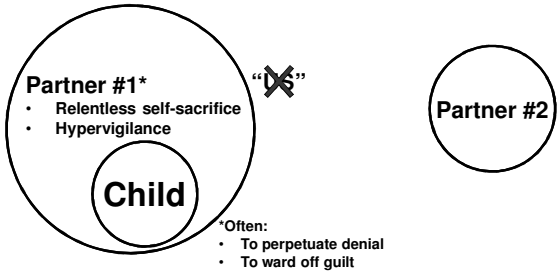
Enmeshment

("My child and I are one.")



***Often:**
- **To perpetuate denial**
- **To ward off guilt**
- **To displace anger or depression**
- **To preserve the illusion of control**
- **May signify pre-existing mental health issues**

www.drcoplan.com

Mother-Son Enmeshment

(data consistent with maternal mental illness)

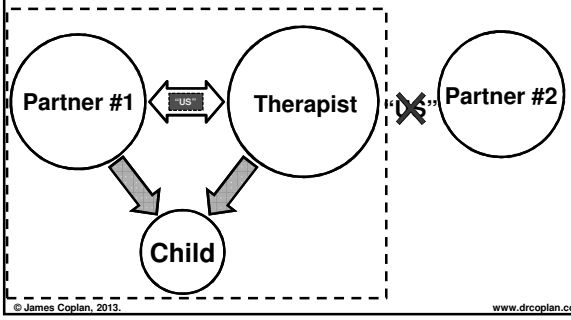
OFFICE OF THE CHILD ADVOCATE STATE OF CONNECTICUT

SHOOTING AT SANDY HOOK ELEMENTARY SCHOOL
REPORT OF THE OFFICE OF THE CHILD ADVOCATE

http://www.ct.gov/oca/lib/oca/sandyhook11212014.pdf

How professionals do unintended harm

(Parent-Therapist bond replaces marital bond)



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"House Rules"

- **Both parents must be present for evaluation & counseling**
- **Exceptions:**
  - **One parent is:**
    - **Incarcerated**
    - **Deceased**
    - **In the armed forces stationed overseas**
    - **Unknown (anonymous sperm/egg donor)**

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My secret weapon

Probe Questions

- **What do you think about *X*?**
- **What do you think about what your partner just said?**
  - **It's OK to comment on what your partner says, but not on your partner directly (no personal attacks)**
- **OR (if partner is absent): If your partner were here, what would he/she have to say?**

My Agendas

- **Both partners need to feel that they have been *listened to* and given a *fair hearing***
  - **Identify areas of consensus and disagreement**
  - **The therapy process becomes the template for future partner-partner interactions (Safe; candid but non-blaming)**
- **"Fixing the problem" is not my goal – at least, not at the beginning**

Vignette #1

- **"*Obedience is very important to me.*"**
  - **Father of 10 y.o. boy with ASD**
    - **Untreated anxiety d/o**
    - **? Personality D/O**
    - **? ASD**
    - **Unsecured assault weapons in the home**
    - **Describes son with ASD as "a predator," because "everything is all about him"**

Vignette #2

- **"*Nobody helps us.*"**
  - **Mother of 14 y.o. boy with ASD**
    - **Mo.: Untreated Anxiety D/O**
    - **Family has no social supports**
    - **Child is on homebound instruction**
    - **Spends hrs/day playing violent video games**
    - **Threatens to "kill" the examiner during evaluation when E. interrupts game play**

Vignette #3: Know what you don't know

- **Sam: 10 year old boy with disruptive behavior and academic underachievement despite being "bright." No prior eval or dx.**
- **My Dx: HFA & Anxiety**
- **Sam's father: Software engineer, dept. head, runs things by the book at work and at home ("strict"). "I don't understand what this is all about. I don't see the problem. My son just needs to apply himself harder!"**

The Boat

Henry goes to a large lake in the summer. Last summer a motorboat sank near his house. The boat had ten men in it. The man who was running the boat brought it very close to the shore when the water was low. The boat hit a big rock under the water. The water came in very fast. All of the men swam to shore.

Q: There's someone in this story who might get in trouble. Who is it?

The Boat

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Q: There's someone in this story who might get in trouble. Who is it?
Sam: *Henry? The ten men?*

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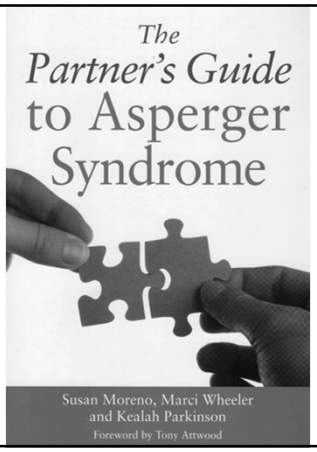
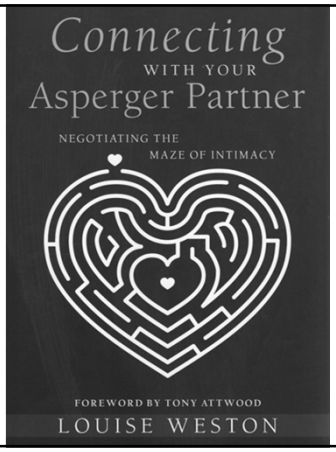
Q: There's someone in this story who might get in trouble. Who is it?
Sam: *Henry? The ten men?*
Sam's father: *I don't have any idea.*





http://www.aamft.org

AAMFT
American Association for Marriage and Family Therapy

Find a Marriage and Family Therapist

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      - ASD and MH communities need to unite
      - Reunify behaviorism, classical psychology, neuropsychology, & psychiatry

IDEA, Section 614(d)(2)(B)

http://idea.ed.gov/explore/view/p/,root,statute,I,B,614,d

(B) Consideration of special factors.--The IEP Team shall--

(i) in the case of a child whose behavior impedes the child's learning or that of others, consider the use of positive behavioral interventions and supports, and other strategies, to address that behavior.

ED.gov U. S. Department of Education
Promoting educational excellence for all Americans

This site was created to provide a "one-stop shop" for resources related to IDEA and its implementing regulations...

- **Comment: A few commenters recommended that Sec. 300.324(a)(2)(i) refer specifically to children with *internalizing and externalizing behaviors*.**
- **Discussion: We do not believe it is necessary to make the recommended change because Sec. 300.324(a)(2)(i) is written broadly enough to *include children with internalizing and externalizing behaviors*.**
- **Changes: None.**

http://idea.ed.gov/explore/view/p/,root,regs,preamble2,prepart2,D,2766

IDEA

- **As a practical matter, however:**
  - **"Behavior" is tacitly interpreted to mean *externalizing behavior***
  - **"Impedes Learning" is equated with *academic failure***

How did we get here?

19th century neuroscientists' dilemma:

How do we construct a science of human behavior?

Mentalism (1800's)

- Telepathy
- Clairvoyance
- Divination
- Precognition
- Psychokinesis
- Mediumship / Séances
- Mind control
- Hypnosis

Franz Anton Mesmer
(1734 –1815)

"Animal Magnetism" → Mesmerism → → → Hypnosis

http://en.wikipedia.org/wiki/Franz_Mesmer

Mentalism

http://en.wikipedia.org/wiki/Mentalism#/media/File:Mind-reading-Russell-Morgan.jpeg

Human Behavior ⇨

Correlative Neuroanatomy / Neuropsychol.
- Wernike, Broca
- Penfield

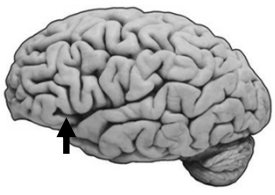
Classical Psychology ("consciousness")
- James

Behaviorism (Externally visible behavior)
- Watson
- Thorndike
- Skinner

Analytic Psychiatry (Introspection)
- Freud

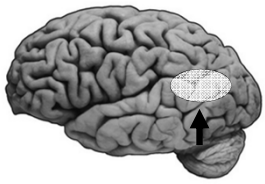
Correlative Neuroanatomy / Neuropsychology

Broca's Area



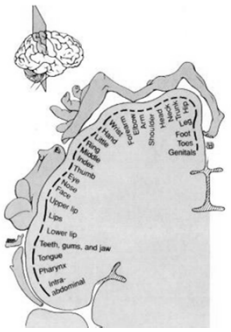
- Paul Broca, 1861
- Severe impairment of speech production
- Language comprehension remains intact ("Broca's aphasia")

Wernike's Area



- Carl Wernicke, 1874
- Ability to speak remains intact, but language comprehension and ability to produce meaningful speech are impaired ("Fluent aphasia")

Wilder Penfield (1891-1976)



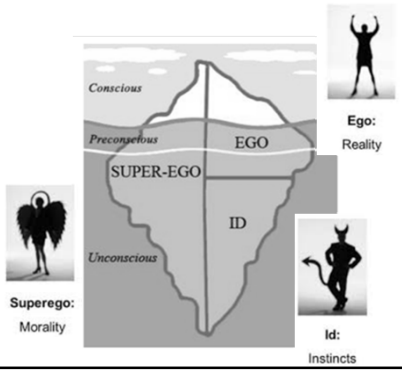
http://editthis.info/psy3241/Wilder_Penfield

Freud: Neuropathologist

"Critical Introduction to Neuropathology" (1885-87)

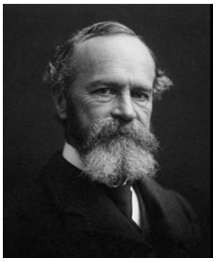
SPECIELLE
PATHOLOGIE UND THERAPIE
HOFRATH PROF. Dr. HERMANN NOTHNAGEL
DIE
INFANTILE CEREBRALLÄHMUNG
Dr. SIGM. FREUD
WIEN 1897.
ALFRED HÖLDER

Freud: Psychoanalytic Theory



William James

1842 –1910)



"Father of American Psychology"
The Principles of Psychology (Harvard, 1890)
- Functional localization: "lower" → "higher" brain centers
- Stream of Consciousness, Emotion, Habit, Will, etc…

http://en.wikipedia.org/wiki/William_James
http://en.wikipedia.org/wiki/The_Principles_of_Psychology

John Broadus Watson

(1878 –1958)

Psychology as the behaviorist views it **(Columbia, 1913): "A purely objective experimental branch of natural science. Its theoretical goal is the prediction and control of behavior. Introspection forms no essential part of its methods, nor is the scientific value of its data dependent upon the readiness with which they lend themselves to interpretation in terms of consciousness."**

http://en.wikipedia.org/wiki/John_B._Watson

Psychology without reference to "consciousness"

- Understanding, Insight, comprehension
- Intention, Desire
- Compliance / Noncompliance
  - "Compliance" and "Non-compliance" presuppose that the subject "understands" what is expected, and has "chosen" to not emit the behavior

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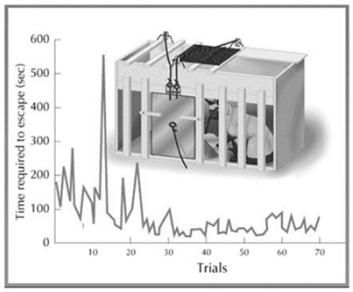
Edward Thorndike
(1874 –1949)

Animal Intelligence: An Experimental Study of the Associative Processes in Animals **(Columbia University, Doctoral Dissertation, 1898)**

http://en.wikipedia.org/wiki/Edward_Thorndike

Thorndike 1905



http://en.wikipedia.org/wiki/File:Puzzle_box.jpg

Law of Effect

Animal Intelligence. Edward Thorndike, 1911

" Of several [possible] responses…to the same situation, those which are…closely followed by satisfaction to the animal will…be more likely to recur. Those which are…followed by discomfort to the animal will…be less likely to occur. The greater the satisfaction or discomfort, the great the strengthening or weakening of the bond"

Skinner, ca. 1950

http://www.youtube.com/watch?v=SUwCgFSb6Nk&NR=1&feature=endscreen

Operant Conditioning

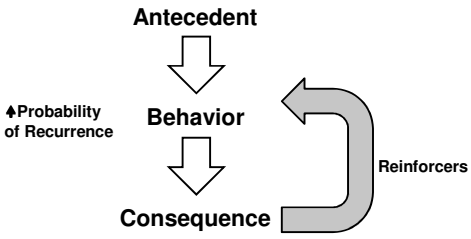
Skinner

- ***Experimental manipulation of the consequences for a given behavior (by the subject) alters probability that that behavior will recur.***

ABA – Ivar Lovaas

- **The Me Book (1981)**

Behaviorism



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Consequences 1: Reinforcers

- **Reinforcers: ↑Recurrence of antecedent behav.**
  - **Positive Reinforcement (adds something)**
    - **Access (to food [Skinner])**
    - **Attention**
  - **Negative Reinforcement (removes something)**
    - **Escape (e.g. from a cage [Thorndike]; from a task)**
    - **Removal of non-preferred food**

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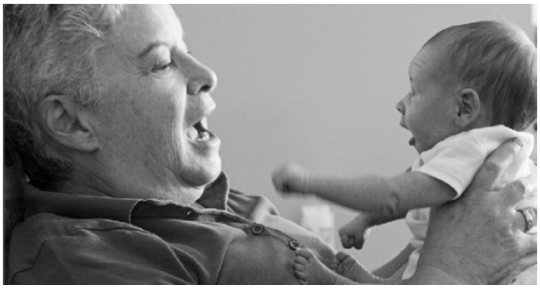
Attention as a reinforcer


Milo, raising on his hind legs for attention.


These male chimpanzees that are grooming each other live in East Africa at a site called Ngogo in the Kibale National Park in Uganda.
Photo by and courtesy of John Mitani

https://larajoseph.wordpress.com/2015/03/11/attention-as-a-reinforcer/
https://kuscholarworks.ku.edu/bitstream/handle/1808/12939/Bayles_ku_0099D_13181_DATA_1.pdf?sequence=1



Consequences 2: Aversives

- Aversives: ↓Recurrence of antecedent behavior
  - Logical Consequences
    - If child refuses to use toilet, child must wear backpack with spare clothes
  - Over-correction
    - If the child spills milk on purpose: child must mop the entire kitchen floor
  - Punishment
    - Loss of privileges
    - Verbal
    - Physical

Besides being ethically questionable and possibly detrimental, these both constitute attention – a reinforcer!

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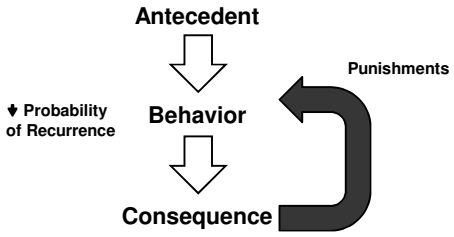
Behaviorism



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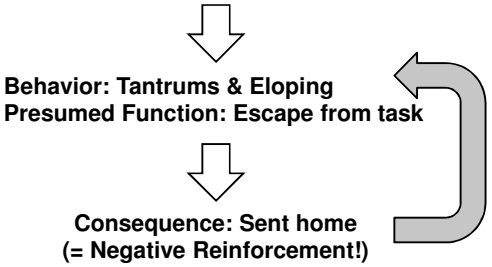
Typical FBA



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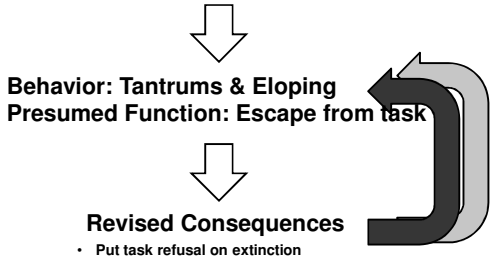
Typical FBA



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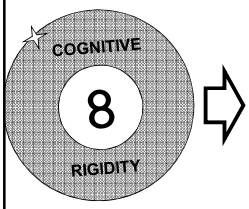
Cognitive Rigidity

(Difficulty shifting mental sets)



"Externalizing Behaviors"

- ***Insistently*** repetitious behavior
- Difficulty w. unmet expectations
- Perfectionism
- Compulsions
- Perseveration
- (Aggression, SIB)

- Perfectionism
- Obsessions
- (Anxiety / Depression)

"Internalizing Behaviors"

Sam

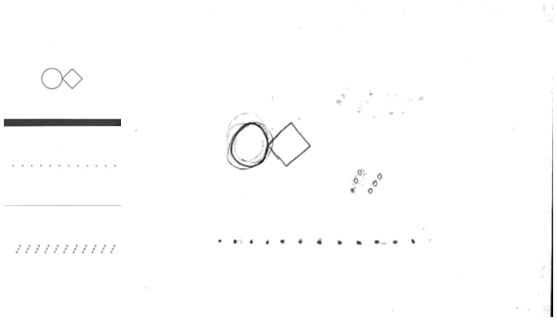
10 y.o. boy with AS, OCD, & perfectionism

Exam: Perfectionism

"Sam earnestly attempted the Bender-Gestalt figures, but became overwhelmed, repeatedly erasing and re-erasing. He went so far as to measure the distance between the dots on one of the stimulus cards with his finger, trying to replicate the spacing exactly. *'If I can't get something right I get angry with myself… Sometimes I take it out on other people,'* he confided. After he had labored mightily over the first few cards, he sighed *'This is torture…'* After he had manfully struggled over a single card for several minutes, we opted to move on to another task."

Perfectionism: "This is torture"

MRN 14-0933



Reclaiming IDEA:
Positive Behavior Support for Internalizing Behavior

- Staff Awareness
  - "Seeing the vase"
  - *It's not the task per se, but the self-inflicted self-punishment for an imperfect job that the child is attempting to avoid*
- Visual Schedules
- Relaxation Techniques
- Abolishing Operations

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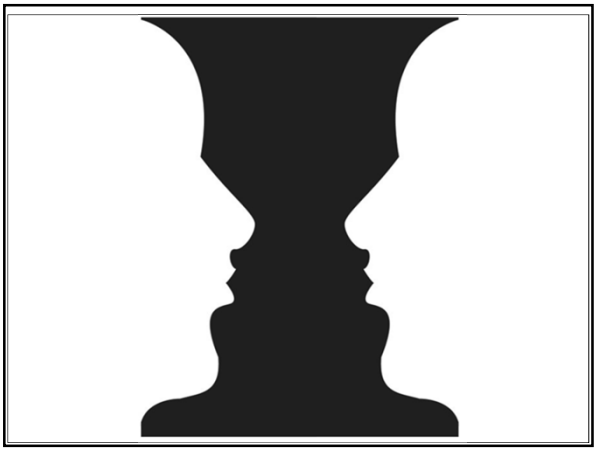
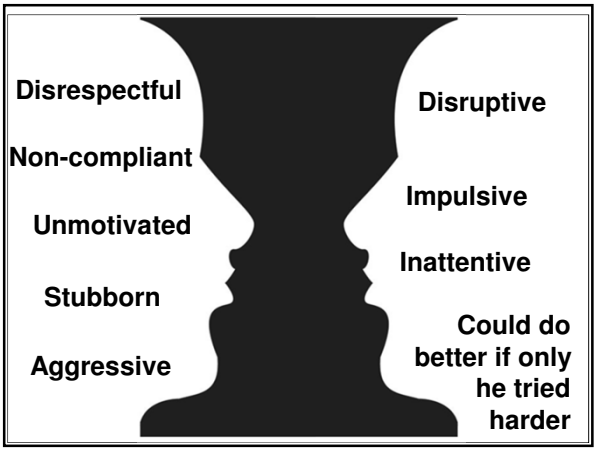
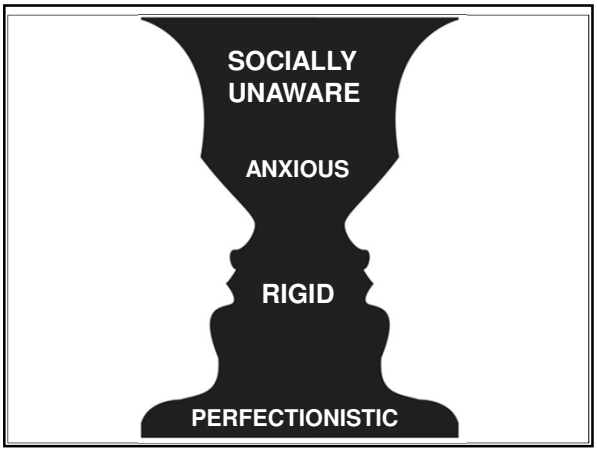






Tony

8 y.o. boy with HFA, Anxiety, and Perfectionism

Teacher's Report: "Tony tries to exclude himself from any 'competition' types of games or activities, as he really dislikes being 'wrong,' 'out,' or to lose. On the times he has had tantrums after being 'out' or when his team has lost, the other children have been very empathetic towards him and he has not lashed out at them. *His frustration appears to be with himself.*"

8 yr old boy with AS
MRN: 14-0916

Not seeing the vase

(ignoring internalizing behavior)

ASSESSMENT SUMMARY:

Antecedents to the behavior of concern	Behavior of concern	Consequences maintaining the behavior of concern	Perceived function of the behavior of concern
Denied Access Transitioning Task Demand (individual) Social Situations (Competitive)	Tantrum (4 levels) Level of Tantrums: 1. Isolation tantrum: eloping from adults or from the classroom/assigned area, not responding or refusing staff prompting 2. Low frustration tantrum: clenching fists, stomping feet, grunting, whining, crumpling/bending objects, or crying. 3. Physical tantrum: aggression is defined	anxiousness entering into regular education classroom increased academic standards difficulty maintaining focus on instructor and tasks limited time frames for task completion increased expectations for written work	*To gain* Attention *To avoid, escape, or postpone* Academic tasks/expectations

www.drcoplan.com MW; MRN 06-0211

Seeing the vase

(recognizing internalizing behavior)

ASSESSMENT SUMMARY:

Antecedents to the behavior of concern	Behavior of concern	Consequences maintaining the behavior of concern	Perceived function of the behavior of concern
~~Denied Access~~ ~~Transitioning~~ ~~Task Demand (individual)~~ ~~Social Situations~~ ~~(Competitive)~~	Tantrum (4 levels) Level of Tantrums: 1. Isolation tantrum: eloping from adults or from the classroom/assigned area, not responding or refusing staff prompting 2. Low frustration tantrum: clenching fists, stomping feet, grunting, whining, crumpling/bending objects, or crying. 3. Physical tantrum: aggression is defined	~~anxiousness entering into regular education classroom~~ increased academic standards difficulty maintaining focus on instructor and tasks limited time frames for task completion increased expectations for written work	~~*To gain*~~ ~~Attention~~ ~~*To avoid, escape, or postpone*~~ ~~Academic tasks/expectations~~

Antecedents	Behaviors	Consequences	Perceived Function
Anxiousness Perfectionism Fear of Failure	Tantrums Eloping Task Refusal	Temporary *reduction* in anxiety via task avoidance (stress reduction via mild SIB?)	Stress Reduction; Avoidance of self-blame for not completing the task perfectly

www.drcoplan.com MW; MRN 06-0211

The Story of Billy's Box - 1

(or, why it's important to ID internalizing behavior)

- **8 y.o. boy with ASD and normal Nonverbal IQ**
- **Severe tantrums at school**
- **Antecedents:**
  - **TRANSITIONS**
- **Function?**
  - **Attention, escape, access?**
  - **"Biological" (i.e. "just part of his ASD")?**

The Story of Billy's Box - 2

(or, why it's important to ID internalizing behavior)

Q: "Billy – You're always getting in trouble at school. What's going on?"

A: "I'm afraid that if I hand in my work, I'll never get a chance to go back and make it perfect."

The Story of Billy's Box - 3

(or, why it's important to ID internalizing behavior)

"Put your papers in the box, and you will be able to go back later and work on them some more, if you want."

Social Skills Deficit + Cognitive Rigidity

"With his teachers, L. is defiant, argumentative and refuses to complete tasks. He manipulates all situations and has much difficulty with the teacher/pupil hierarchy. He is very comfortable telling adults what to do and why… *He has great difficulty seeing the consequences of his actions and views punishment or consequences as personal attacks….* "

LC: 9 y.o. boy with superior IQ & AS
MRN 10-0660

Social Skills Deficit + Cognitive Rigidity

"L's IEP includes a Positive Behavior Support Plan, with goals that focus on *compliance*, and *awareness of the feelings of others*.

Specific target behaviors include "Refusal to comply with task," "Time off task," and "Making noises." The "Perceived Functions" of these behaviors are listed as "Escape from work, self-stimulation, sensory, and attention-seeking."

LC: 9 y.o. boy with superior IQ & AS
MRN 10-0660

Social Skills Deficit + Cognitive Rigidity

"We are pleased to see that L. has a Positive Behavior Support Plan, but we are dismayed that it does not consider *perfectionism* as an antecedent, in which case L's refusals may not be for the purpose of escape from task *per se*, but *to avoid self-criticism for not being able to do a task perfectly*.

Liam's Behavior Plan calls for him to recognize the feelings of others, which is fair. By the same token, his Behavior Plan should also require the adults to make an effort to figure out what *Liam* may be feeling – not just react to the surface topography of the behavior."

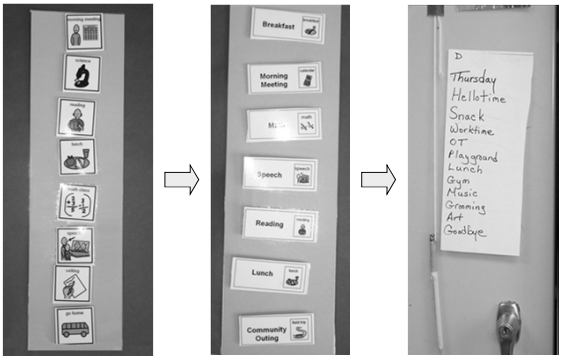
LC: 9 y.o. boy with superior IQ & AS
MRN 10-0660

Positive Behavior Support Plan for Internalizing Behavior

- **Staff Awareness**
- **Visual Schedules**
  - **What am I supposed to be doing now?**
  - **What am I supposed to be doing next?**
  - **What do I do if there is a change in plan?**
- **Relaxation Techniques**
- **Abolishing Operations**

www.drcoplan.com

Visual Schedules



Positive Behavior Support Plan for Internalizing Behavior

- **Staff Awareness**
- **Visual Schedules**
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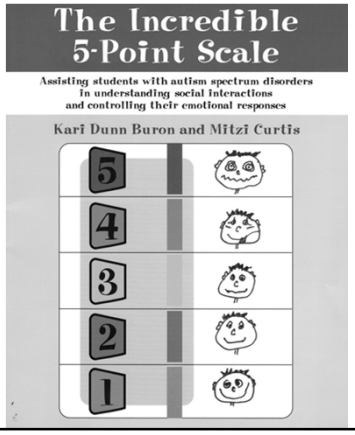
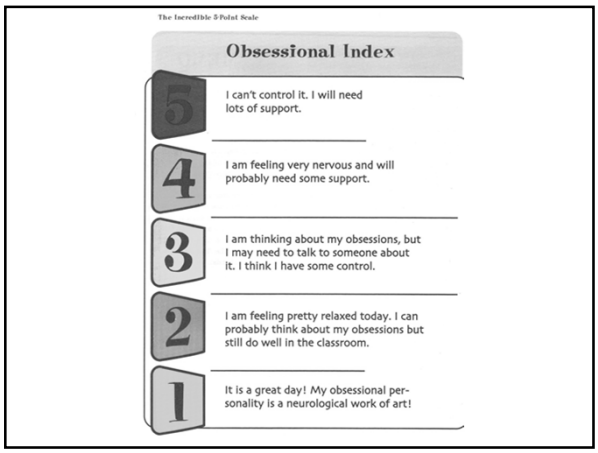
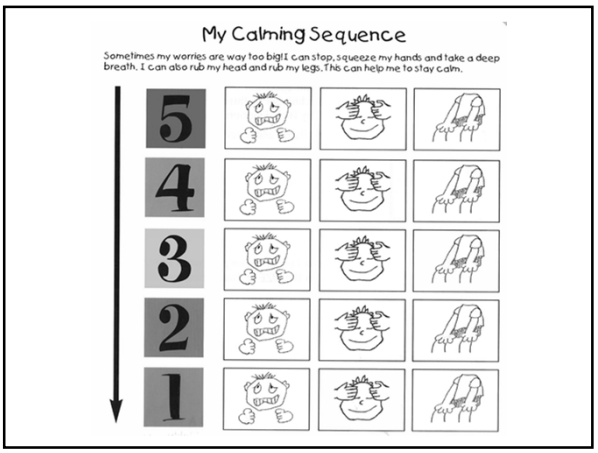
www.drcoplan.com







Positive Behavior Support Plan for Internalizing Behavior

- Staff Awareness
- Visual Schedules
- Relaxation Techniques

➢ Abolishing Operations (long before task)

- ➢ Educate child about his/her ASD
- ➢ Build self-esteem
- ➢ Cognitive Behavioral Therapy / Abolishing Opserations
  - *It's OK if I don't get it exactly right.*
  - *I can come back later.*
  - *I can try again.*
  - *I will not die.*

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Motivating Operations (MO)

http://en.wikipedia.org/wiki/Motivating_operation

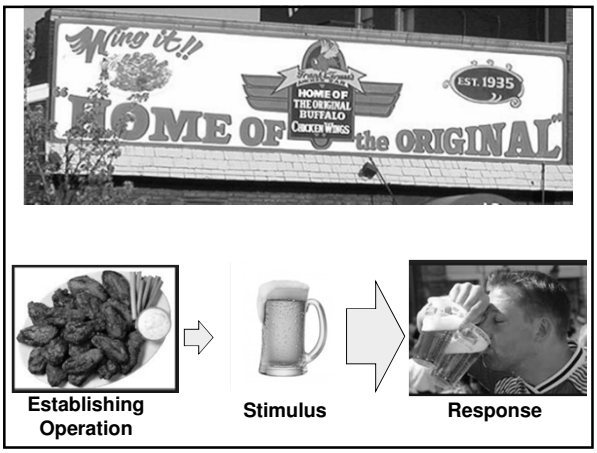
- "Motivating operations affect whether a person wants or does not want a stimulus at a given moment, which helps explain [the person's] behavior at that point in time."

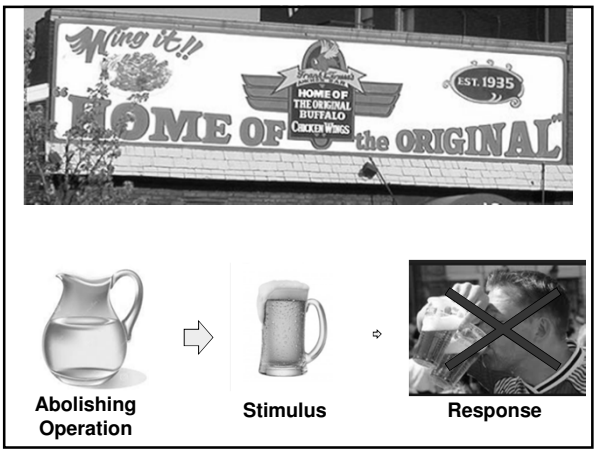
Motivating Operations (MO)

http://en.wikipedia.org/wiki/Motivating_operation

- MOs that ↑ the reinforcing or punishing qualities of a stimulus are termed ***Establishing Operations (EO)***
- MOs that ↓ the reinforcing or punishing qualities of a stimulus are termed ***Abolishing operations (AO)***

Stimulus Desired Response





FBA for Internalizing Behavior

Antecedent (task demand)

⇩

Behavior: Tantrums & Eloping
Presumed Function: *Escape self-punishment*

⇩

?

"I can't do it perfectly!" → Agitation / SIB / "task avoidance" / inability to let go

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FBA for Internalizing Behavior

A.O.

"Mistakes are OK"
"I will not die"
"I can come back later"
etc.

Antecedent (task demand)

⇩

Behavior: Tantrums & Eloping
Presumed Function: *Escape self-punishment*

⇩

?

~~"I can't do it perfectly!" → Agitation / SIB / "task avoidance" / inability to let go~~

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Outline

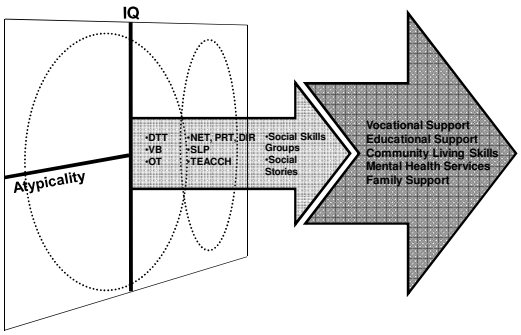
- Patting the elephant
- Under the hood
- ➢ It takes a village
  - Treatment:
    - Primary prevention – *Brave new world*?
      - CNVs – carrier screening for ASD and MH risk
      - Pre / Perinatal intervention: Oxytocin and the GABA switch
    - Secondary intervention (symptom-oriented)
      - Child-Centered
        - At home: self-awareness, self-esteem
        - Mental Health services & Psychopharmacology
      - Parent and Family Centered: Nature *and* Nurture
        - Intro to Family Systems Theory
    - ➢ Tertiary intervention (system-oriented)
      - At school: Reclaiming IDEA: Positive Behavior Support for Internalizing Behavior
      - Routine MH screening of children w. ASD, and routine screening of *family health*
      - ➢ Adult services for "survivors" of childhood autism
      - ASD and MH communities need to unite
      - Reunify behaviorism, classical psychology, neuropsychology, & psychiatry

Transition to Adulthood

Our son turned 13 last year. We are noticing that…the world interacts very differently to an autistic child vs. an autistic man.

MRN 04-0011

Progression of Interventions



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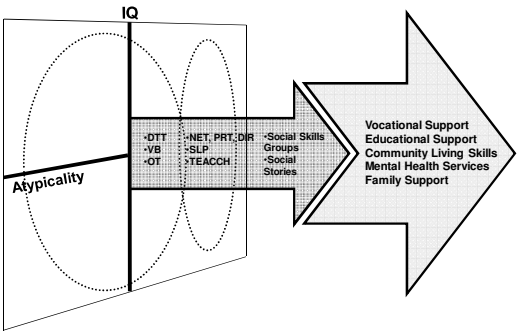
Progression of Interventions



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AMERICAN childhood CANCER ORGANIZATION

LONG TERM FOLLOW-UP CLINICS FOR SURVIVORS OF CHILDHOOD CANCER

The majority of children diagnosed with cancer will survive. However, survivorship can come with a price in the form of long-term medical, psychosocial, and/or neurocognitive problems due to chemotherapy, radiation, or surgery. Children who have been treated for cancer should be seen by specialists in late effects of childhood cancer. A list of late effects clinics is kept on the ped-onc resource center (thanks to Nancy Keene):

Late Effects Clinics

http://www.acco.org/about-childhood-cancer/treatment-and-survivorship/late-effects/

http://www.mskcc.org/pediatrics/adult-survivors-childhood
http://www.uchicagokidshospital.org/specialties/cancer/survivors

Adult Services for "Survivors" of Childhood ASD

- **Social contact**
- **Job coaching / Career counseling**
- **Partner / Family support**
- **Mental health services**
- **Self-Advocacy (e.g. GRASP, AANE)**

GRASP

AANE ASPERGER/AUTISM NETWORK
Empowering Individuals • Building Community

Outline

- **Patting the elephant**
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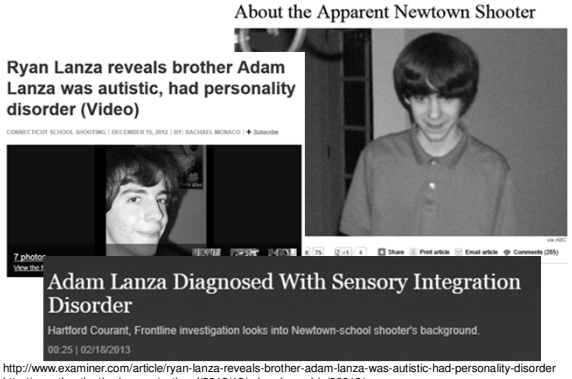
      - ➢ **ASD and MH communities need to unite**
      - **Reunify behaviorism, classical psychology, neuropsychology, & psychiatry**

Adam Lanza: What We Think We Know About the Apparent Newtown Shooter



http://www.examiner.com/article/ryan-lanza-reveals-brother-adam-lanza-was-autistic-had-personality-disorder
http://www.theatlanticwire.com/national/2012/12/adam-lanza-bio/60018/
http://abcnews.go.com/Health/video/cancer-survivor-catches-fire-at-oregon-hospital-18538818

AUTISMCANADA FOUNDATION — THE PREMIER RESOURCE FOR INFORMATION ON AUTISM SPECTRUM DISORDERS

Autism Canada's Statement On The Sandy Hook Elementary School Tragedy 12/17/2012

- **It has been reported that the shooter at Sandy Hook Elementary School had autism. In the weeks and months to come there will be much more information about his condition, but today it has never been more important to understand that *autism / Asperger's is not a mental health condition. Autism is a neurological condition…..***

AUTISM RESEARCH INSTITUTE
Autism is Treatable

ARI Statement on the Newtown, CT Tragedy

The staff at the Autism Research Institute is deeply saddened by yesterday's tragic events at Sandy Hook Elementary School in Newtown, Connecticut…

Some public comments have drawn potentially inaccurate and stigmatizing conclusions about a link between the diagnosis [of autism] and a propensity for violence and lack of empathy…

Autism is not a mental health disorder - it is a neurodevelopmental disorder…

AUTISM SOCIETY
Improving the Lives of All Affected by Autism

Autism Society of America Statement 12/17/2012

- **No evidence exists to link autism and premeditated violence…**
- **Individuals with autism who act aggressively typically do so because they are reacting to a situation...**
- ***Many of the individuals with Asperger's syndrome who have committed crimes had co-existing psychiatric disorders…***

People want immediate or simple answers when an unimaginable tragedy like this occurs. Autism did not cause this horror…

http://www.autismspeaks.org/news/news-item/statement-bob-and-suzanne-wright

We have a problem here…

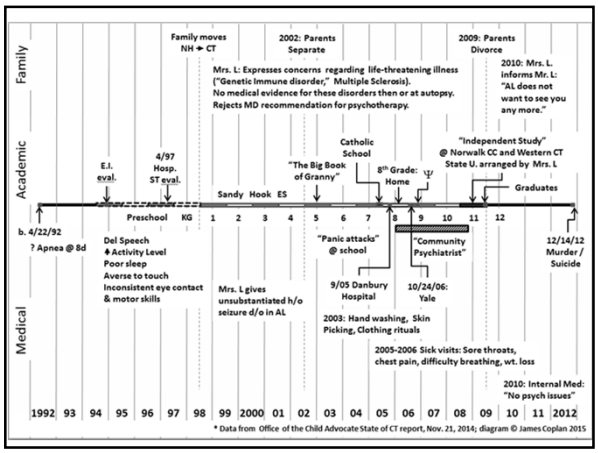
(3 problems, actually)

1. **There is no bright line between Autism Spectrum D/O and "Psychiatric" disorders**
2. **Shifting responsibility onto persons with "mental illness":**
   - **Stigmatizes the mentally ill, and**
   - **Ignores the mental health needs of persons with ASD**

OFFICE OF THE CHILD ADVOCATE — STATE OF CONNECTICUT

SHOOTING AT SANDY HOOK ELEMENTARY SCHOOL
REPORT OF THE OFFICE OF THE CHILD ADVOCATE

http://www.ct.gov/oca/lib/oca/sandyhook11212014.pdf



OCA Report
Mrs. Lanza

- **"A pattern of attempts to bend or manage the environment for AL"**
  - ***"I would like his emphasis to be on learning rather than coping"***
- **Rejects medical advice for medication and appropriate psychotherapy and academic placement for AL**
- **"A dynamic of mutual dependency" between Mrs. L and AL, accompanied by progressive isolation of AL from outside contact (public school, Mr. L)**
- **"Parentification" of AL: Mrs. L unburdening herself regarding her own worries, with AL trying to reassure her**

OCA Report – School System

"The school system cared about AL's success but also unwittingly enabled Mrs. Lanza's preference to accommodate and appease AL through the educational plan's lack of attention to social-emotional support, failure to provide related services, and agreement to AL's plan of independent study and early graduation at age 17"

OCA Report
Evaluation by Yale Child Study Ctr: 10/24/06 (9th Grade)

"Beyond the impact of OCD symptoms on himself and his mother, we are very concerned about AL's increasingly constricted social and educational world. Much of emphasis has been on finding curricular level of instruction. Inability to tolerate even minimal interaction with even older more mature classmates will have grave consequences for his future education and social and occupational adaptation unless means of remediation are found. Inability to interact with classmates will prove increasingly deleterious to education..."

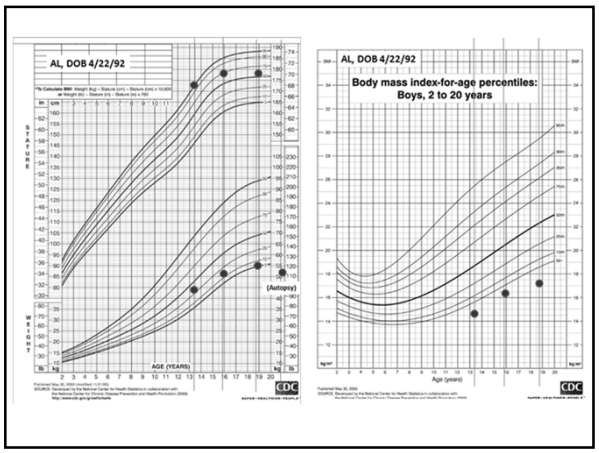
OCA Report

Is there a Reluctance to Serve Youths' Social-Emotional Learning Needs in School?

…Social Emotional, developmental, and behavioral health needs are sometimes considered parenthetical to the learning process. It is not uncommon for schools not to have a social worker or other therapeutic support staff in the building. It is also not uncommon for an Individual Education Plan to refer to social-emotional or mental health needs and indicate that those needs are being met in the community by an outpatient provider.

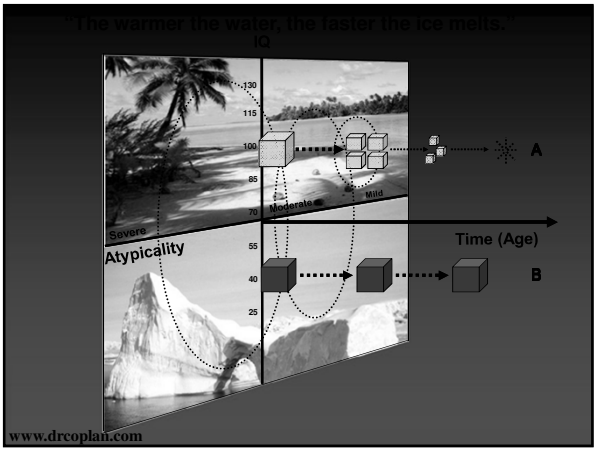
Care that did not follow best practices

- **Primary Care**
  - **No f/u of weight loss**
  - **No f/u of OCD**
- **Psychiatric Care**
  - **Community psychiatrist: facilitated mother's agenda rather than treating AL**
- **Educational services**
  - **Did not evaluate in timely or complete manner**
  - **Did not address Mental Health / Social issues**



Summary

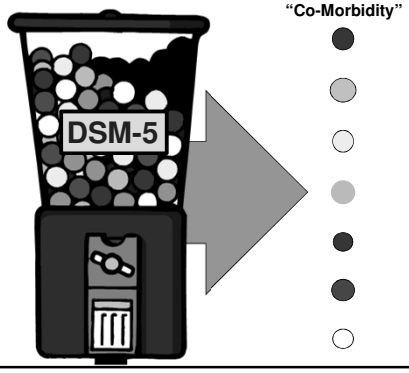
- ASD has a natural history of improvement over time
  - Changes follow a predictable sequence
- Any degree of atypicality can be accompanied by any level of IQ
  - The warmer the water, the faster the ice melts
- 3D model
  - To monitor change over time, and anticipate future needs

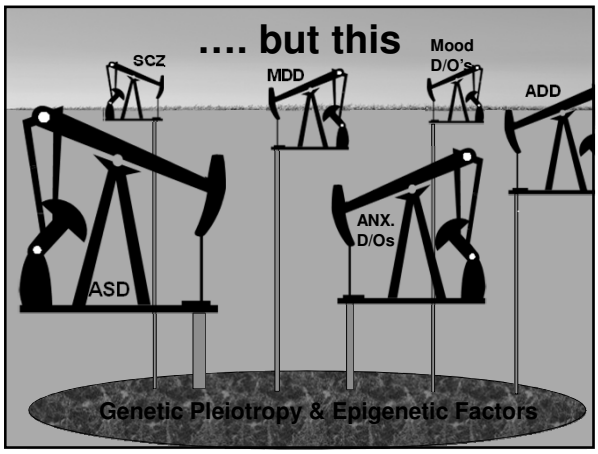


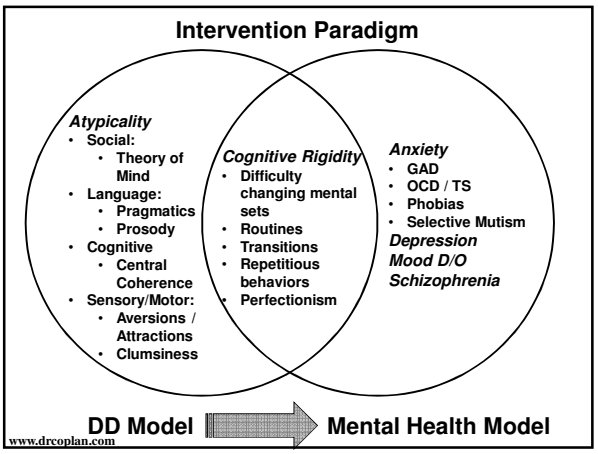
Summary

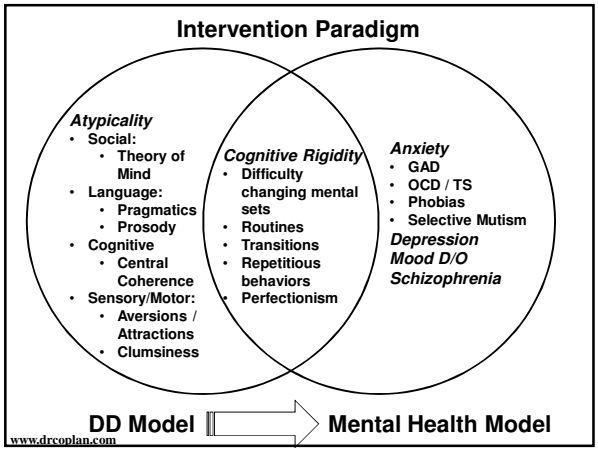
- ASD has a Natural History
- ASD and Psychiatric Symptoms
  - Not Co-Morbidity, but Continuum and Metamorphosis
    - MH issues often overshadow atypicality
  - Parents are at increased risk for clinical or sub-clinical impairment (atypicality or "non-ASD" mental health disorder) which – if untreated - can negatively impact the child's prognosis

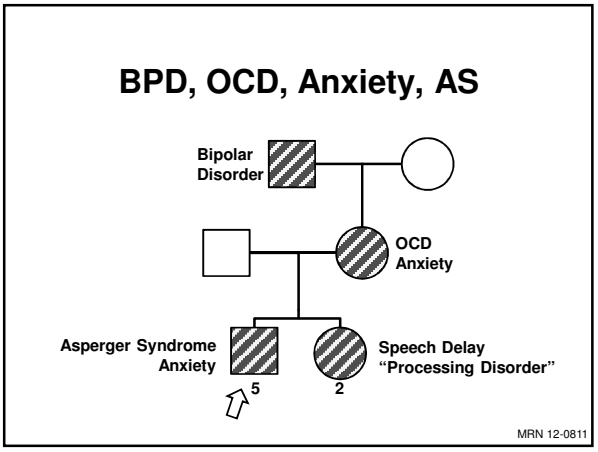
Not this…..











Summary

- ASD has a Natural History
- ASD and Psychiatric Symptoms
- Intervention: Child, family, and system-level
  - Positive Behavior Support for Internalizing Behavior
  - Family function and family therapy as needed
  - First step: Get both parents into the office

System Change

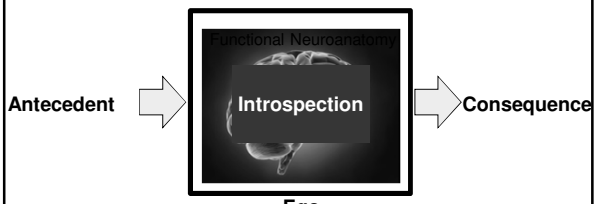
- The Autism community needs to ally itself with (rather than run from) the mental health community
- Barriers to change:
  - Fear / Stigma
  - The lasting harm done by Bruno Bettelheim
  - Professional / Institutional Turf

System Change

- We need to heal the 4-way split between psychiatry, classical psychology, neuropsychology, and behaviorism

1900-2000

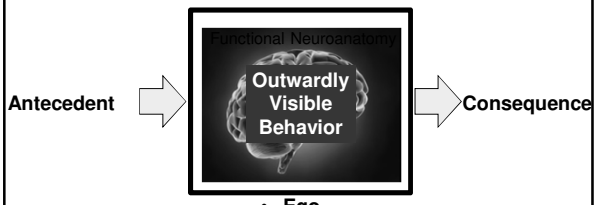
Brain = "Black Box" (Psychoanalyst)



- Ego
- Superego
- Id

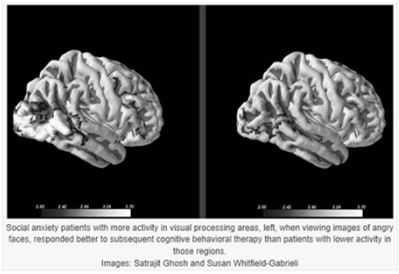
1900-2000

Brain = "Black Box" (Behaviorist)



- Ego
- Superego
- Id

Private mental events aren't so private any more

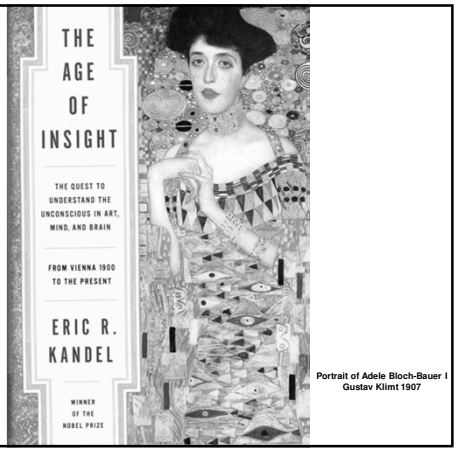


Social anxiety patients with more activity in visual processing areas, left, when viewing images of angry faces, responded better to subsequent cognitive behavioral therapy than patients with lower activity in those regions.
Images: Satrajit Ghosh and Susan Whitfield-Gabrieli

http://scitechdaily.com/brain-scans-help-predict-whether-patients-will-respond-to-therapy/

Private mental events aren't so private any more

- If Freud, Watson, Thorndike, Skinner, and James were alive today, they would all be doing neuroimaging
  - Freud would be localizing the Ego, Superego and Id
  - Thorndike would know exactly what "satisfaction to the animal" meant
  - James would have objective parameters for "stream of consciousness"
  - Etc.



Portrait of Adele Bloch-Bauer I
Gustav Klimt 1907

Behaviorism: Benefits & Open Questions

- Innumerable studies demonstrate efficacy of operant conditioning as a way to shape or extinguish *specific behaviors*
- Evidence for impact on *long-term development* is not as clear
  - Ethical problems with randomization
  - Lack of sham treatment arm
  - Inadequate length of follow-up (i.e. 20 yr.)
- Thorndike (1911): Cats did not learn by observation (something humans can do). Are there other differences between species (perhaps as a function of the mirror neuron system), that ought to inform Behaviorism as applied to humans?
- "Private mental events"
  - Is there a valid distinction between "emitting the target behavior" vs. "understanding what is expected"?
    - Quantifying the "Aha!" phenomenon

Crystal Ball-Gazing

- "ASD" (a clinical Dx) will be augmented (or transcended) by a classification scheme rooted in neurobiology (brain regions, neurotransmitters, CNVs, etc.)
- The distinction between ASD as a "developmental disorder" and the various "mental health disorders" will continue to erode and eventually disappear
- Combinatorial genetics / epigenetics will account for the majority of cases
  - Knudsen's 2-Hit hypothesis: Genetic vulnerability + specific environmental trigger may apply in some cases
- Primary prevention may become possible. Many ethical issues!!

Additional Reading

- ***From Kanner to DSM-5: Autism as an Evolving Diagnostic Concept.*** **Fred R. Volkmar and James C. McPartland. Child Study Center, Yale University, New Haven, CT. Annu. Rev. Clin. Psychol. 2014. 10:193–212. Available on-line at clinpsy.annualreviews.org**
- ***Autism.*** **Meng-Chuan Lai, Michael V Lombardo, Simon Baron-Cohen. Lancet 2014; 383: 896–910**

JFKI 1978

"If I have seen further it is by standing on the shoulders of giants."

Thank you!

AD