The Present and Future of Biomedical Research on Autism

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What causes autism?

There are likely to be many causes of autism and many types of autism?

AutismS not Autism

What causes autism?

Genes
G_1, G_2, G_3,,,,,,,,,,,,,,,,,,,,,,,,,,,,,G_n

Environment
Factor $_1$, Factor $_2$…….Factor $_n$

Autism Type A | Autism Type B | Autism Type C

Recent genetic findings

Defined mutations, genetic syndromes and de novo copy number variation probably account for about 10–20% of cases, with none of these known causes accounting for more than 1–2%.

None of the molecules or syndromes currently linked to the ASDs has been proven to selectively cause autism.

Abrahams and Geschwind., *Nature Reviews Genetics*, 2008

ASD-related syndromes

Table 1 | ASD-related syndromes

Syndrome	Gene(s) associated with the syndrome	Proportion of patients with the syndrome that have an ASD	Proportion of patients with an ASD that have the syndrome	Refs
15q duplication	Unknown	High	1–2%	101
Angelman syndrome	UBE3A (and others)	>40%	Rare	102, 103
16p11 deletion	Unknown	High	~1%	20, 35, 44
22q deletion	SHANK3	High	~1%	21, 22, 104
Cortical dysplasia-focal epilepsy syndrome	CNTNAP2	~70%	Rare	37
Fragile X syndrome	FMR1	25% of males; 6% of females	1–2%	105
Joubert syndrome	Several loci	25%	Rare	106
Potocki–Lupski syndrome	Chromosome position 17p11	~90%	Unknown	107
Smith–Lemli–Optiz syndrome	DHCR7	50%	Rare	108
Rett syndrome	MECP2	All individuals have Rett syndrome	~0.5%	109
Timothy syndrome	CACNA1C	60–80%	Unknown	24
Tuberous sclerosis	TSC1 and TSC2	20%	~1%	110

Abrahams and Geschwind., *Nature Reviews Genetics*, 2008

Copy Number Variation

Strong Association of De Novo Copy Number Mutations with Autism

Jonathan Sebat,[1]* B. Lakshmi,[1] Dheeraj Malhotra,[1]* Jennifer Troge,[1]* Christa Lese-Martin,[2] Tom Walsh,[3] Boris Yamrom,[1] Seungtai Yoon,[1] Alex Krasnitz,[1] Jude Kendall,[1] Anthony Leotta,[1] Deepa Pai,[1] Ray Zhang,[1] Yoon-Ha Lee,[1] James Hicks,[1] Sarah J. Spence,[4] Annette T. Lee,[5] Kaija Puura,[6] Terho Lehtimäki,[7] David Ledbetter,[2] Peter K. Gregersen,[5] Joel Bregman,[8] James S. Sutcliffe,[9] Vaidehi Jobanputra,[10] Wendy Chung,[10] Dorothy Warburton,[10] Mary-Claire King,[3] David Skuse,[11] Daniel H. Geschwind,[12] T. Conrad Gilliam,[13] Kenny Ye,[14] Michael Wigler[1]†

We tested the hypothesis that de novo copy number variation (CNV) is associated with autism spectrum disorders (ASDs). We performed comparative genomic hybridization (CGH) on the genomic DNA of patients and unaffected subjects to detect copy number variants not present in their respective parents. Candidate genomic regions were validated by higher-resolution CGH, paternity testing, cytogenetics, fluorescence in situ hybridization, and microsatellite genotyping. Confirmed de novo CNVs were significantly associated with autism ($P = 0.0005$). Such CNVs were identified in 12 out of 118 (10%) of patients with sporadic autism, in 2 out of 77 (3%) of patients with an affected first-degree relative, and in 2 out of 196 (1%) of controls. Most de novo CNVs were smaller than microscopic resolution. Affected genomic regions were highly heterogeneous and included mutations of single genes. These findings establish de novo germline mutation as a more significant risk factor for ASD than previously recognized.

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Brain Pathology

The trajectory of brain development, rather than the end product, may be the most distinguishing feature of the neuropathology of autism.

What is the evidence for a role of the amygdala in autism?

Autism MRI Study Design

Male subjects (n=98), age 7.5-18.5 years

Diagnostic tests: ADOS, ADIR, IQ

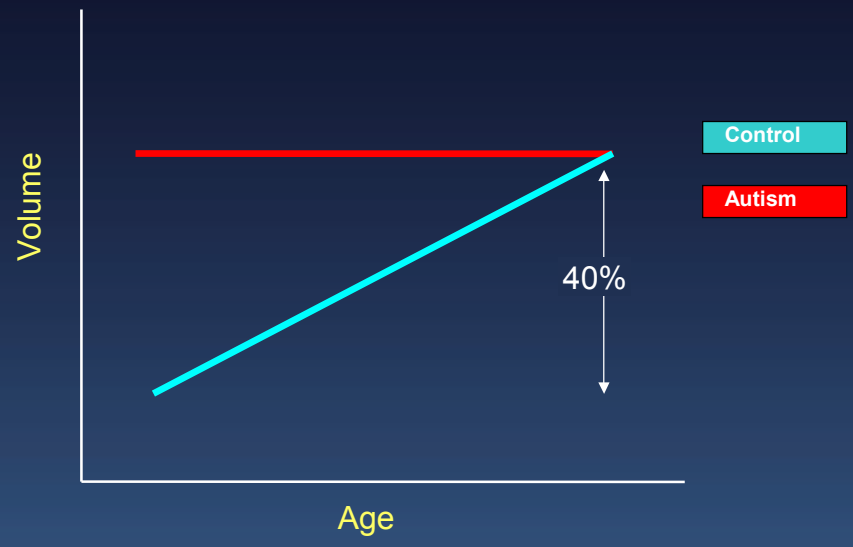
Diagnostic groups:

- Low Functioning Autism (n=17)
- High Functioning Autism (n=25)
- Asperger Syndrome (n=25)
- Normal Control (n=25)

Excluded: seizure disorder, Fragile X
Imaging: 1.5T at UC Davis & 3T at Stanford University
Analyze software package

Schumann et al
J. Neuroscience (2004) 24(28)
6392-6401

Summary of Amygdala Growth

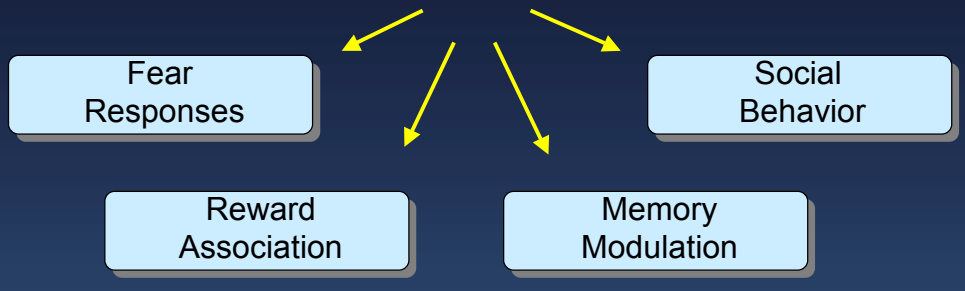


Conclusions

The amygdala is pathological in autism.

Which behavioral impairments might result from amygdala pathology?

The Amygdala



Hypothesis

The Amygdala is a Protection Device

- **Inhibits behavior to allow time for evaluation.**
- **Evaluates environmental stimuli (both inanimate objects and other organisms) for possible danger.**
- **If danger is detected, orchestrates other brain regions to produce appropriate responses.**

Why look at the immune system?

- A healthy immune system is necessary for normal development of the nervous system.
- There is ongoing communication between these two systems throughout life.

Autoantibodies from Children with ASD

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Detection of autoantibodies to neural cells of the cerebellum in the plasma of subjects with autism spectrum disorders

Sharifia Wills [a,e], Maricel Cabanlit [a,e], Jeff Bennett [b,d], Paul Ashwood [c,d,e], David G. Amaral [b,d], Judy Van de Water [a,d,e,*]

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THE ROLE OF MATERNAL ANTIBODIES TO FETAL BRAIN IN AUTISM

Available online at www.sciencedirect.com

ScienceDirect

NeuroToxicology 29 (2008) 226–231

NeuroToxicology

Autism: Maternally derived antibodies specific for fetal brain proteins

Daniel Braunschweig [a,g,h], Paul Ashwood [b,g,h], Paula Krakowiak [c,g,h], Irva Hertz-Picciotto [c,g,h], Robin Hansen [d,g,h], Lisa A. Croen [e], Isaac N. Pessah [f,g,h], Judy Van de Water [a,g,h,*]

An Immunological Model of Autism in the Nonhuman Primate

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Available online at www.sciencedirect.com
ScienceDirect
Brain, Behavior, and Immunity 22 (2008) 806–816

BRAIN, BEHAVIOR, and IMMUNITY
www.elsevier.com/locate/ybrbi

Stereotypies and hyperactivity in rhesus monkeys exposed to IgG from mothers of children with autism ☆

Loren A. Martin [a,1], Paul Ashwood [b,c], Daniel Braunschweig [d], Maricel Cabanlit [d], Judy Van de Water [c,d], David G. Amaral [a,c,*]

The M.I.N.D. Institute

Research provides hope for prevention, treatments and improving quality of life