JAMES COPLAN, M.D.
Neurodevelopmental Pediatrician · Author · Speaker
Making Sense of Autistic Spectrum Disorders

www.drcoplan.com

James Coplan, MD
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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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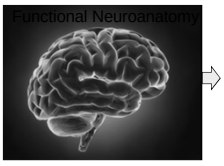
Outline

Risk Factors
- Proven
- Speculative



Clinical Features → Treatment & Outcome

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

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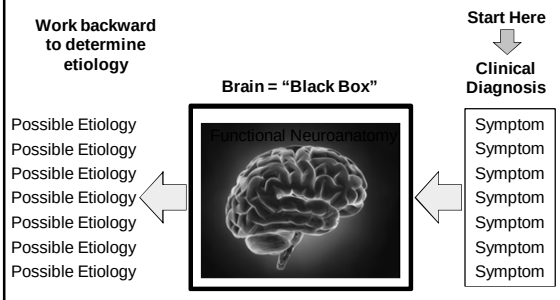
We must, then, assume that these children have come into the world with an innate inability to form the usual, biologically provided affective contact with people, just as other children come into the world with innate physical or intellectual handicaps. If this assumption is correct, a further study 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

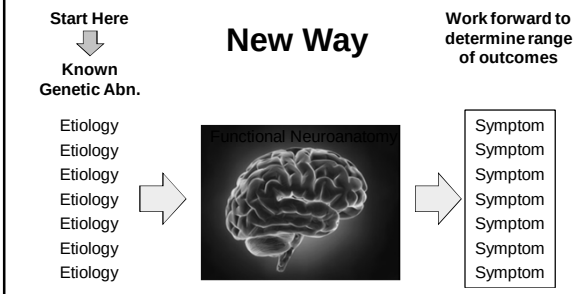
Traditional Medical Practice
("What's the matter with my patient?")



Working back

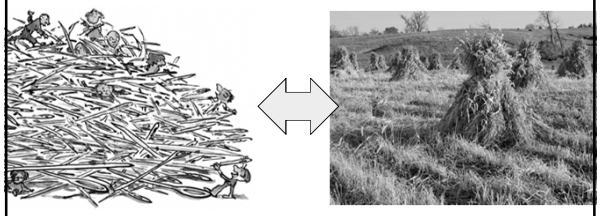
- **PKU: Asbjørn Følling (1934)**
  - **2 siblings with severe ID, and an unusual odor to the urine**

http://www.pkunews.org/about/history.htm

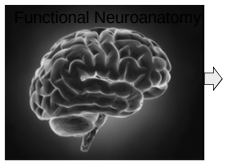


New Way
(What does this needle do?)

New Way
(Many needles, many haystacks)

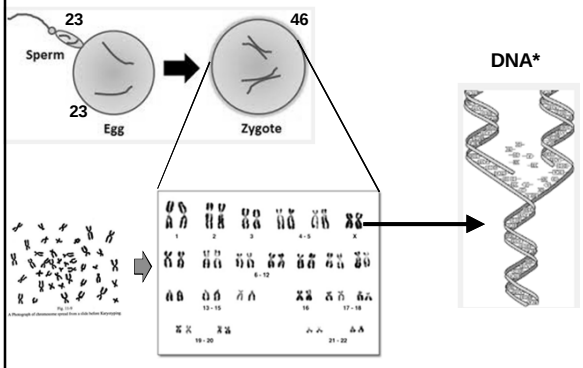


Risk Factors
- Genetic



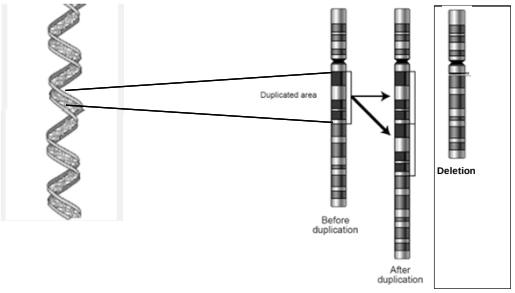
Clinical Features → Treatment & Outcome

A quick review



*6 feet of DNA per cell, or 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: ~ 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**

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"

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"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**

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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

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"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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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
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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

Holly A. Stessman,[1] Raphael Bernier,[2] and Evan E. Eichler[1,3,*]
[1]Department of Genome Sciences, University of Washington, Seattle, WA 98195, USA
[2]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA 98195, USA
[3]Howard Hughes Medical Institute, University of Washington, Seattle, WA 98195, USA
*Correspondence: eee@gs.washington.edu

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

Holly A. Stessman,[1] Raphael Bernier,[2] and Evan E. Eichler[1,3,*]
[1]Department of Genome Sciences, University of Washington, Seattle, WA 98195, USA
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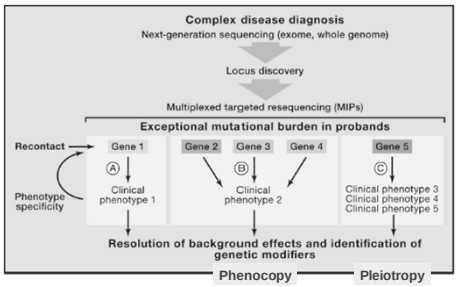

Figure 1. Schematic of Genotype-First Approach for ASD

Review

Feature Review

2013

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

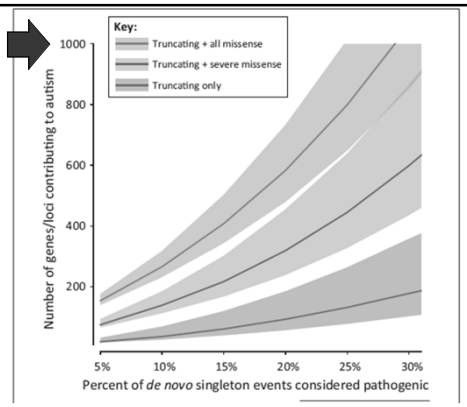

Figure 1. Estimating the number of autism spectrum disorder (ASD) / intellectual disability (ID) risk genes. Krumm, 2013

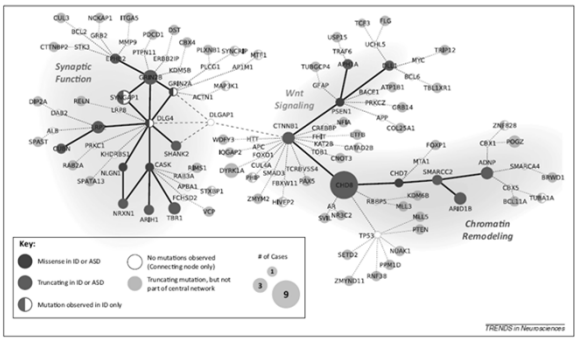

Figure 3. Predicted proteins disrupted by genic de novo mutations in autism spectrum disorder (ASD) and intellectual disability (ID) form a central connected network. Krumm 2013

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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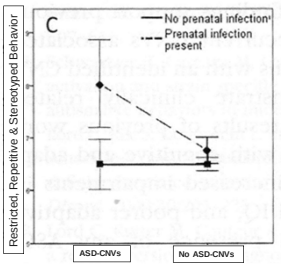

ARTICLE

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[1], Solveig R. Davidsdottir[1], Larus J. Gudmundsson[1], Gudbjorn F. Jonsson[1], Berglind Stefansdottir[1], Isafold Helgadottir[1], Magnus Haraldsson[1,3], Birna Jonsdottir[1], Johan H. Thygesen[1], Adam J. Schwarz[5], Michael Didriksen[6], Tine B. Stensbol[6], Michael Brammer[4], Shitij Kapur[4], Jonas G. Halldorsson[1], Stefan Hreidarsson[10], Evald Saemundsen[3,10], Engilbert Sigurdsson[3,3] & Kari Stefansson[1]

16 JANUARY 2014 | VOL 505 | NATURE | 361

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

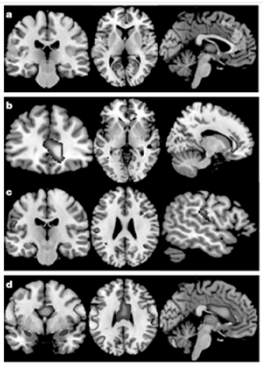

Figure 3. Dose-dependent alterations in brain structure in 15q11.2 (BP1-BP2) CNV carriers. Stefansson 2014

Food for thought

- **Since nominally "asymptomatic" carriers of specific CNVs (which are known to be associated with SCZ or ASD) have demonstrable cognitive and neuroanatomic changes, were is the real boundary for "disease"?**

JAMA Psychiatry. 2015 Mar 4. doi: 10.1001/jamapsychiatry.2014.3028. [Epub ahead of print]

Heritability of Autism Spectrum Disorder in a UK Population-Based Twin Sample.

Colvert E[1], Tick B[1], McEwen F[2], Stewart C[3], Curran SR[4], Woodhouse E[5], Gillan N[6], Hallett V[7], Lietz S[8], Garnett T[9], Ronald A[9], Plomin R[1], Rijsdijk F[1], Happé F[1], Bolton P[2].

- **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**

JAMA Psychiatry. 2015 Mar 4. doi: 10.1001/jamapsychiatry.2014.3028. [Epub ahead of print]

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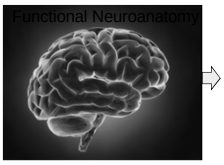
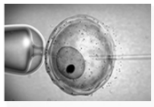
- **Correlations among monozygotic twins (range, 0.77-0.99) were significantly higher than for dizygotic twins (range, 0.22-0.65), giving heritability estimates of 56% to 95%**
- **The liability to ASD and a more broadly defined high-level autism trait phenotype in this large population-based twin sample derives primarily from additive genetic and, to a lesser extent, nonshared environmental effects**

Risk Factors
- Genetic
- Pre & Perinatal



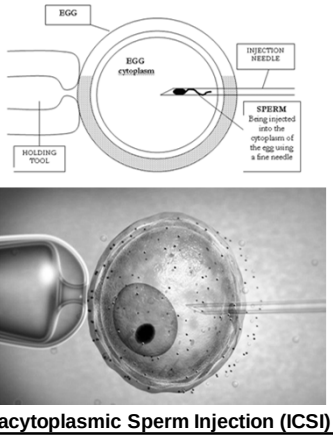
Clinical Features → Treatment & Outcome

1978



OR: ICSI

Gamete Intrafallopian Transfer ("GIFT")



Intracytoplasmic Sperm Injection (ICSI)

Original Investigation

Autism and Mental Retardation Among Offspring Born After In Vitro Fertilization

Sven Sandin, MSc; Karl-Gösta Nygren, PhD; Anastasia Iliadou, PhD; Christina M. Hultman, PhD; Abraham Reichenberg, PhD

JAMA 2013

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.

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JAMA 2013

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.

Cohort Studies

	Outcome		
Exposure Status	Disease	No Disease	Risk of Dz
Exposed	a	b	a /(a+b)
Unexposed	c	d	c /(c+d)

Enroll & Follow → "RISK"

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?

"The power of 1"

- **Relative Risk (RR) or Odds ratio (OR), and (95% Confidence Interval):**
  - **1 or greater: Means the odds are *equal or increased***
  - **1 or less: Means the odds are *equal or decreased***
  - **If the 95% CI spans 1 (i.e., the upper bound is >1 and the lower bound is <1), then the risk (or odds) "might be increased, or might be decreased"**

Original Investigation

Autism and Mental Retardation Among Offspring Born After In Vitro Fertilization

Sven Sandin, MSc; Karl-Gösta Nygren, PhD; Anastasia Iliadou, PhD; Christina M. Hultman, PhD; Abraham Reichenberg, PhD

JAMA 2013

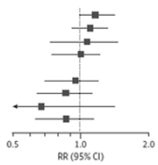
RESULTS

- **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)**

Comparison of Offspring Born After Any In Vitro Fertilization vs Being Spontaneously Conceived (Reference)—All Offspring

A Relative risk of autistic disorder

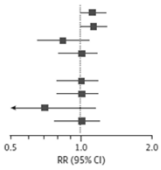
	No. of Cases		No. of Offspring		RR (95% CI)
	IVF	Spontaneous	IVF	Spontaneous	
All offspring					
Crude	103	6856	30959	2510166	1.22 (1.01-1.49)
Adjusted	103	6856	30959	2510166	1.14 (0.94-1.39)
Preterm birth	35	665	5942	143688	1.10 (0.78-1.54)
Term birth	68	6191	25017	2366478	1.00 (0.79-1.28)
Singletons					
Crude	54	6683	22228	2455493	0.96 (0.74-1.26)
Adjusted	54	6683	22228	2455493	0.89 (0.68-1.17)
Preterm birth	7	596	1844	120702	0.71 (0.34-1.50)
Term birth	47	6087	20384	2334791	0.89 (0.67-1.19)



All models were adjusted for sex, attained age, birth year, paternal age categorically, maternal age categorically, maternal psychiatric history at offspring birth (yes or no), paternal psychiatric history at offspring birth (yes or no), except for "crude," which was adjusted for sex, attained age, and birth year. Term and preterm births are subgroups of the data. IVF indicates in vitro fertilization; RR, relative risk.

B Relative risk of mental retardation

	No. of Cases		No. of Offspring		RR (95% CI)
	IVF	Spontaneous	IVF	Spontaneous	
All offspring					
Crude	180	15647	30959	2510166	1.16 (1.00-1.35)
Adjusted	180	15647	30959	2510166	1.18 (1.01-1.36)
Preterm birth	70	2127	5942	143688	0.87 (0.69-1.11)
Term birth	110	13520	25017	236478	1.01 (0.84-1.22)
Singletons					
Crude	101	15178	22228	2455494	1.01 (0.83-1.23)
Adjusted	101	15178	22228	2455494	1.01 (0.83-1.24)
Preterm birth	17	1875	1844	120702	0.74 (0.46-1.20)
Term birth	84	13303	20384	2334791	1.01 (0.81-1.25)



All models were adjusted for sex, attained age, birth year, paternal age categorically, maternal age categorically, maternal psychiatric history at offspring birth (yes or no), paternal psychiatric history at offspring birth (yes or no), except for "crude," which was adjusted for sex, attained age, and birth year. Term and preterm births are subgroups of the data. IVF indicates in vitro fertilization; RR, relative risk.

Original Investigation

Autism and Mental Retardation Among Offspring Born After In Vitro Fertilization

Sven Sandin, MSc; Karl-Gösta Nygren, PhD; Anastasia Iliadou, PhD; Christina M. Hultman, PhD; Abraham Reichenberg, PhD

JAMA 2013

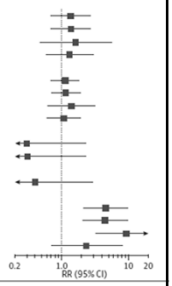
For specific procedures, IVF with ICSI for paternal infertility was associated with a small increase in the RR for autistic disorder and mental retardation compared with IVF without ICSI, fresh.

The prevalence of these disorders was low, and the increase in absolute risk associated with IVF was small.

2. Comparison of Offspring Born After Specific IVF Procedures vs IVF Without ICSI, Fresh Embryo (Reference)—All Offspring

A Relative risk of autistic disorder by IVF procedures

	No. of Cases		No. of Offspring		RR (95% CI)
	Specific Procedure	Reference Procedure	Specific Procedure	Reference Procedure	
IVF without ICSI, frozen					
Crude	10	53	2777	16668	1.44 (0.73-2.85)
Adjusted	10	53	2777	16668	1.46 (0.74-2.89)
Preterm birth	3	17	453	3626	1.69 (0.49-5.79)
Term birth	7	36	2342	13042	1.39 (0.62-3.14)
ICSI, fresh					
Crude	31	53	9241	16668	1.16 (0.73-1.85)
Adjusted	31	53	9241	16668	1.20 (0.75-1.91)
Preterm birth	10	17	1562	3626	1.47 (0.66-3.26)
Term birth	21	36	7679	13042	1.11 (0.64-1.93)
ICSI, frozen					
Crude	1	53	1477	16668	0.32 (0.04-2.34)
Adjusted	1	53	1477	16668	0.33 (0.05-2.40)
Preterm birth					
Term birth	1	36	1287	13042	0.42 (0.06-3.09)
ICSI, fresh surgery					
Crude	8	53	628	16668	4.64 (2.17-9.92)
Adjusted	8	53	628	16668	4.60 (2.14-9.88)
Preterm birth	5	17	107	3626	9.54 (3.43-26.6)
Term birth	3	36	521	13042	2.42 (0.74-7.97)



In vitro fertilization (IVF) without intracytoplasmic sperm injection (ICSI), fresh embryo transfer is the reference category. All models were adjusted for sex, attained age, birth year, paternal age categorically, maternal age categorically, maternal psychiatric history at offspring birth (yes or no), paternal psychiatric history at offspring birth (yes or no), except for "crude," which was are adjusted for confounding sex, attained age, and birth year. Term and preterm births are subgroups of the data. Groups in the figures without error bars do not have sufficient data to allow an estimation of the confidence intervals. For the same reason, ICSI, frozen embryo, and surgically extracted sperm are not shown. RR indicates relative risk.

Human Reproduction, Vol.28, No.3 pp. 812–818, 2013
Advanced Access publication on January 4, 2013 doi:10.1093/humrep/des430

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Autism spectrum disorders in IVF children: a national case–control study in Finland

V. Lehti[1], A.S. Brown[2,3], M. Gissler[1,4,5], M. Rihko[1], A. Suominen[1], and A. Sourander[1,*]

- **Finnish Prenatal Study of Autism, a nested case–control study based on a national birth cohort, to identify pregnancy, infancy and childhoood risk factors for ASDs**
- **Two national registers for 4,164 autistic cases and their 16,582 matched controls born in 1991–2005.**
- **Data on IVF were collected from the Finnish Medical Birth Register**
  - **Four controls were matched to each case**
- **Date were adjusted for maternal age, SES, parity, and child's birth order, singleton vs multiple birth, gestational age, and gender**

Case-Control Studies

	Outcome		
Exposure Status	Disease ("Cases")	No Disease ("Controls")	Risk of Dz
Exposed	a	b	a /(a+b)
Unexposed	c	d	c /(c+d)

Risk is unknown

(a/c) = Odds that Cases were exposed

(b/d) = Odds that Controls were exposed

ODDS RATIO = (a/c) / (b/d)
Are the odds increased that persons with disease were more likely to have been exposed, compared to persons w/o disease?

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 (singletons 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)**

Lehti et al 2013

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.

OXFORD JOURNALS
Human Reproduction Update
Hum. Reprod. Update (November/December 2014) 20 (6): 840-852. doi: 10.1093/humupd/dmu033

A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously

1. Gabija Lazaraviciute1,
2. Miriam Kauser1,
3. Sohinee Bhattacharya1,
4. Paul Haggarty2 and
5. Siladitya Bhattacharya1,*

"Heterogeneity in the types of fertility treatment, the imprinted regions studied, the tissues used and the methods of measurement, reduce our ability to assess the full effect of ART on DNA methylation and imprinting. More controlled studies, using standardized methodologies, in larger, better clinically defined populations are needed." (Stay tuned….)

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.

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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).

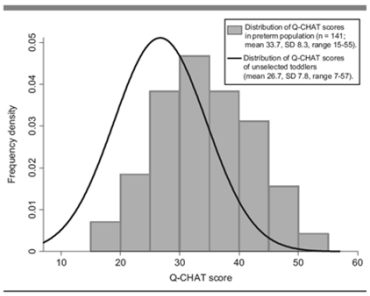
ORIGINAL ARTICLES
www.jpeds.com • The Journal of Pediatrics

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[3], 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.

Wong 2014

Table II. Item-specific distribution of Q-CHAT scores

Q-CHAT item	Score (% of responses) 0	1	2	3	4	Difference in distribution compared with general population (P)
Items exploring social-relatedness						
1. Look when name is called*	49.6	44.7	5.0	0.0	0.7	.13
2. Eye contact*	52.5	44.0	2.8	0.7	0.0	.004
3. Protoimperative pointing*	68.8	25.5	3.5	0.7	1.4	.58
4. Protodeclarative pointing*	61.7	24.1	11.3	0.7	2.1	.56
5. Pretend play*	64.5	22.0	7.8	2.1	3.5	.02
6. Follow a gaze*	53.6	37.1	7.1	0.7	1.4	.45
7. Offer comfort	34.8	32.6	24.6	4.3	3.6	.04
8. Use simple gestures*	76.6	18.4	3.5	0.7	0.7	.28
9. Check reaction	33.3	32.6	22.0	9.9	2.1	<.001
Restricted, repetitive, stereotyped behavior						
10. Line objects up†	7.1	10.6	40.4	24.1	17.7	<.001
11. Interest maintained by spinning object†	16.8	43.1	26.3	6.6	7.3	<.001
12. Adapt to change in routine*	23.4	58.2	17.0	1.4	0.0	<.001
13. Do the same thing over and over again	8.5	7.8	13.5	23.4	46.8	<.001
14. Echolalia	2.8	3.5	19.1	25.5	48.9	.06
15. Unusual finger movement†	53.2	10.1	12.9	13.7	10.1	<.001
16. Maintenance of interest†	23.9	24.6	30.4	13.0	8.0	<.001
17. Twiddle objects repetitively†	33.1	14.4	17.3	24.5	10.8	<.001
18. Stare at nothing with no purpose*	59.6	22.7	9.2	5.0	3.5	.15
Communication abnormalities						
19. Understand child's speech	18.4	36.9	31.2	12.1	1.4	<.001
20. Number of words	17.9	17.9	41.4	19.3	3.6	.69
21. Typicality of first words*	56.2	34.3	4.4	1.5	3.6	.02
22. Use of hand as tool	7.8	5.0	10.6	36.2	40.4	<.001
Sensory abnormalities						
23. Sniff or lick unusual objects	15.9	14.5	20.3	29.0	20.3	<.001
24. Walk on tiptoe†	13.5	22.0	46.8	9.9	7.8	<.001
25. Oversensitive to noise†	23.4	36.9	21.3	9.2	9.2	<.001

*χ^2 test was performed by combining proportions with scores 2, 3, and 4.
†χ^2 test was performed by combining proportions with scores 3 and 4.

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*

Table III. Univariable associations of neonatal and sociodemographic factors with Q-CHAT scores

Variable	n	Coefficient (Q-CHAT score)	95% CI	z-statistic	P
Gestation (per completed wk)	141	−0.77	−1.61-0.06	−1.82	.07
Birthweight z-score (per point increase)	126	0.07	−1.41-1.55	0.09	.09
Male sex	141	0.27	−2.54-3.07	0.19	.85
Singleton pregnancy	141	3.80	−0.42-8.01	1.76	.08
White ethnicity	141	−7.55	−10.2 to −4.86	−5.51	.001
Maternal age (per y)	141	−0.17	−0.40-0.07	−1.38	.17
Cesarean delivery	132	−2.22	−5.38-0.93	−1.38	.17
Length of mechanical ventilation (per d)	139	0.10	−0.01-0.20	1.84	.07
Supplemental oxygen requirement at 36 wk post-menstrual age	141	1.30	−2.06-4.67	0.76	.45
IMD quintile (per quintile increase in deprivation)	141	2.07	1.04-3.11	3.94	<.001

IMD = Index of Multiple Deprivation

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")

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**

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]

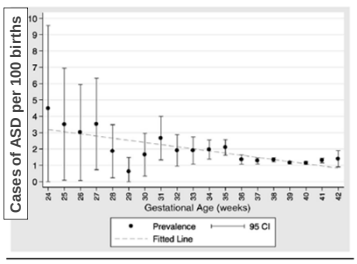


Figure. Prevalence of KP ASD by gestational age.

ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

J Pediatr 2014;164:20-5

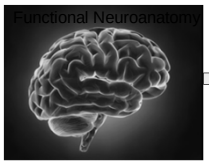
Prevalence and Neonatal Factors Associated with Autism Spectrum Disorders in Preterm Infants

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.

Risk Factors
- Genetic
- Pre & Perinatal
- Immunologic



Clinical Features → Treatment & Outcome

Molecular Psychiatry (2014) 19, 259–264
© 2014 Macmillan Publishers Limited All rights reserved 1359-4184/14
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)	1.32 (0.83–2.26)	0.23
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,*]

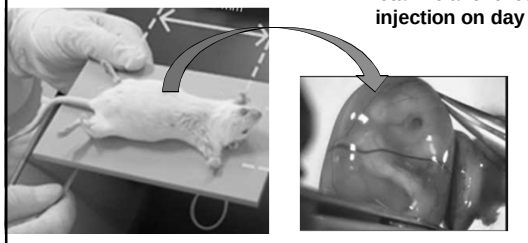
[a] Department of Pathology and Laboratory Medicine, UC Davis, 95817 Sacramento, CA, United States
[b] Institute for Pediatric Regenerative Medicine and Shriners Hospitals for Children Northern California, 95817 Sacramento, CA, United States
[c] M.I.N.D. Institute, UC Davis, 95817 Sacramento, CA, United 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

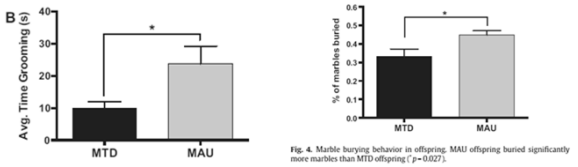


Fig. 4. Marble burying behavior in offspring. MAU offspring buried significantly more marbles than MTD offspring ($p = 0.027$).

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

Contents lists available at ScienceDirect
Peptides
journal homepage: www.elsevier.com/locate/peptides
ELSEVIER
2014

Autistic children display elevated urine levels of bovine casomorphin-7 immunoreactivity

Oleg Sokolov[a,*], Natalya Kost[a], Olga Andreeva[a], Ekaterina Korneeva[b], Viktor Meshavkin[a], Yulia Tarakanova[a], Aleksander Dadayan[c], Yurii Zolotarev[c], Sergei Grachev[d], Inna Mikheeva[b], Oleg Varlamov[e], Andrey Zozulya[a]

[a] Mental Health Research Center of RAMS, Moscow, Russia
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[d] Institute of Bioorganic Chemistry RAS, Moscow, Russia
[e] Oregon National Primate Research Center, OR, United States

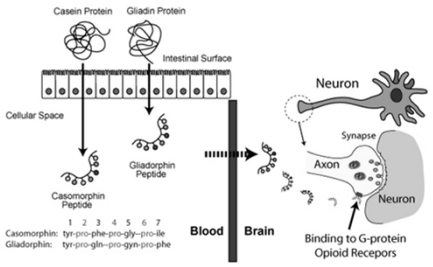
Casomorphins (CM): exogenous opioid peptides from milk casein

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 exorphins in the brain may directly modulate the opioid and other neurotransmitter systems, leading to the development of ASD"

Opioid-excess hypothesis

Neuronal Receptors for Casein and Gliadin Peptides



https://www.peds.ufl.edu/divisions/genetics/_style/images/casomorphin-diag.jpg

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

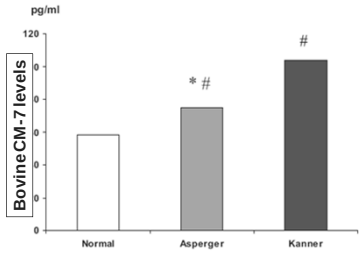


Fig. 1. Bovine CM-7 in the urine of 10 healthy and 10 autistic children. # significantly different from a normal group, $p < 0.05$; * significantly different from Kanner group ($n = 5$), $p < 0.05$.

Sokolov 2014

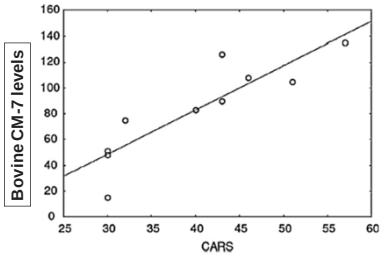


Fig. 2. Bovine CM-7 content in urine and clinical scores by the Childhood Autism Rating Scale (CARS). Spearman rank correlation 0.85, $p < 0.01$.

BCPT
Basic & Clinical Pharmacology & Toxicology, 2014, 114, 128–136
Doi: 10.1111/bcpt.12154

MiniReview

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

Aletta D. Kraneveld[1], Caroline G.M. de Theije[1], Floor van Heesch[1], Yuliya Borre[1], Sander de Kivit[1], Berend Olivier[1], Mechiel Korte[1] and Johan Garssen[1,2]

[1]Division of Pharmacology, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands and [2]Department of Immunology, Nutricia Research, Utrecht, The Netherlands

(Received 15 July 2013; Accepted 4 September 2013)

Abstract: Disturbed bidirectional pathways between the (central) nervous system and immune system have been implicated in various mental disorders, including depressive and neurodevelopmental disorders. In this minireview, the role of the neuro-immune axis and its targetability in relation to major depression and autism spectrum disorder will be discussed. All together, the management of these and possibly other multi-factorial mental disorders needs a new and integrated therapeutic approach. Pharmacologically bioactive molecules as well as medical nutrition targeting the (gut)–immune–brain axis could be such an approach.

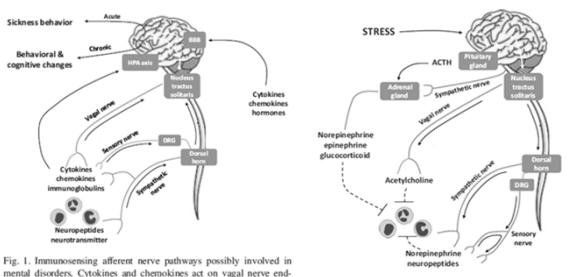


Fig. 1. Immunosensing afferent nerve pathways possibly involved in mental disorders. Cytokines and chemokines act on vagal nerve endings leading to behavioural and cognitive deficits. Lymphocyte-derived neurotransmitters and neuropeptides act on sensory nerve endings and modulate pain sensation. Cytokines, like IL1β, act on the hypothalamus and pituitary to produce CRH and ACTH leading to a corticoid response. Leucocyte-derived cytokines, chemokines and hormones cross the blood–brain barrier (BBB) and affect the CNS. Adapted from [1].

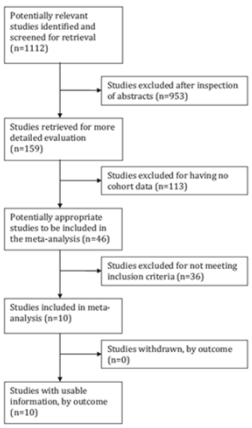
Fig. 2. Immunomodulating efferent nerve pathways possibly involved in mental disorders. Vagal nerve-derived acetylcholine acts on innate immune cells, such as macrophages and dendritic cells, to dampen pro-inflammatory cytokine release. Hormones from the hypothalamus–pituitary–adrenal axis influence lymphocyte function. Released neurotransmitters and neuropeptides from sympathetic and sensory nerve ending, respectively, regulate the function of immune cells. Adapted from [1].

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

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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

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

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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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Study name	Odds ratio	Lower limit	Upper limit	p-Value
Madsen et al. (2002)	0.92	0.68	1.24	0.59
Madsen et al. (2002) a	0.83	0.65	1.06	0.14
Verstraeten et al. (2003)	1.00	0.92	1.09	1.00
Hviid, et al. (2003)	0.85	0.60	1.20	0.36
Hviid, et al. (2003) a	1.12	0.88	1.43	0.36
Andrews et al. (2004)	0.99	0.88	1.12	0.87
Uchiyama, Kurosawa, & Inaba (2007)	0.62	0.32	1.20	0.15
	0.98	0.92	1.04	0.53

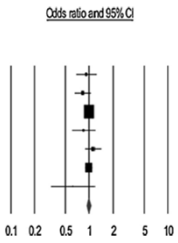


Fig. 2. Combined estimate for vaccines and autism or ASD.

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*

L.E. Taylor et al. / Vaccine 32 (2014) 3623–3629

Group by Vaccine Type	Study name	Odds ratio	Lower limit	Upper limit	p-Value
Hg	Verstraeten et al. (2003)	1.00	0.92	1.09	1.00
Hg	Andrews et al. (2004)	0.99	0.88	1.12	0.87
Hg		1.00	0.93	1.07	0.92
MMR	Madsen et al. (2002)	0.92	0.68	1.24	0.59
MMR	Madsen et al. (2002) a	0.83	0.65	1.06	0.14
MMR	Uchiyama, Kurosawa, & Inaba (2007)	0.62	0.32	1.20	0.15
MMR		0.84	0.70	1.01	0.07
Thimerosal	Hviid, et al. (2003)	0.85	0.60	1.20	0.36
Thimerosal	Hviid, et al. (2003) a	1.12	0.88	1.43	0.36
Thimerosal		1.00	0.77	1.31	0.97

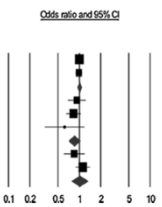
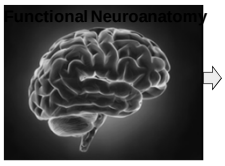


Fig. 4. Pooled estimate for mercury (Hg), MMR vaccines, and thirmerosal.

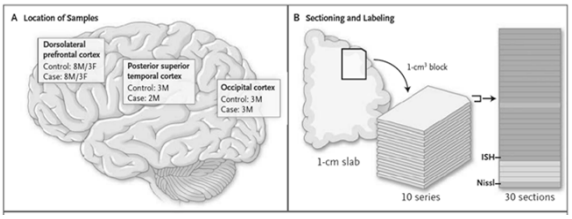
Risk Factors
- Genetic
- Pre & Perinatal
- Immunologic



Clinical Features → Treatment & Outcome

Patches of Disorganization in the Neocortex of Children with Autism

Rich Stoner, Ph.D., Maggie L. Chow, Ph.D., Maureen P. Boyle, Ph.D., Susan M. Sunkin, Ph.D., Peter R. Mouton, Ph.D., Subhojit Roy, M.D., Ph.D., Anthony Wynshaw-Boris, M.D., Ph.D., Sophia A. Colamarino, Ph.D., Ed S. Lein, Ph.D., and Eric Courchesne, Ph.D.



N ENGL J MED 370;13 NEJM.ORG MARCH 27, 2014
The New England Journal of Medicine

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- **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**

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- **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.**

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- **"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."**

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"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 cortexes and potentially influence symptom expression."

N ENGL J MED 370;13 NEJM.ORG MARCH 27, 2014
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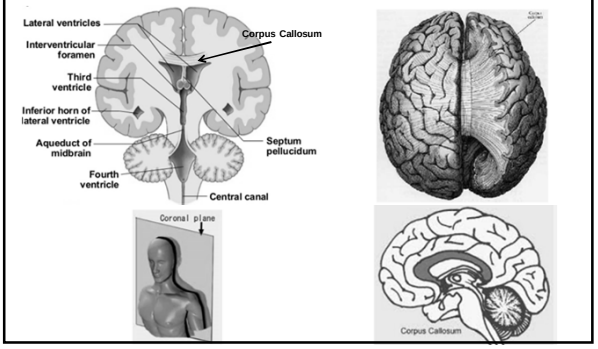
Corpus callosum



doi:10.1093/brain/awu070 Brain 2014: 137; 1813–1829 | 1813
BRAIN
A JOURNAL OF NEUROLOGY

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.

doi:10.1093/brain/awu070 Brain 2014: 137; 1813–1829 | 1813
BRAIN
A JOURNAL OF NEUROLOGY

Agenesis of the corpus callosum and autism: a comprehensive comparison

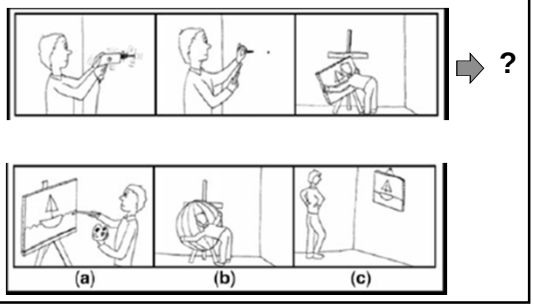
Results
8/26 of ACC subjects presented with autism. However, more formal diagnosis additionally involving recollective parent-report regarding childhood behaviour showed that only 3/22 met complete formal criteria for an ASD (parent reports were unavailable for four subjects).

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.

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



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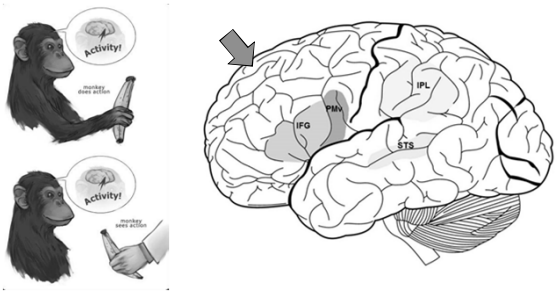
In typically developing controls, Theory of Mind tasks activated the Medial Prefrontal Cortex (MPFC) and the posterior superior temporal sulcus (pSTS) at the Tempero-Parietal Junction (TPJ), as well as the portions of the Mirror Neuron System (ventral premotor region). In subjects with ASD, there was decreased activation of the MNS, and decreased connectivity between MPFC and TPJ

Mirror Neuron System



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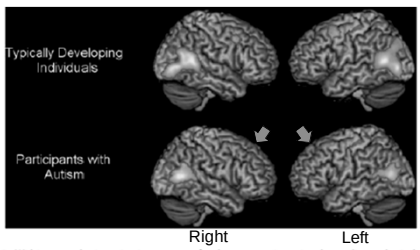

Fig. 2 Within-group brain activation patterns for the contrast intentional causality > physical causality in three different groups. Recruitment of posterior superior temporal sulci and TPJ in all participant groups. In addition, while the whole group and control participants recruited ventral premotor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

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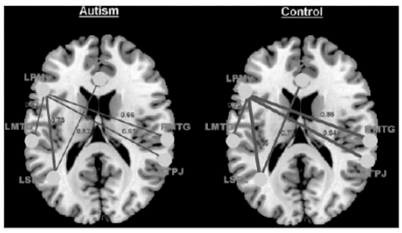

Fig. 3 Significantly weaker functional connectivity in participants with autism, relative to controls, in ToM-related areas and ventral premotor areas during intentional causal attribution.

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

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

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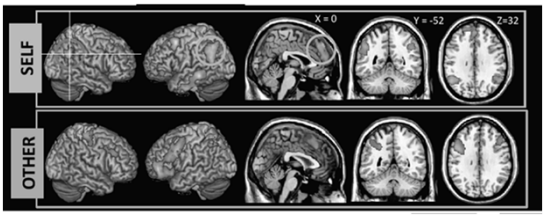
"The simulation theory of mindreading suggests that others' actions are understood by 'putting ourselves in their shoes'. At the neural level, this may be accomplished by a mirror mechanism…. The functional underconnectivity found in participants with ASD between the mirroring and mentalizing systems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

Introspection

Awareness of *one's own* thoughts & feelings

ToM and Introspection



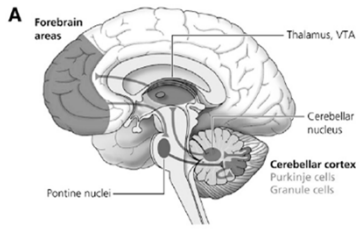
Theory of Mind for you, and for me: behavioral and **neural similarities** and **differences in thinking about beliefs of the self and other**
Gweon H, Young L and , Saxe R, Dept of Brain and Cognitive Sciences, MIT

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

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



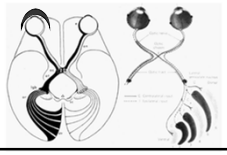
The Cerebellum, Sensitive Periods, and Autism

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

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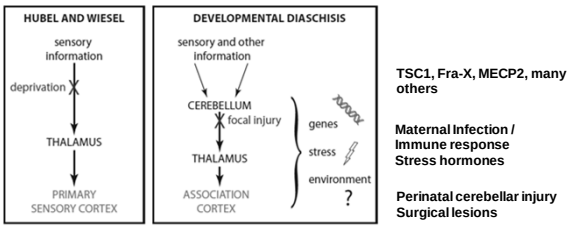


TSC1, Fra-X, MECP2, many others

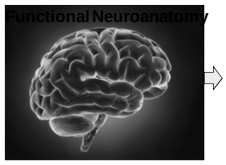
Maternal Infection / Immune response
Stress hormones

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.

Risk Factors
- Genetic
- Pre & Perinatal
- Immunologic

→ Functional Neuroanatomy



→ Clinical Features → Treatment & Outcome

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"**

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

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

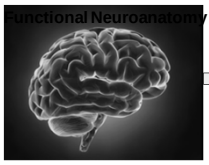
Results:

- **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

Risk Factors
- Genetic
- Pre & Perinatal
- Immunologic



Clinical Features → Treatment & Outcome

Conditional Knockout Mice

Why choose Ozgene to create your knockout mice?

Ozgene is considered the leader in custom designed knockout mice, and we have over two decades of experience creating knockout mice for pivotal medical research globally. In fact, Dr Koentgen and Dr Suess were the first to develop and publish a C57BL/6 knockout mouse in 1993.

Our knockout mouse projects now use goGermline, the revolutionary new technology to generate germline mice fast and efficiently. All of our knockout projects have resulted in germline transmission. This gives us a proven track record, which is evidenced by the multitude of research projects that have resulted in successful publications.

We understand that as a researcher, it is very important that you can track your project. You can access your knockout mouse projects in real-time by logging onto your secure project portal, myOzgene.

A custom designed Vivarium has been built on-site so that we are in complete control of your project. You can trust that we never farm out any stage of your project, which ensures less risk and higher quality knockout mice. Why risk your project to anyone else?

For a complimentary assessment to generate your knockout mice

http://www.ozgene.com/services/knockouts?gclid=CjwKEAjwjKOpBRChjsTyichFy3QSJADPLgTNtNWawKmadhGBMTIBxU_pDBcWxCSy0rYuO9Xld.xm_ohoCdBjw_wcB

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.**

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

ORIGINAL PAPER

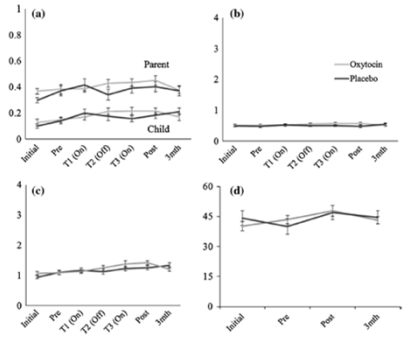
Nasal Oxytocin for Social Deficits in Childhood Autism: A Randomized Controlled Trial

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

J Autism Dev Disord (2014) 44:1720–1732
DOI 10.1007/s10803-014-2049-2

ORIGINAL PAPER

A Parent-Mediated Intervention That Targets Responsive Parental Behaviors Increases Attachment Behaviors in Children with ASD: Results from a Randomized Clinical Trial

Michael Siller · Meghan Swanson · Alan Gerber · Ted Hutman · Marian Sigman

Published online: 2 February 2014

Preschool-Based Social Communication Treatment for Children With Autism: 12-Month Follow-Up of a Randomized Trial

Anett Kaale, MSEd, Morten W. Fagerland, PhD, Egil W. Martinsen, MD, PhD, Lars Smith, PhD

JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY
VOLUME 53 NUMBER 2 FEBRUARY 2014

Brain Imaging Behav. 2015 Mar;9(1):74-88. doi: 10.1007/s11682-014-9331-y.

Heterogeneity of neural mechanisms of response to pivotal response treatment.

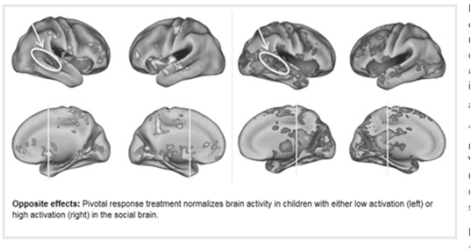
Ventola P[1], Yang DY, Friedman HE, Oosting D, Wolf J, Sukhodolsky DG, Pelphrey KA.

- **Functional magnetic resonance imaging (fMRI) identified brain responses during a biological motion perception task conducted prior to and following 16 weeks of PRT treatment. Overall, the neural systems supporting social perception in these 10 children were malleable through implementation of PRT**
- **Our results support further investigation into the differential effects of particular treatment strategies relative to specific neural targets…creating individually tailored interventions customized to the behavioral and neural characteristics of a given person**

Brain Imaging Behav. 2015 Mar;9(1):74-88. doi: 10.1007/s11682-014-9331-y.

Heterogeneity of neural mechanisms of response to pivotal response treatment.

Ventola P[1], Yang DY, Friedman HE, Oosting D, Wolf J, Sukhodolsky DG, Pelphrey KA.



Opposite effects: Pivotal response treatment normalizes brain activity in children with either low activation (left) or high activation (right) in the social brain.

http://sfari.org/news-and-opinion/news/2014/brain-normalizing-therapy-points-to-new-kind-of-biomarker#refs

Design and Development of a Virtual Dolphinarium for Children With Autism

Yiyu Cai, Noel K. H. Chia, Daniel Thalmann, Norman K. N. Kee, Jianmin Zheng, and Nadia M. Thalmann

IEEE = Institute of Electrical & Electronics Engineers

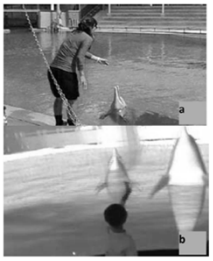


Fig. 4. (a) A professional instructor training a real dolphin in the UWS Dolphin Lagoon and (b) a child with autism acting as a dolphin trainer in the Virtual Dolphinarium.

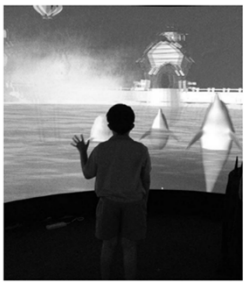


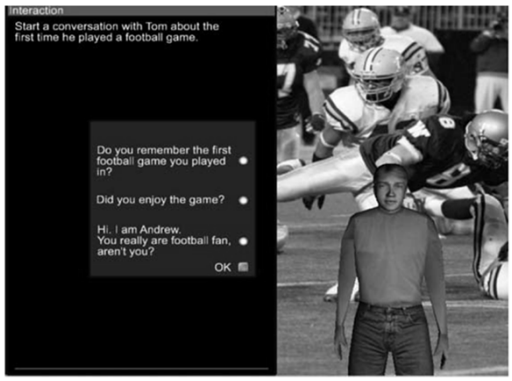
Fig. 5. Engaging a child with autism through 3-D immersive visualization and hand gesturing.

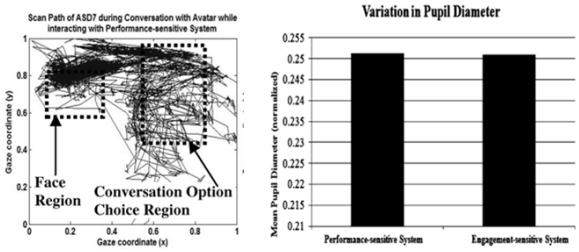
IEEE TRANSACTIONS ON NEURAL SYSTEMS AND REHABILITATION ENGINEERING, VOL. 21, NO. 1, JANUARY 2013 55

Design of a Virtual Reality Based Adaptive Response Technology for Children With Autism

Uttama Lahiri, *Member, IEEE*, Esubalew Bekele, *Student Member, IEEE*, Elizabeth Dohrmann, Zachary Warren, and Nilanjan Sarkar, *Senior Member, IEEE*

Fig. 1. Snapshot of avatar narrating his tour experience to a sea beach within VR environment.





Neurofeedback training produces normalization in behavioural and electrophysiological measures of high-functioning autism

Jaime A. Pineda , Karen Carrasco , Mike Datko , Steven Pillen , Matt Schalles

DOI: 10.1098/rstb.2013.0183 . Published 28 April 2014
PHILOSOPHICAL TRANSACTIONS B

"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"

Neurofeedback training produces normalization in behavioural and electrophysiological measures of high-functioning autism

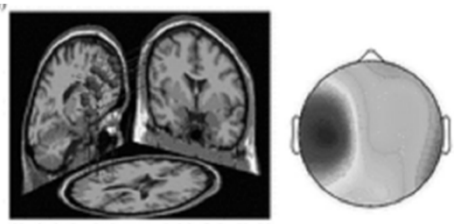
Subjects:
13 ASD (10 males; mean age = 11 yr; range = 7–17 yr) and 11 TD (7 males; mean age = 10 yr; range = 8–17 yr)

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.

Neurofeedback training produces normalization in behavioural and electrophysiological measures of high-functioning autism

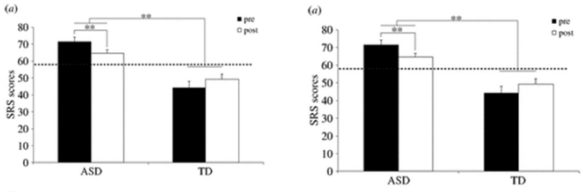
- **In order for the video clip or DVD to play, power in the 8–12 Hz band (mu) recorded at the C4 electrode site had to be maintained *above* a pre-determined threshold for at least 1s, while theta (4–8 Hz) and beta (13–30 Hz) activity had to remain *below* pre-determined thresholds.**
- **When the theta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

Neurofeedback training produces normalization in behavioural and electrophysiological measures of high-functioning autism



mu cluster centred on the left pre-central gyrus

Neurofeedback training produces normalization in behavioural and electrophysiological measures of high-functioning autism



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).

Neurofeedback training produces normalization in behavioural and electrophysiological measures of high-functioning autism

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**

ORIGINAL ARTICLES

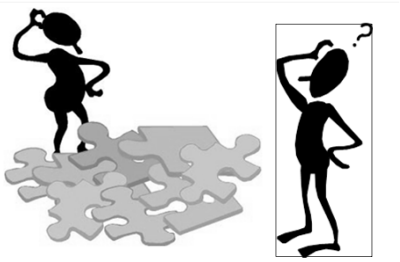
www.jpeds.com • The Journal of Pediatrics

The Use of Listening Devices to Ameliorate Auditory Deficit in Children with Autism

Gary Rance, BEd, DipAud, MSc, PhD[1], Kerryn Saunders, MBBS(Hons), RACP[2], Peter Carew, BSc, MAud[1], Marlin Johansson, BSc, MAud[1], and Johanna Tan, BSc, MAud[1]

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

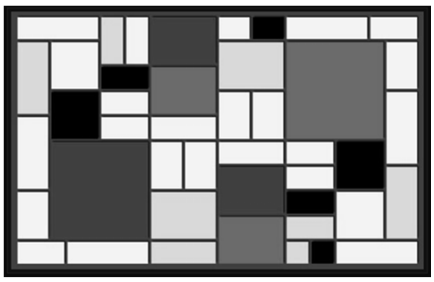
- Example: Fra-X
  - Male vs. Female phenotype (milder in females!)
  - Pre-mutation (anxiety d/o, ovarian failure)
  - FRAXS ataxia in PGF's ("Parkinson-like")

It's time to re-conceptualize the relationship between ASD and "Mental Illness"

Psychatric Symptoms in ASD: Paradigm Shift

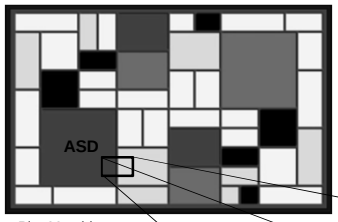
- Not "Comorbidity," but
- Continuum, and
- Metamorphosis

Comorbidity:
***A*, *B*, *C*…. *etc.* are completely different entities, that sometimes happen to co-exist.**



Piet Mondrian (1872-1944) – Line over Form

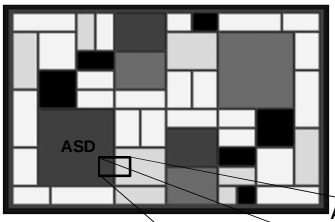
As DSM would have it…..



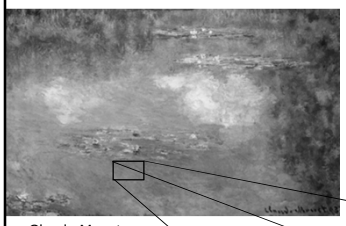
Piet Mondrian
Line over Form

Comorbidity

Reality…..



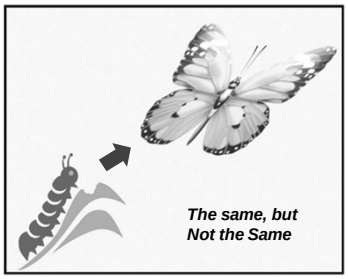
Continuum:
ASD *shades into* Mental Illness, with no 'bright line' of separation



Claude Monet
Water Lillies

Continuum

Not Piet Mondrian, but Claude Monet…



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**

www.drcoplan.com

Not uNtil philosophers become kiNgs, aNd kings become philosophers, will we have the perfect republic.

Plato
~ 428 – 348 BCE

19th century neuroscientists' dilemma

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

Human Behavior ⇨

Correlative Neuroanatomy / Neuropsychol.
- **Wernike, Broca**
- **Penfield**

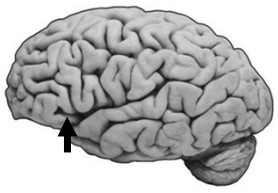
Classical Psychology ("consciousness")
- **James**

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

Analytic Psychiatry (Introspection)
- **Freud**

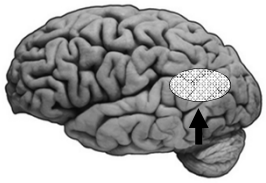
Correlative Neuroanatomy / Neuropsychology

Broca's Area



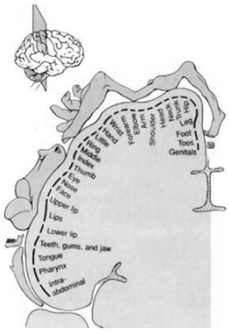
- **Paul Broca, 1861**
- **Severe impairment of speech production**
- **Language comprehension remains intact ("Broca's aphasia")**

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)



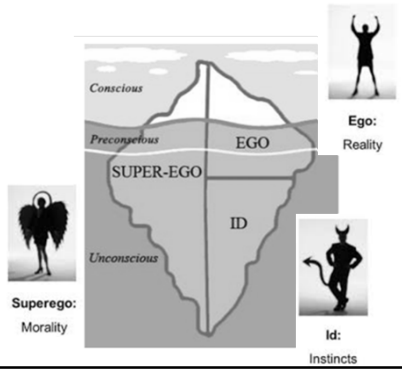
http://editthis.info/psy3241/Wilder_Penfield

Freud: Neuropathologist

"Critical Introduction to Neuropathology" (1885-87)

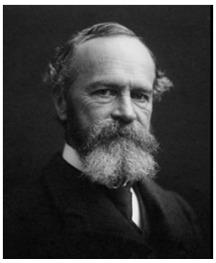
SPECIELLE
PATHOLOGIE UND THERAPIE
HOFRATH PROF. Dr. HERMANN NOTHNAGEL
DIE
INFANTILE CEREBRALLÄHMUNG
VON
Dr. SIGM. FREUD
Privatdocent an der Universität Wien.
WIEN 1897.
ALFRED HÖLDER

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**

www.drcoplan.com

Psychology without reference to "consciousness"

- Understanding, Insight, comprehension
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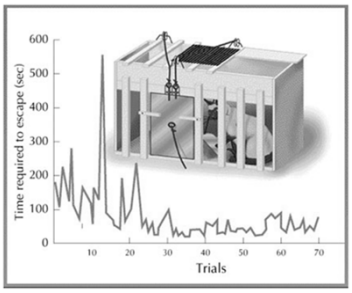
www.drcoplan.com

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



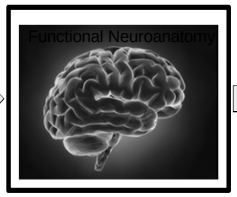
http://en.wikipedia.org/wiki/File:Puzzle_box.jpg

Skinner, ca. 1950

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

1900-2000

Brain = "Black Box" (Behaviorist)

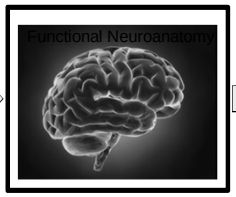
Antecedent → 

→ Consequence

- Ego
- Superego
- Id

1900-2000

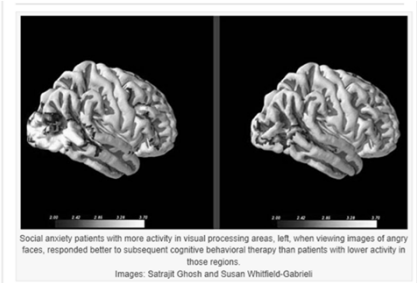
Brain = "Black Box" (Psychoanalyst)

Antecedent → 

→ Consequence

- Ego
- Superego
- Id

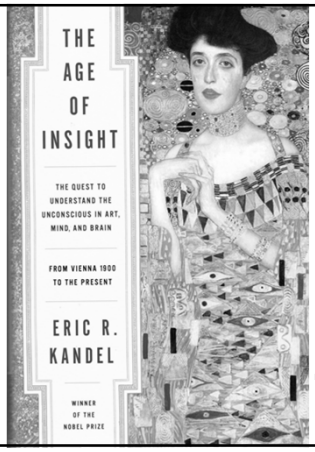
2015: Private mental events aren't so private any more



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

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.

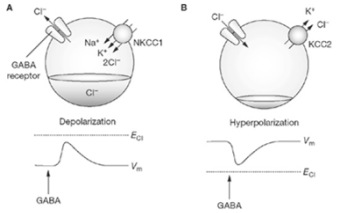


Portrait of Adele Bloch-Bauer I
Gustav Klimt 1907

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



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

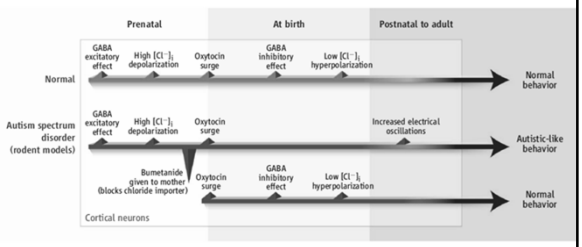
Oxytocin Surge (Birth)

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
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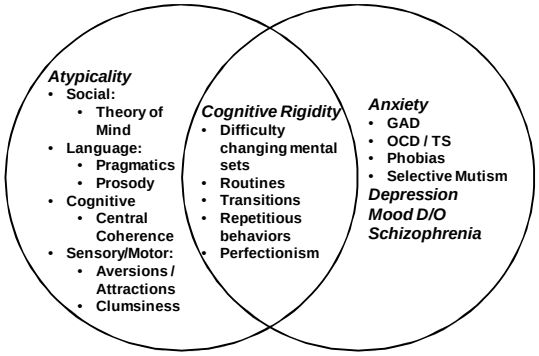
Intervention Paradigm



DD Model ⇨ **Mental Health Model**

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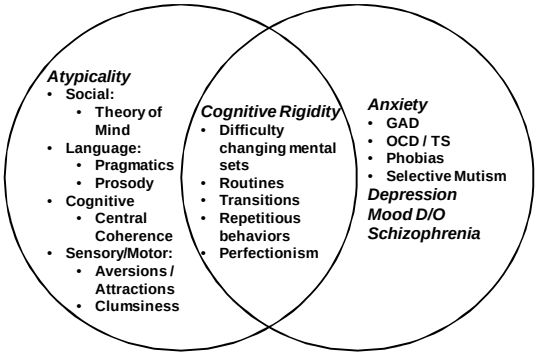
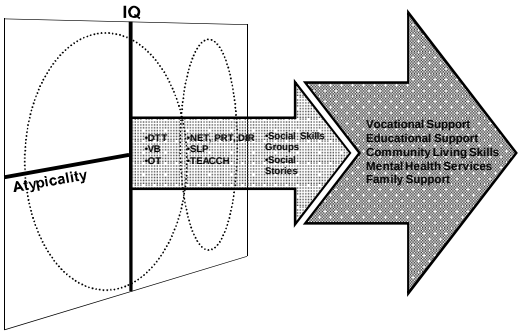
Intervention Paradigm



DD Model ⇨ **Mental Health Model**

www.drcoplan.com

Progression of Interventions



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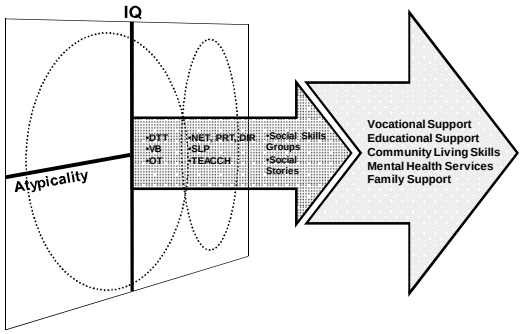
Progression of Interventions



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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

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"**

Leo Kanner
1894-1981

JFKI 1978

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

Thank you