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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Risk Factors
- Proven
- Speculative

Clinical Features
- Treatment
- Outcome

Outline

---

Functional Neuroanatomy

Clinical Features
- Treatment & Outcome

---

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

We must, then, assume that these children have come into the world with an innate inability to form the usual, biologically provided affective contact 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. – Leo Kanner, 1943

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PATHOLOGY

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Traditional Medical Practice
(“What’s the matter with my patient?”)

PKU: Asbjørn Følling (1934)
- 2 siblings with severe ID, and an unusual odor to the urine
  
  http://www.pkunews.org/about/history.htm

Working back

New Way
(What does this needle do?)

New Way
(Many needles, many haystacks)
A quick review

Risk Factors
- Genetic

Functional Neuroanatomy

Clinical Features
- Treatment & Outcome

Copy Number Variations (CNVs)

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

Auszum Keynote
© James Coplan, MD
April 29, 2015

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DNA*

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

Human genome: ~ 20,000 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

Global variation in copy number in the human genome

Richard Redon*, Shuqueer Labib*a*, Rikke E. Fisk*a, Lars Feodor*a

Journal content
- Article
  - Global variation in copy number in the human genome
  - Richard Redon*, Shuqueer Labib*a*, Rikke E. Fisk*a, Lars Feodor*a

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

Nature
International weekly journal of science

FULL TEXT
- 1 of 4
- 1 of 4

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“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.”

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.

16p11.2 has been associated with
- ASD
- Schizophrenia
- Bipolar disorder
- Developmental Delay
- Body weight regulation
How and why does this variation occur?

https://simonsvipconnect.org/
“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.”

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.

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?

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

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

• 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.

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

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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. As none of these CNVs hitherto described are fully penetrant for the diseases, and both schizophrenia and autism affect cognition, 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

Food for thought

- Since nominally “asymptomatic” carriers of specific CNVs (which are known to be associated with SCZ or ASD) have demonstrable cognitive and neuroanatomic changes, were is the real boundary for “disease”?
Objectives: To establish the relative contributions of genetic and environmental factors for ASD and a broader autism phenotype

Subjects: Twins Early Development Study: All twin pairs born in England & Wales from 1/1/94 through 12/31/96

Correlations among monozygotic twins (range, 0.77-0.99) were significantly higher than for dizygotic twins (range, 0.22-0.65), giving heritability estimates of 56% to 95%

The liability to ASD and a more broadly defined high-level autism trait phenotype in this large population-based twin sample derives primarily from additive genetic and, to a lesser extent, nonshared environmental effects.
DESIGN, SETTING, AND PARTICIPANTS A population-based, prospective cohort study using Swedish national health registers. Offspring born between 1982 and 2007 were followed up for a clinical diagnosis of autistic disorder or mental retardation until December 31, 2009. The exposure of interest was IVF, categorized according to whether intracytoplasmic sperm injection (ICSI) for male infertility was used and whether embryos were fresh or frozen. For ICSI, whether sperm were ejaculated or surgically extracted was also considered.

MAIN OUTCOMES AND MEASURES Relative risks (RRs) for autistic disorder and mental retardation comparing spontaneously conceived offspring with those born after an IVF procedure and comparing 5 IVF procedures used in Sweden vs IVF without ICSI with fresh embryo transfer, the most common treatment. We also analyzed the subgroup restricted to singletons.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposure Status</th>
<th>Disease</th>
<th>No Disease</th>
<th>Risk of Dz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>a</td>
<td>b</td>
<td>a/ (a+b)</td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>c</td>
<td>d</td>
<td>c/ (c+d)</td>
<td></td>
</tr>
</tbody>
</table>

Risk Ratio (Relative Risk; RR) = Risk of Dz (exposed) / Risk of Dz (unexposed) = [a/ (a+b)] / [c/ (c+d)]

RR > 1.0 means that the Risk Factor is associated with Risk of Disease
CI = Confidence Interval (usually set at “95%”)

Risk: What is the risk of contracting disease after exposure? Risk Ratio (RR): Is the risk of contracting disease greater in persons who have been exposed, c/w persons who have not been exposed?

RESULTS
- Of ~2.5 million infants, 30,959 (1.2%) were conceived by IVF
- Compared with spontaneous conception, IVF treatment overall was not associated with an increased risk for autistic disorder but was associated with a small but statistically significantly increased risk of mental retardation.
  - RR for autistic disorder following IVF vs. spontaneous conception: 1.14 (95% CI, 0.94-1.39)
  - RR for mental retardation: 1.18 (95% CI, 1.01-1.36)
For specific procedures, IVF with ICSI for paternal infertility was associated with a small increase in the RR for autistic disorder and mental retardation compared with IVF without ICSI, fresh. The prevalence of these disorders was low, and the increase in absolute risk associated with IVF was small.

Lehti et al 2013

63 children with ASD (1.51%) and 229 non-ASD controls (1.38%) were born after IVF.

No significant association was found between IVF and ASDs for all births (singleton and multiple births) (OR): 0.9, 95% CI: 0.7–1.3) or ASD subtypes

- Childhood autism (OR: 0.8, 95% CI: 0.4–1.5)
- Asperger’s syndrome (OR: 0.9, 95% CI: 0.5–1.6)
- Other PDD (OR: 1.0, 95% CI: 0.6–1.6)
When only singletons were included, there was an association between IVF and Asperger’s syndrome in an unadjusted analysis (OR: 2.0, 95% CI: 1.1–3.5) but this was not significant when adjusted for mother’s socioeconomic status or parity. Lehti et al 2013

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Lehti et al 2013

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Lehti et al 2013

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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.

Wong J Peds 2014

Table II: Exome-specific distribution of Q-CHAT scores

- 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


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”)
Functional Neuroanatomy

Risk Factors
- Genetic
- Pre & Perinatal
- Immunologic

Clinical Features & Treatment

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

A. Brown, D. A. Sevander,
S. Vinicka-Vir-Sabarko,
M. Korchou,
J. Sundby,
and H. M. Saccari

- 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

Table III: Association between SP ASD and neonatal risk factors in infants (~4 wk gestational age, KPMC, births from 2000-2007)

<table>
<thead>
<tr>
<th>Variable</th>
<th>KPMC ASD</th>
<th>No ASD</th>
<th>SHR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>0.95</td>
<td>1.00</td>
<td>0.99</td>
<td>0.94-1.05</td>
</tr>
<tr>
<td>Birthweight</td>
<td>1.00</td>
<td>0.98</td>
<td>0.96</td>
<td>0.93-0.99</td>
</tr>
<tr>
<td>Gestational age</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.99-1.01</td>
</tr>
<tr>
<td>Foot length</td>
<td>1.00</td>
<td>1.01</td>
<td>1.02</td>
<td>1.00-1.04</td>
</tr>
<tr>
<td>Apgar score</td>
<td>0.95</td>
<td>0.94</td>
<td>0.93</td>
<td>0.91-0.96</td>
</tr>
<tr>
<td>Delivery mode</td>
<td>0.98</td>
<td>1.00</td>
<td>0.98</td>
<td>0.96-1.00</td>
</tr>
<tr>
<td>Delivery mode</td>
<td>0.98</td>
<td>1.00</td>
<td>0.98</td>
<td>0.96-1.00</td>
</tr>
</tbody>
</table>

Seropositivity of Anti-nuclear antibodies (ANA)
- Children with ASD: 25%
- Children with normal development: 4%

Significant difference (p < 0.001).

Additional notes:

- Elevated CRP levels in ASD compared to non-ASD controls

Published October 23, 2014: J Pediatr 2014;164:20-5

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

© James Coplan, MD

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

Journal of Neurommunology

Stem exacerbation

Geban A. Mostafa, Dalia A. El-Shemy, Laila Y. Al-Ayyubi

- 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 normal development: 4%
- Significant difference (p < 0.001).

Behavioral Brain Research

Research report:

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

Jasmin Camacho, Karen Jones, Elaine Miller, Jeanette Arntz, Stephen Necter, Judy Van de Water, Veronica Martinez-Cerdeño

- Department of Neurology and Neuroscience, University of California, San Diego, USA
- Department of Pediatrics, University of California, San Diego, USA
- Department of Psychiatry, University of California, San Diego, USA
- Departments of Psychiatry and Behavioral Sciences, UC Davis, USA

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Page 13
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 injection on day 14

Behavioral testing on postnatal day 25

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

Opioid-excess hypothesis

"According to this hypothesis, genetic predisposition and/or early exposure to environmental stressors may lead to functional alterations in the gut, reduced proteolytic activity, and the increased permeability of the gut mucosa. These factors, possibly in combination with low levels of circulating peptidases and increased blood-brain barrier permeability, may cause hyperpeptidemia and accumulation of opioid peptides such as CM in the blood and the brain. Thus, chronically elevated levels of endorphins in the brain may directly modulate the opioid and other neurotransmitter systems, leading to the development of ASD"
Sokolov 2014

- 4 - 8 year old children with ASD (n = 10) and healthy control children (n = 10).
- First morning urine samples
- ELISA (enzyme linked immune assay) for urinary Casomorpin

Sokolov 2014

- Bovine CM-7 levels

Sokolov 2014

- The Neuro-Immune Axis: Prospect for Novel Treatments for Mental Disorders

- 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


Vaccine 2014

Data extracted:
(1) Study design
(2) Country of study
(3) Sample sizes (including total number of participants, and number of participants in each treatment arm)
(4) Type, dose and timing of vaccination
(5) Outcome measure (including development of autistic disorder, other autism spectrum disorder, or autistic disorder with regression)
(6) Measures of effect (including calculated odds and risk and risk ratios and the confounding variables for which they were adjusted

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
• Postmortem samples children with autism and unaffected children age 2-15
• 25 gene marker panel
• Focal regions 5 to 7 mm in length of reduced expression or unusual patterns of markers
  • Children with ASD: 10 / 11
  • Typically developing children: 1 / 11

Because we sampled only small portions of cortex yet observed focal patches in nearly every case sample, the most parsimonious explanation is that pathological patches are widespread across prefrontal and temporal cortex in children with autism.

“Our data support a probable dysregulation of layer formation and layer-specific neuronal differentiation at prenatal developmental stages..... consistent with an early prenatal origin of autism or at least prenatal processes that may confer a predisposition to autism.”

“Given the well-described phenotypic heterogeneity in autism, the presence of a relatively similar pathological feature across cases was unexpected. However, the features that we describe here may explain some of the heterogeneity of autism: disorganized patches in different locations could disrupt disparate functional systems in the prefrontal and temporal cortices and potentially influence symptom expression.”
Agenesis of the corpus callosum and autism: a comprehensive comparison

Agenesis of the corpus callosum (ACC) is a congenital condition in which the corpus callosum fails to develop; such individuals exhibit localized deficits in non-literal language comprehension, humour, theory of mind and social reasoning.

We directly compared a group of 26 adults with ACC to a group of 28 adults with a diagnosis of ASD but no neurological abnormality. All participants had full scale intelligence quotient scores >78. Groups were matched on age, handedness, and gender ratio. Dx was based on clinical presentation & ADOS, plus early developmental Hx as supplied by parents.

Results: 8/26 of ACC subjects presented with autism. However, more formal diagnosis additionally involving recollective parent-report regarding childhood behaviour showed that only 3/22 met complete formal criteria for an ASD (parent reports were unavailable for four subjects).

We found no relationship between intelligence quotient and autism symptomatology in ACC, nor evidence that the presence of any residual corpus callosum differentiated those who exhibited current autism spectrum symptoms from those who did not.

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 MNS, and decreased connectivity between MPFC and TPJ.
"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."

- 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

Risk Factors
- Genetic
- Pre & Perinatal
- Immunologic

Psychiatric Symptom Impairment in Children with Autism Spectrum Disorders

- 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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence (%)</th>
<th>impairment*</th>
<th>DSM-IV criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD (any type)</td>
<td>83%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>53%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>23%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>70%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>48%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Social phobia</td>
<td>9%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Major Depressive D/O, Dysphoria</td>
<td>45%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Manic episode</td>
<td>53%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>48%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Any disorder</td>
<td>94%</td>
<td>94%</td>
<td></td>
</tr>
</tbody>
</table>

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

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

- 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
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

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

Mark R. Bodis-Wollner, Elyse MacDonald, 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

http://www.jamesshine.com/541.html

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Conditional Knockout Mice

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For a complimentary assessment of your knockout mouse project:

http://www.ozgene.com/services/knockouts

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DOI: 10.1007/s00213-015-2999-3

ORIGINAL PAPER

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

Mark R. Bodis-Wollner, Elyse MacDonald, 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

---

Box 1: Long-term and short-term follow-up of patients diagnosed with Asperger’s disorder or a PDD-NOS phenotype.

- 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. Excluded: 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.
Autism spectrum disorder (ASD) is a neurodevelopmental condition exhibiting impairments in behaviour, social and communication skills. These deficits may arise from aberrant functional connections that impact synchronization and effective neural communication. 

We tested the efficacy of NFT in reducing symptoms in children with ASD by targeting training to the mirror neuron system (MNS) via modulation of EEG mu rhythms.
Subjects:
13 ASD (10 males; mean age = 11 yr; range = 7–17 yr) and 11 TD (7 males; mean age = 10 yr; range = 8–17 yr)

All subjects completed ~30 h of NFT, in biweekly 45-60 minute sessions, consisting of 15 minute segments of viewing preferred videos / DVD’s, interspersed with rest periods.

In order for the video clip or DVD to play, power in the 8–12 Hz band (mu) recorded at the C4 electrode site had to be maintained above a pre-determined threshold for at least 1s, while theta (4–8 Hz) and beta (13–30 Hz) activity had to remain below pre-determined thresholds.

When the theta and beta rhythms exceeded threshold, the video or DVD would pause. To resume playing, the subject had to focus and maintain levels of these frequencies above (mu rhythm) and below (theta, beta) threshold for at least 1s.

Comment:
• Absence of a Sham Treatment Group undercuts the import of any perceived behavioral improvements in the ASD subjects
• Small numbers, short length of follow-up
• EEG changes: in some instances the ASD group showed greater improvement than the TD group, but starting from a lower baseline. The meaning of this improvement in the real world is unclear

Pre-and Post-NFT parent completion of the Social Responsiveness Scale (SRS), the Autism Treatment Evaluation Checklist (ATEC) and the Vineland Adaptive Behaviour Scales (Vineland-II; not shown).

Children with ASD suffer auditory figure/ground problems severe enough to exacerbate the communication deficits central to the disorder and to delay academic progress. The most significant predictor of educational performance in children with ASD is their ability to understand speech and maintain concentration in the presence of background noise. Sustained use of FM listening devices can enhance speech perception in noise, aid social interaction, and improve educational outcomes in children with ASD.
What does it all mean?

Where is the boundary of ASD vs. “Normal”?

- DSM5 rejects the concept of “subclinical” disorders, but population based genetic, neuroanatomic, and neuropsychological data tell a different story.

There is no such thing as “Autism Spectrum Disorder”

- Rather, there are myriad different conditions with discrete etiologies and overlapping clinical presentations
  - “ASD is a disorder of subsets”
- Example: “Bright’s Disease”
  - Now broken down into numerous distinct forms of chronic kidney disease

There is no such thing as “Autism Spectrum Disorder”

- With a lab-centric focus, the clinical boundaries of what we consider “ASD” to be will shift
  - Male:Female ratio
  - AS returns?
  - Social Pragmatic Language D/O
  - BAP
- Example: Fra-X
  - Male vs. Female phenotype (milder in females!)
  - Pre-mutation (anxiety d/o, ovarian failure)
  - FRAFX ataxia in PGF’s (“Parkinson-like”)

Psychiatric Symptoms in ASD: Paradigm Shift

- Not “Comorbidity,” but
- Continuum, and
- Metamorphosis

It’s time to re-conceptualize the relationship between ASD and “Mental Illness”
Comorbidity:
A, B, C,... etc. are completely different entities, that sometimes happen to co-exist.

As DSM would have it....

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

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

**19th century neuroscientists’ dilemma**

- How do we construct a science of human behavior, on an equal footing with the physical sciences?

**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”)

Not until philosophers become kings, and kings become philosophers, will we have the perfect republic.

Plato – 428 - 348 BCE
Wilder Penfield (1891-1976)

http://editthis.info/psy3241/Wilder_Penfield

Freud: Neuropathologist

"Critical Introduction to Neuropathology" (1885-87)

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

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...


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

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.”

Psychology without reference to “consciousness”

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Edward Thorndike (1874 – 1949)

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


Thorndike 1905


Skinner, ca. 1950

http://www.youtube.com/watch?v=sjvzGjSW4t6sk&NR=1&feature=endscreen

1900-2000

Brain = “Black Box” (Behaviorist)

Antecedent → Brain → Consequence
  - Ego
  - Superego
  - Id

1900-2000

Brain = “Black Box” (Psychoanalyst)

Antecedent → Brain → Consequence
  - Ego
  - Superego
  - Id
2015: Private mental events aren’t so private any more

It’s time to re-integrate behaviorism, psychiatry, classical psychology, and neuropsychology

- 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
  - Etc.

Treatment, Prognosis, Acceptance

- Primary prevention (i.e., pre-Dx; e.g. fetal therapy)
  - Ethical issues:
    - Where does “ASD” overlap w. “variation of normal”?
    - If we can avert ASD, can we create super-geniuses?
- Secondary intervention (i.e., post Dx)
  - Targeted gene or drug therapy postnatally
  - Can hands-on therapy “grow new neurons”?
- Tertiary intervention (goal is not “cure”)
  - Real-world functioning
  - Fixing society, rather than the individual with ASD

The GABA Switch

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

**Oxytocin Surge (Birth)**

Excitatory (depolarization) \[\rightarrow\] Inhibitory (hyperpolarization)
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)

Intervention Paradigm

DD Model  Mental Health Model

Progression of Interventions
LONG TERM FOLLOW-UP CLINICS FOR SURVIVORS OF CHILDHOOD CANCER

The majority of children diagnosed with cancer will survive. However, many will experience long-term medical, psychological, and/or social problems due to chemotherapy, radiation, or surgery. Children who have been treated for cancer should be monitored periodically to prevent late effects of childhood cancer. A list of late effects clinics is kept on the post-treatment resource center (thanks to Nancy James).

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)**

**Pharmacotherapy**

- As an adjunct to face-to-face therapy (CBT, family therapy, etc.)
- Not a “crutch,” any more than using a puffer for asthma is a crutch
- Earlier may be better than later
  - Self-image is forming: “I am competent” vs. “I am incompetent”

**Thank you**

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Leo Kanner
1894-1981

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