Infant Brain and Behavior Development in Autism

Joseph Piven
Carolina Institute for Developmental Disabilities
University of North Carolina

Infant Brain Imaging Study (IBIS)
an NIH Autism Center of Excellence

Development During Infancy in Children with Autism

RISK

environmental

genetic

DEVELOPMENT

?

DIAGNOSIS/TREATMENT

autism spectrum disorder

social-communication deficits
ritualistic-repetitive behavior

BIRTH

2-3 YEARS

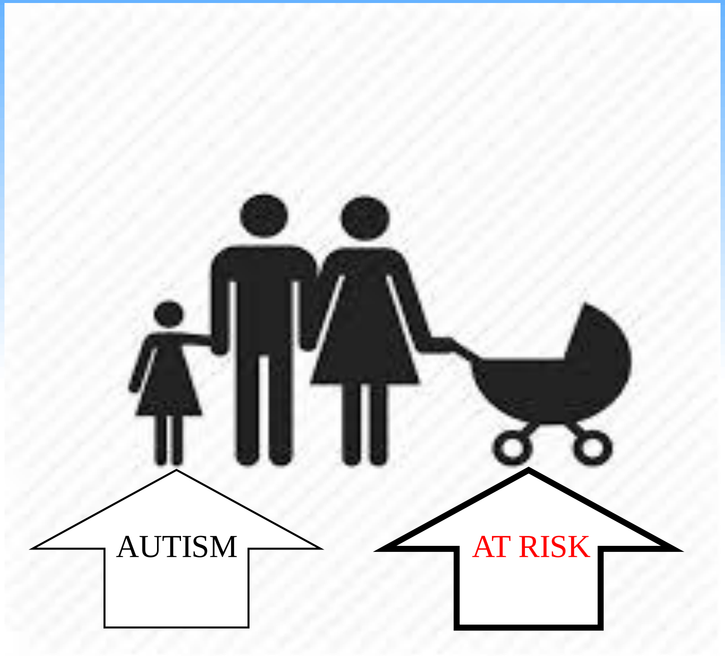
- **autism is a genetic/heritable disorder** (Folstein and Rutter, 1977; twin study)

'Infant Sibling' Studies: A New Autism Research Paradigm

risk of having a 2nd child with autism (or, recurrence risk) is ~ 20%

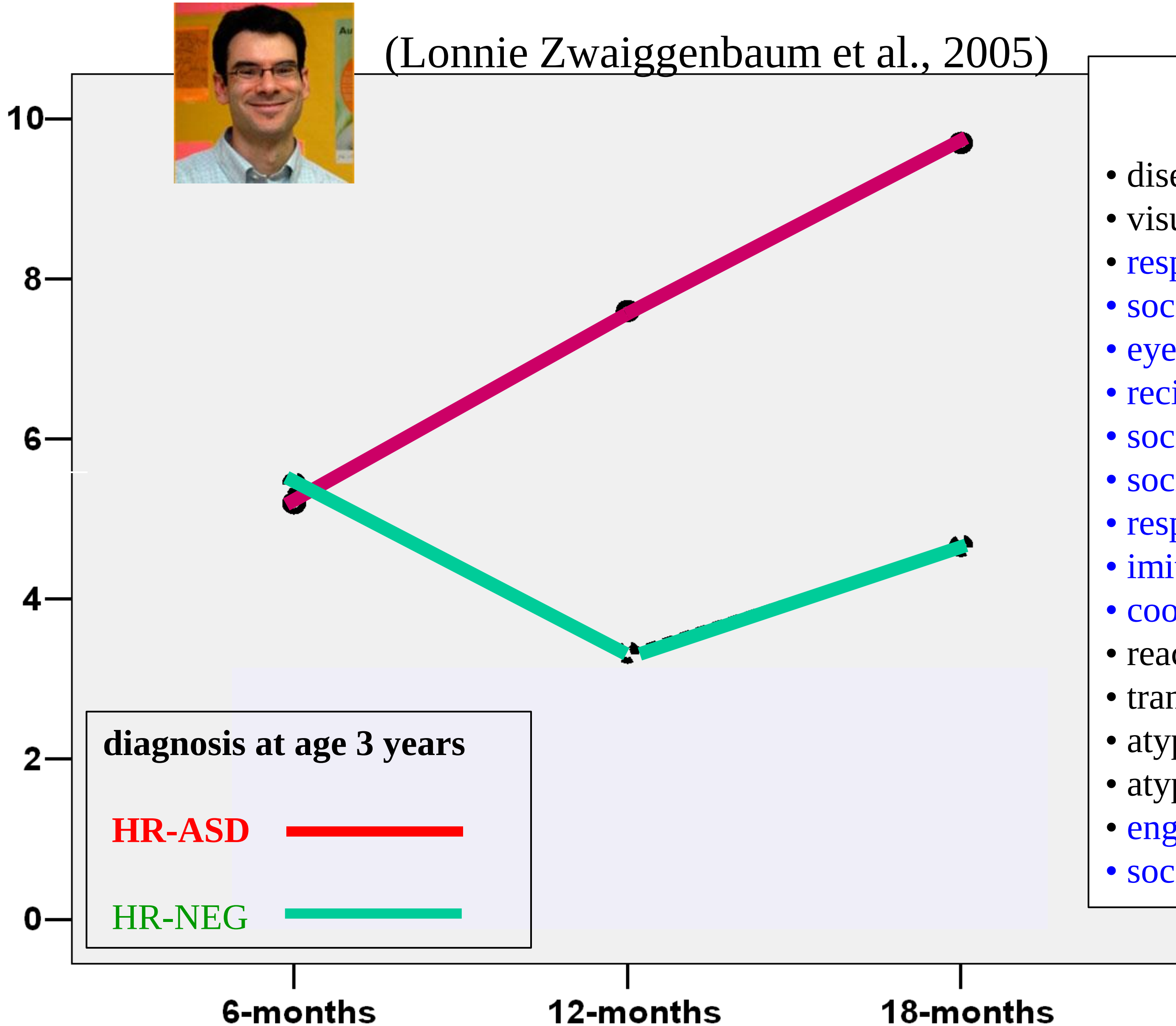
~ 20 fold greater than risk in the general population.

Ozonoff et al, 2010



Autism Observation Scale for Infants: Scores ASD and Non ASD Siblings

(Lonnie Zwaiggenbaum et al., 2005)

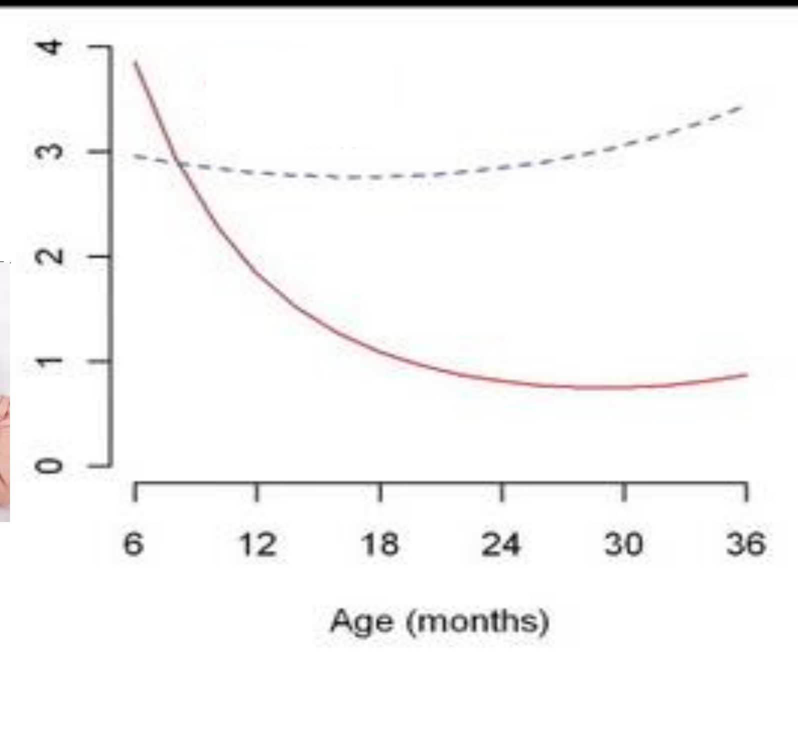


AOSI

- disengagement of attention
- visual tracking
- response to name
- social babbling
- eye contact
- reciprocal social smiling
- social anticipation
- social interest and affect
- response to facial emotion
- imitation
- coordinate eye gaze - action
- reactivity
- transitions
- atypical motor behaviors
- atypical sensory behaviors
- engagement
- social referencing

A **Pre-Symptomatic Period** in the Development of Autism

Gaze to Faces



children **without** autism at age 3

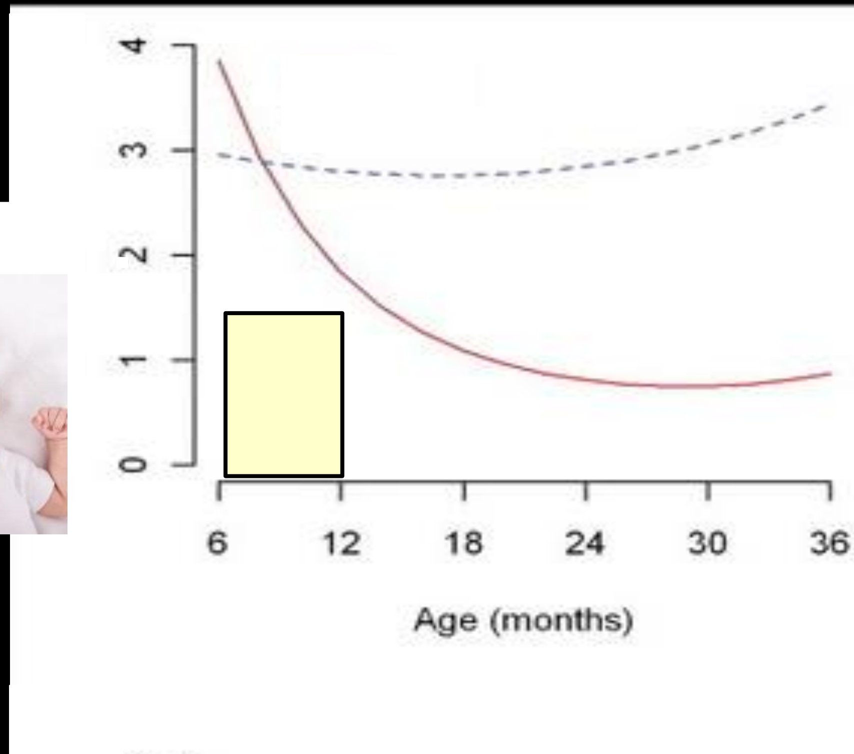
children **with** autism at age 3

High risk infant sibling studies have demonstrated that the defining social deficits in autism emerge in the latter part of the first and second years of life

Ozonoff et al (2010)

A **Pre-Symptomatic Period** in the Development of Autism

Gaze to Faces



visual orienting/attention
- Elison et al 2013

motor delay
- Flanagan et al 2012
- Estes et al 2015
- Iverson et al., 2019

visual reception
- Estes et al 2015

eye tracking/faces/social scenes
- Jones and Klin 2012
- Chawarska et al 2013

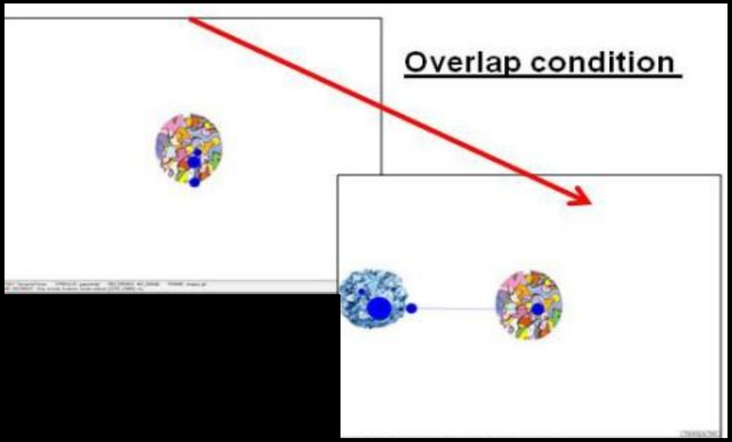
response to name
- Miller et al 2018

High risk infant sibling studies have demonstrated that the defining social deficits in autism emerge in the latter part of the first and second years of life

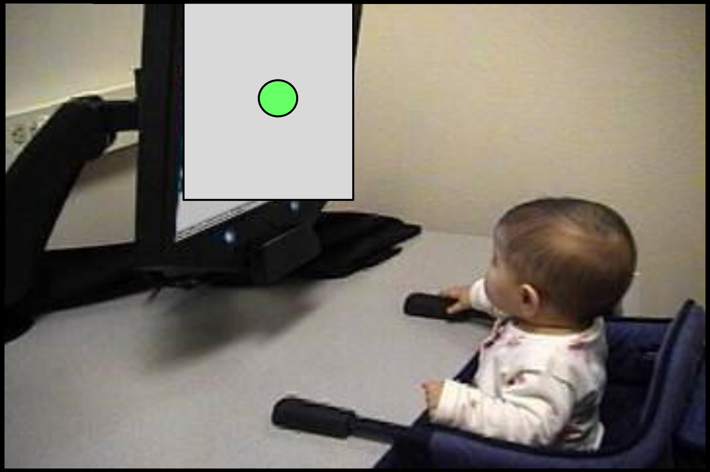
Ozonoff et al (2010)

Visual Orienting in Infants at High Risk for Autism

Gap Overlap Paradigm



Orienting to salient information in the environment, during infancy, is critical for early cognitive development

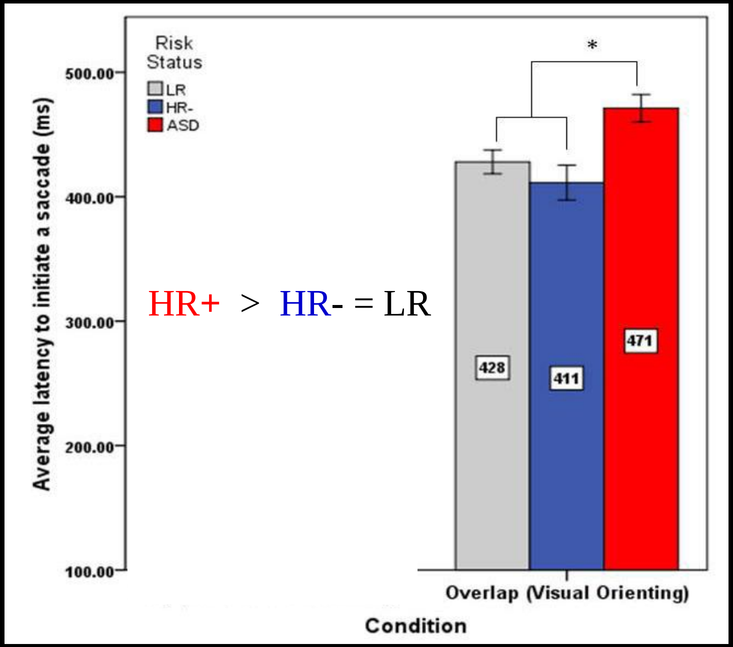


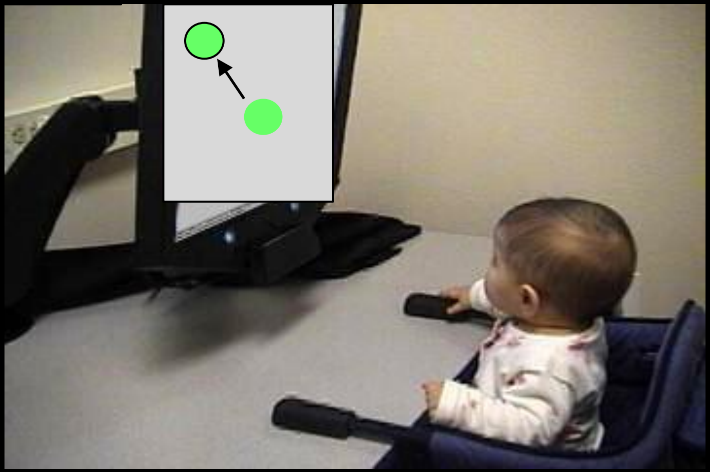
How quickly do infants shift or orient their gaze from a central to a peripheral stimulus ?

Elison et al, American Journal of Psychiatry (2013)

Visual Orienting in Infants at High Risk for Autism

at 6 months of age, HR infants later classified with ASD (at 24 months) oriented more slowly to the peripheral stimulus





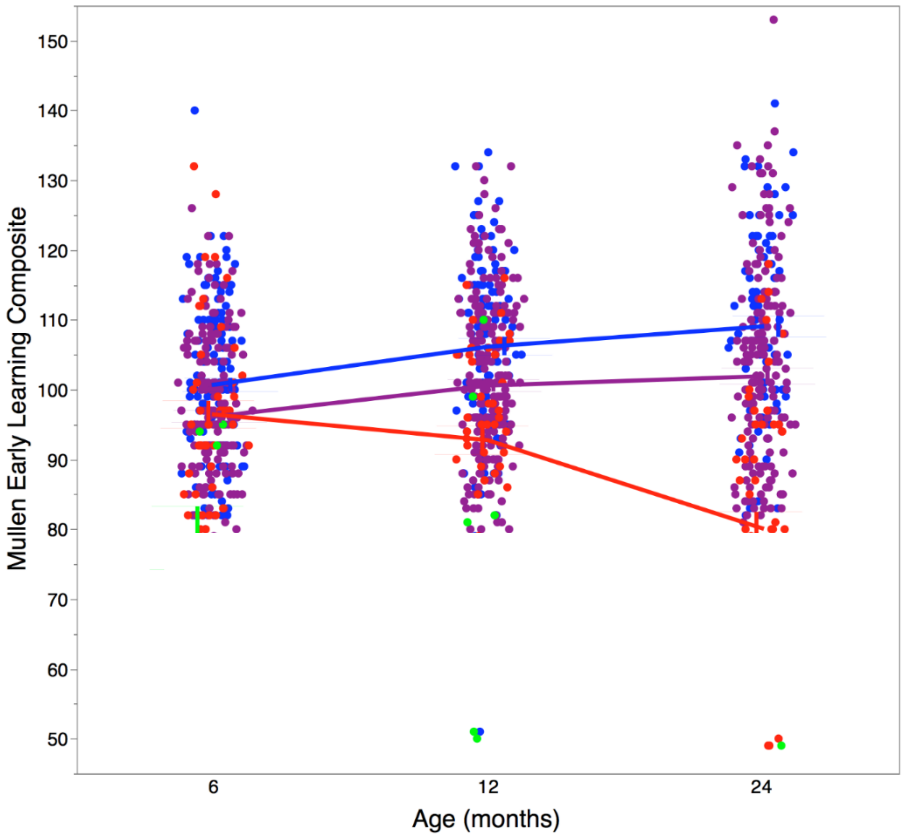
Elison et al, American Journal of Psychiatry (2013)

Emergence of Autistic Social Deficits

Courtesy of Lonnie Zwaigenbaum, M.D.

Cognitive Development in Autism Spectrum Disorder: 6-24 months

High Risk-ASD (N=58); High Risk-non ASD (N=212); Low Risk-Typical (N=109)

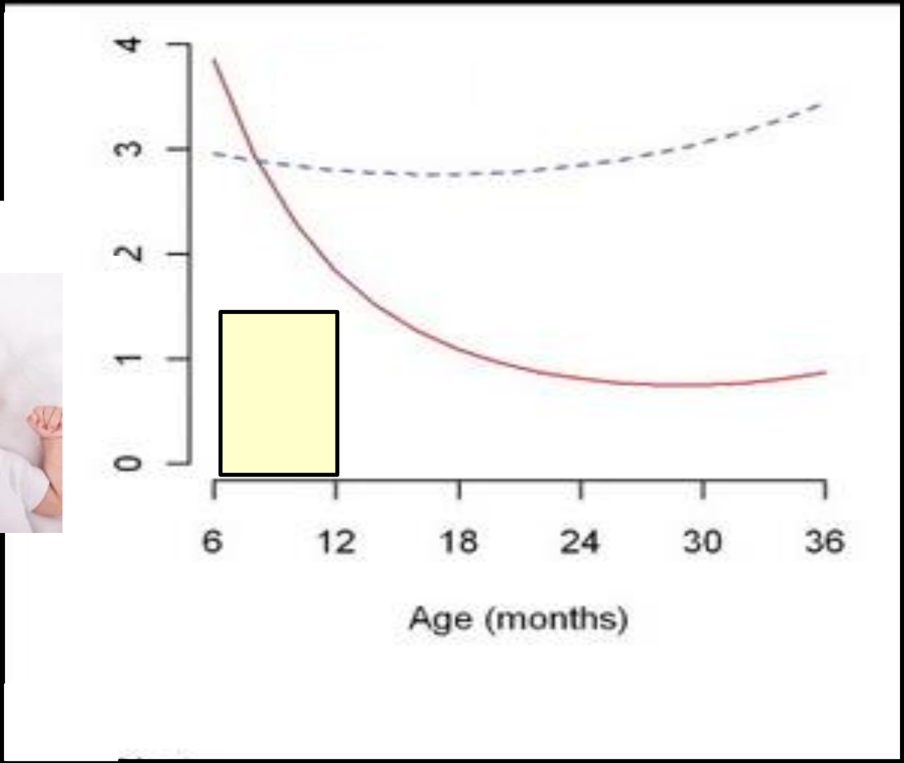


Estes et al., 2015

unpublished data, slide not included

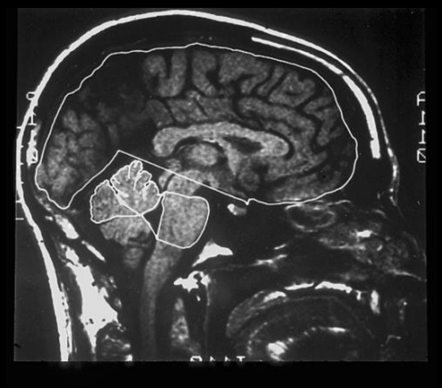
A **Pre-Symptomatic Period** in the Development of Autism

Gaze to Faces

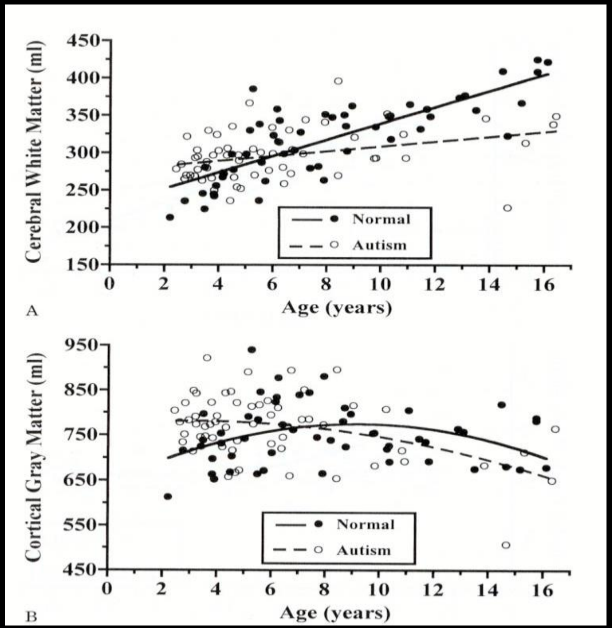


High risk infant sibling studies have demonstrated that the defining social deficits in autism emerge in the latter part of the first and second years of life

Ozonoff et al (2010)



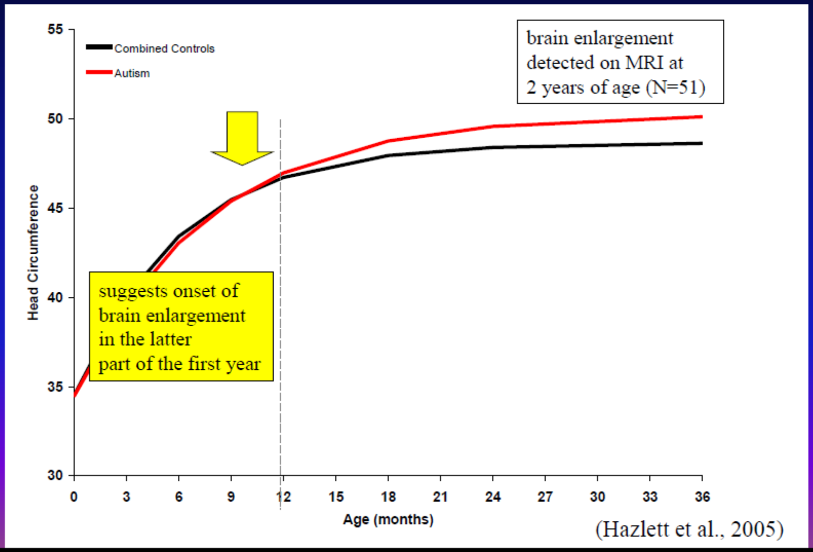
Piven et al., Biological Psychiatry 1992;
Piven et al. American J Psychiatry,1995



Courchesne et al., Neurology, 2001

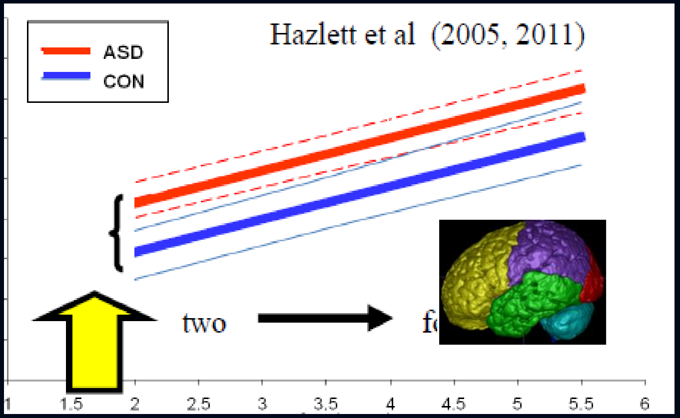
The Timing of Brain Overgrowth:
Clues from Head Circumference

(Hazlett et al., 2005)

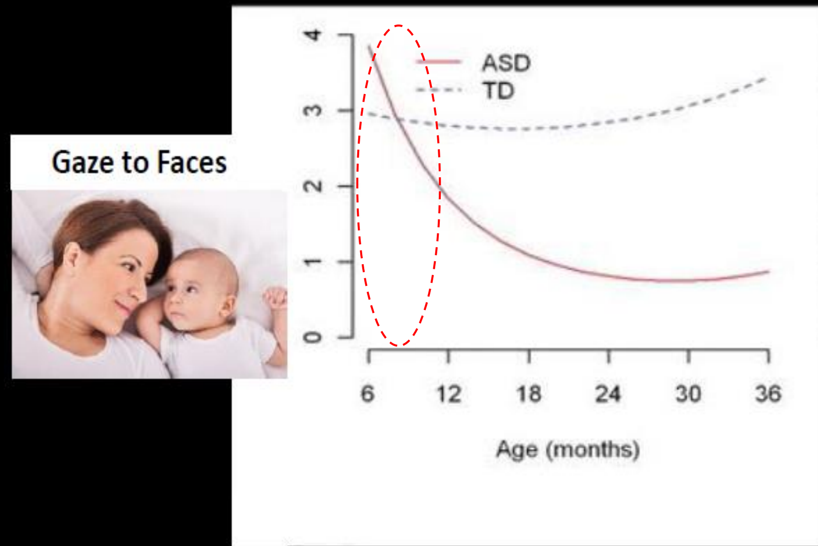


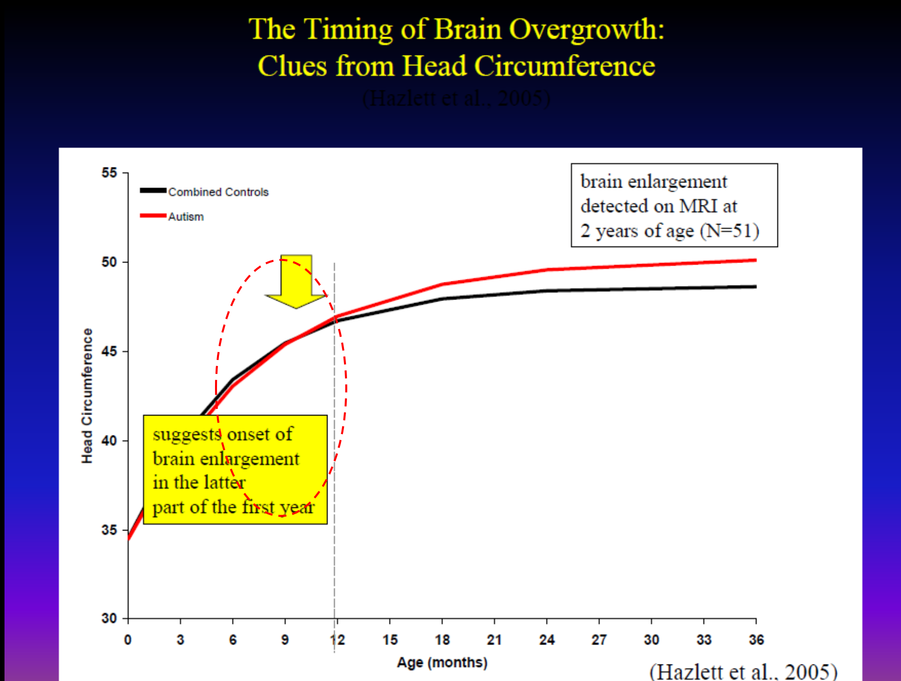
Brain Volume

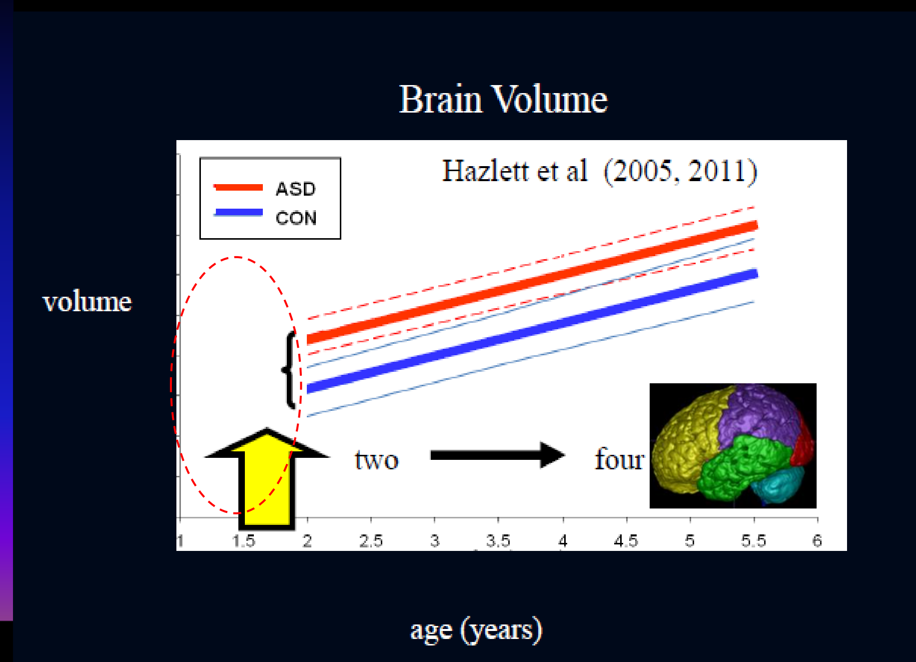
volume



age (years)


Gaze to Faces
ASD
TD
4
3
2
1
0
6
12
18
24
30
36
Age (months)


The Timing of Brain Overgrowth:
Clues from Head Circumference
(Hazlett et al., 2005)
Combined Controls
Autism
brain enlargement
detected on MRI at
2 years of age (N=51)
suggests onset of
brain enlargement
in the latter
part of the first year
Head Circumference
55
50
45
40
35
30
0
3
6
9
12
15
18
21
24
27
30
33
36
Age (months)
(Hazlett et al., 2005)


Brain Volume
ASD
CON
Hazlett et al (2005, 2011)
volume
two
four
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
age (years)

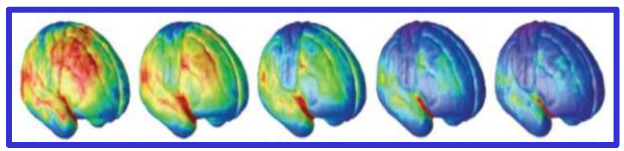
Dramatic Changes Take Place in the Brain of a Child Developing Autism

RISK

environmental

genetic

DEVELOPMENT



brain doubles in size from 2 to 52 weeks

Knickmeyer et al (2008)

DIAGNOSIS/TREATMENT

autism spectrum disorder

social-communication deficits
ritualistic-repetitive behavior

BIRTH

2-3 YEARS

Infant Brain Imaging Study (IBIS) Network

An NIH-funded Autism Center of Excellence (ACE) Network

Children's Hospital of Philadelphia | U Washington | Washington U in St Louis | UNC

400 high and low familial-risk infants assessed at: 6-12-24 months

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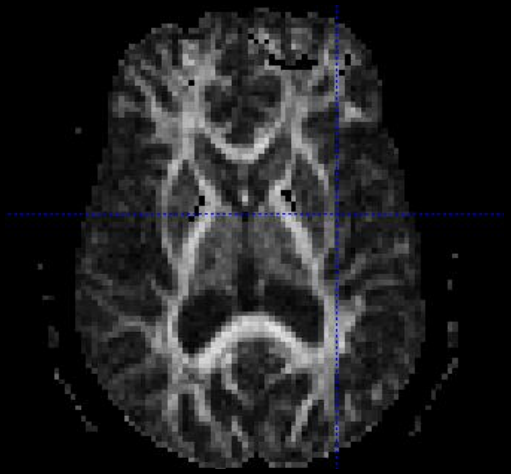
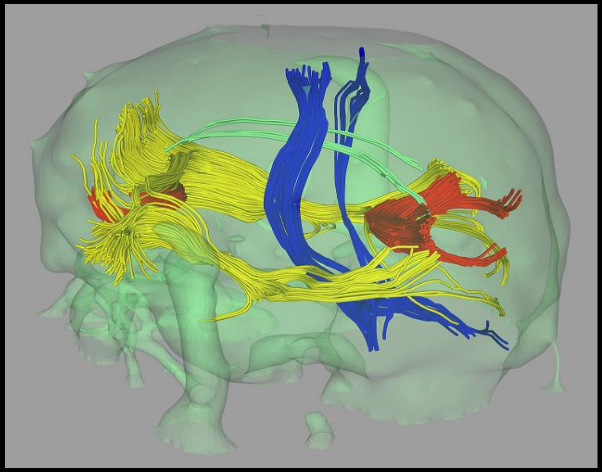
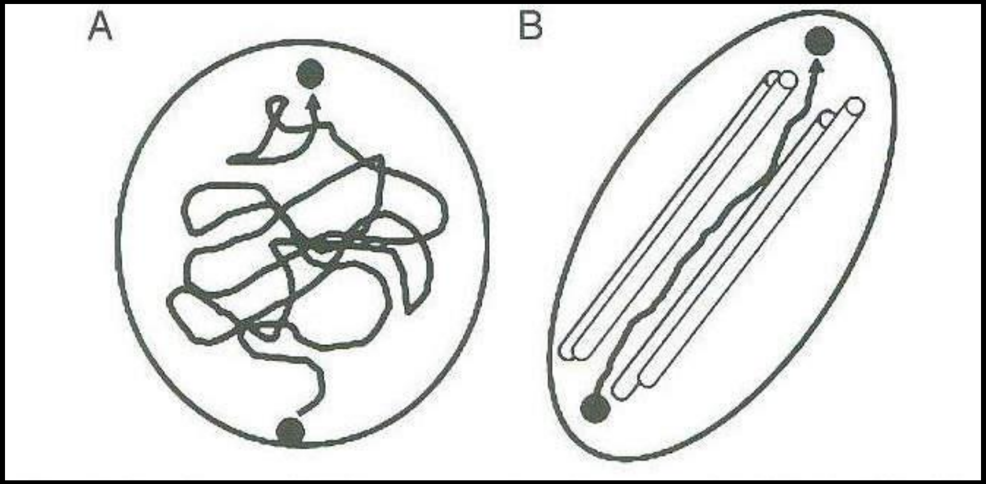
400 high and low familial-risk infants assessed at: 6-12-24 months

1. **development**
2. **cascading changes in brain and behavior**
3. **mechanisms and therapeutic targets**
4. **prediction: clinical implications**

Diffusion Tensor Imaging (DTI)





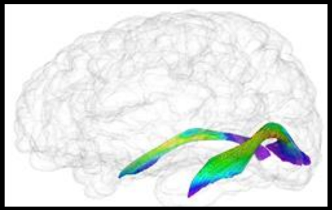


Longitudinal DTI (Fractional Anisotropy) in High Risk Infants <u>With and Without Autism</u> at 6, 12 and 24 Months

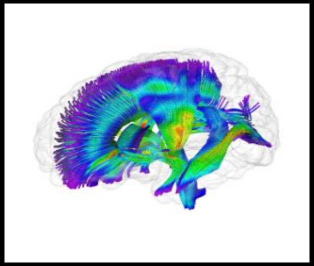
Wolff et al., *American J Psychiatry* (2012)

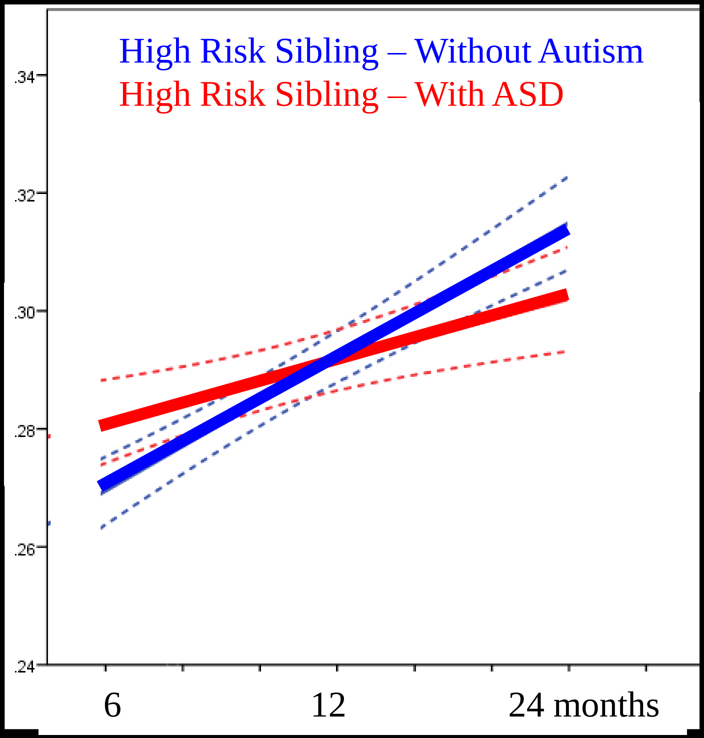
Jason Wolff
U. Minnesota

Inferior Longitudinal Fasciculus



12/15 white matter tracts



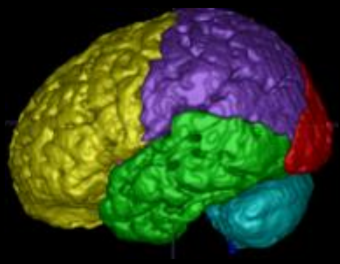


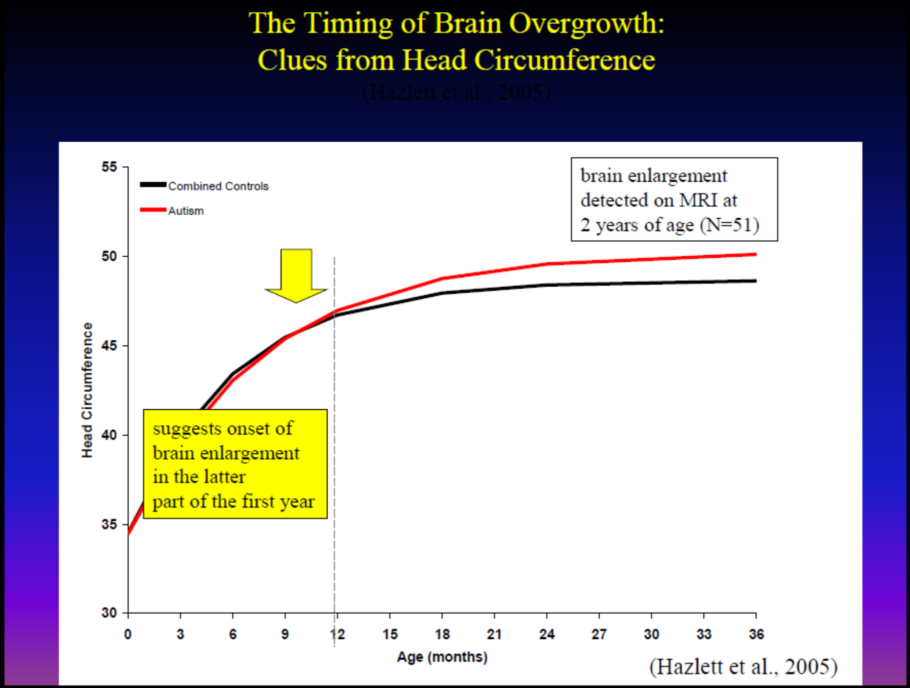
The *neural signature* of autism is <u>change</u>

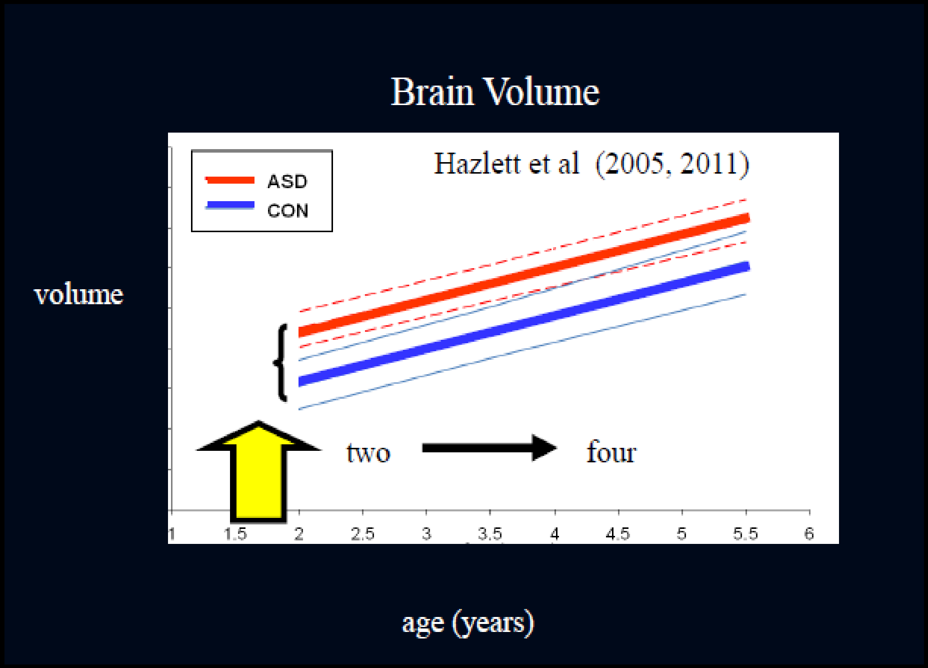
<u>Development</u> itself is the key to understanding developmental disorders

Annette Karmiloff-Smith (1998)

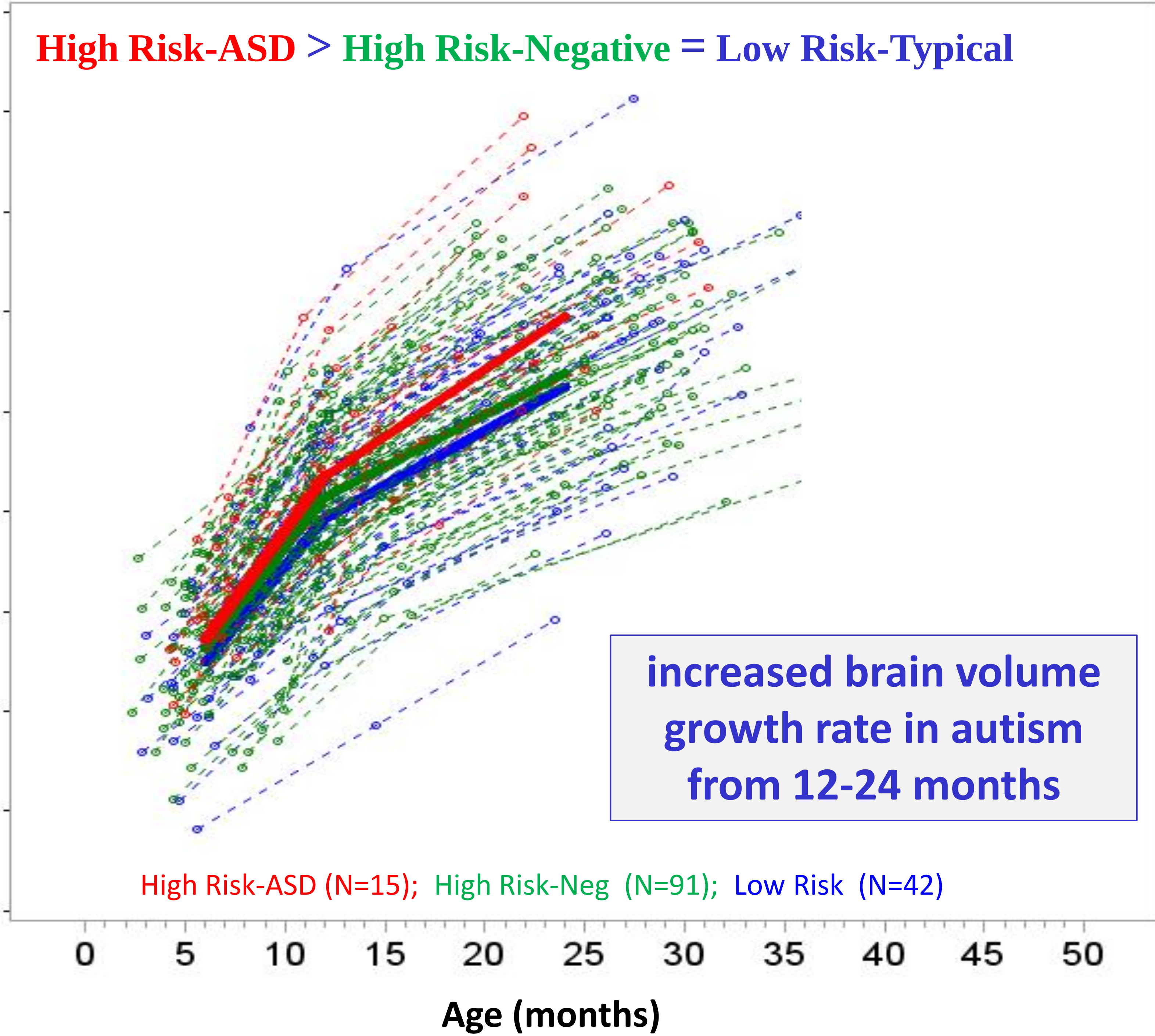
Increased Brain Volume in Autism

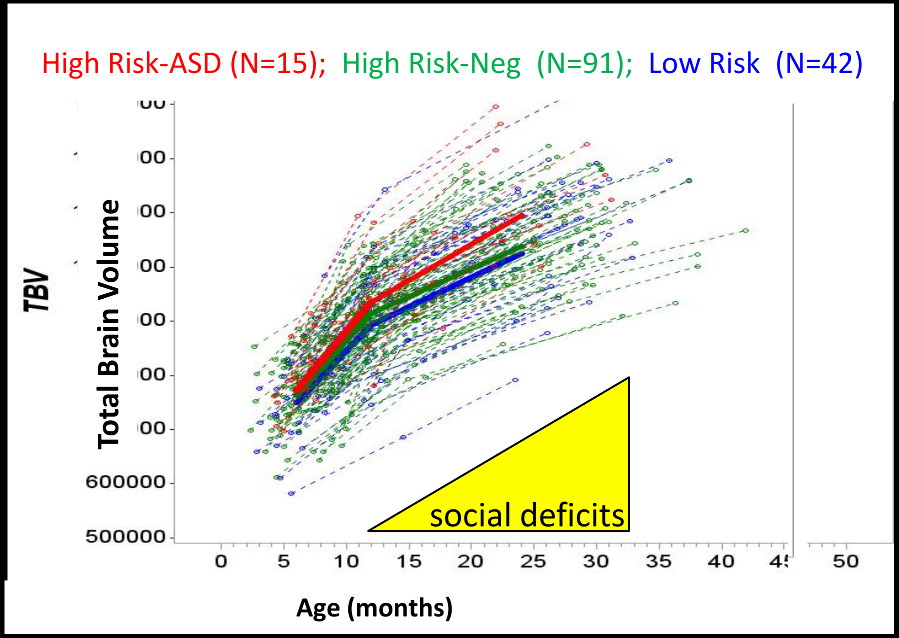







Heather Hazlett
Nature (2017)

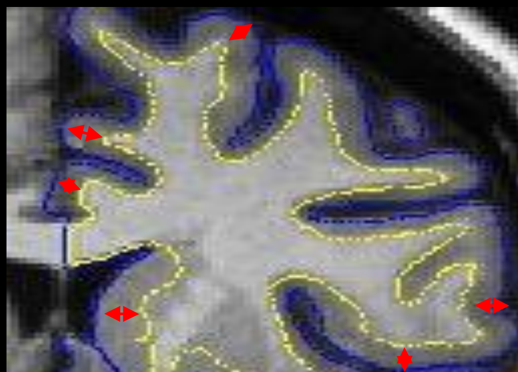


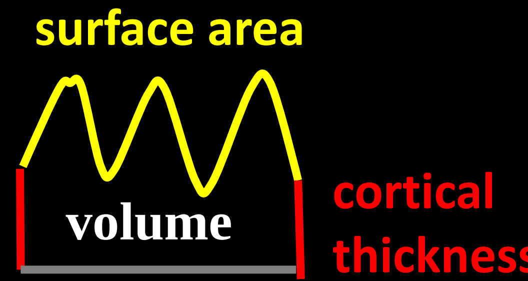


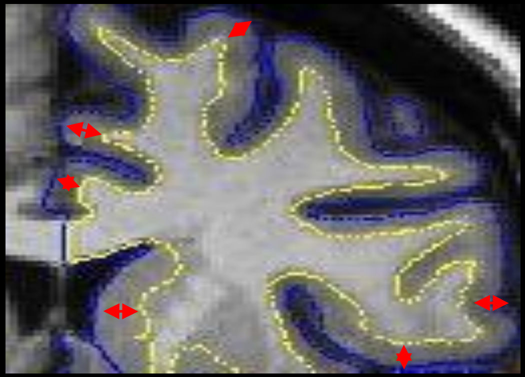
increased brain volume **growth rate** was associated **with the emergence of autistic social deficits <u>not</u> repetitive behaviors (ADOS; CSBS)**

Hazlett et al., Nature (2017)

surface area x cortical thickness =
total brain volume

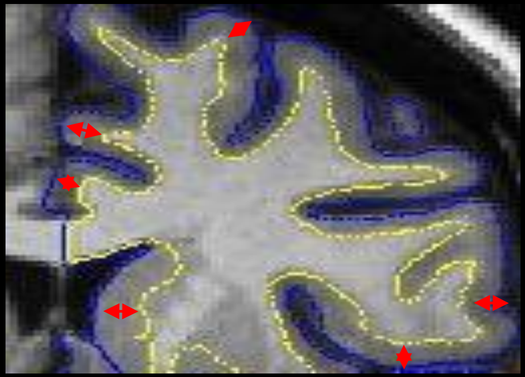


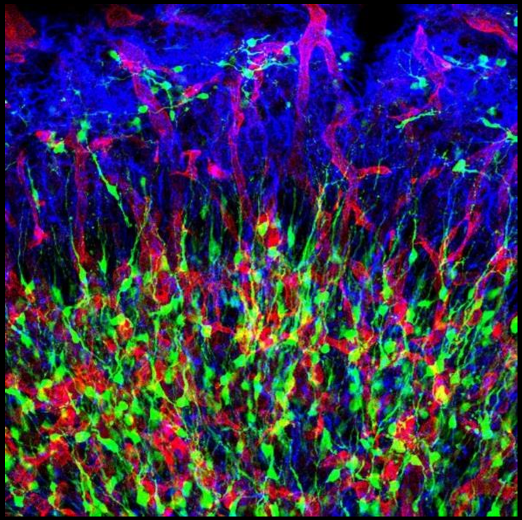




Rationale:

- genetic architecture: **surface area** differs from **cortical thickness**





neural progenitor cells

Rationale:

- genetic architecture: **surface area** differs from **cortical thickness**
- mechanism: neural progenitor cell proliferation influences cortical surface area

Early Brain Overgrowth in Autism Associated With an Increase in Cortical Surface Area Before Age 2 Years *Arch Gen Psychiatry. 2011;68(5):467-476*

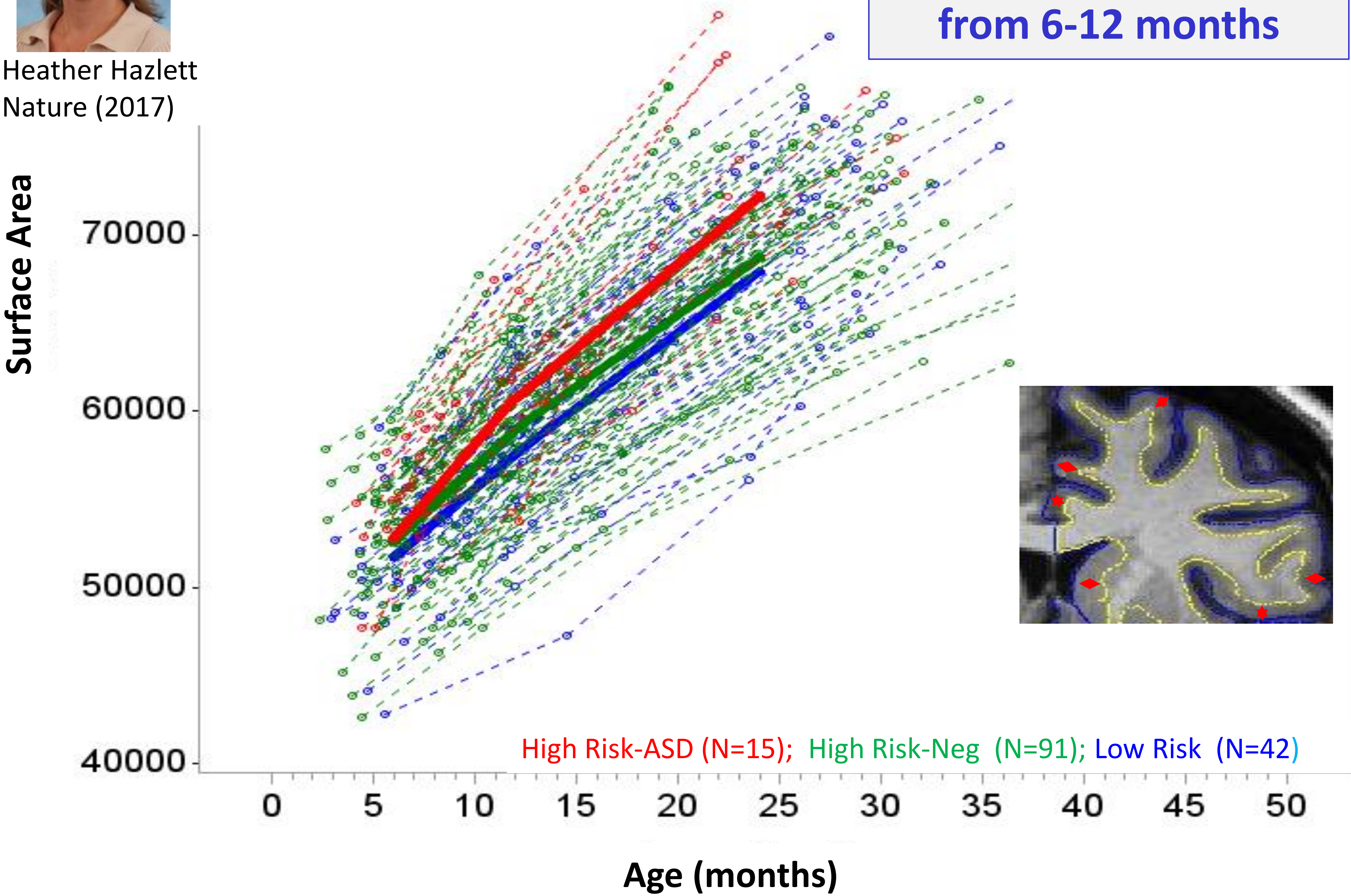
Heather Cody Hazlett, PhD; Michele D. Poe, PhD; Guido Gerig, PhD; Martin Styner, PhD; Chad Chappell, MA; Rachel Gimpel Smith, BA; Clement Vachet, MS; Joseph Piven, MD

Rationale:

- genetic architecture: **surface area** differs from **cortical thickness**
- mechanism: neural progenitor cell proliferation
- surface area not cortical thickness increased at 2 and 4 years of age in ASD (Hazlett et al., 2011)

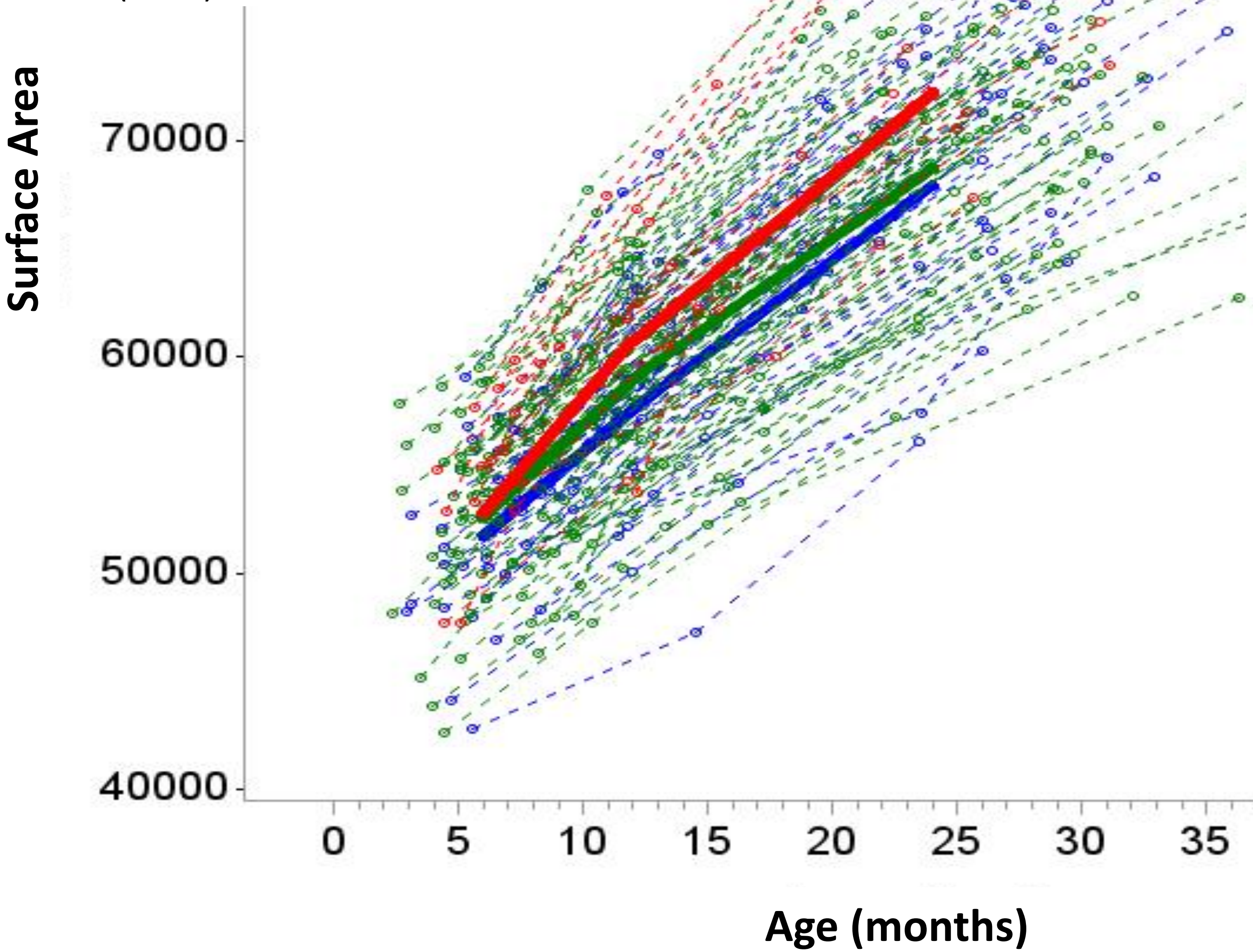
Heather Hazlett
Nature (2017)

increased surface area growth rate in autism from 6-12 months



Heather Hazlett
Nature (2017)

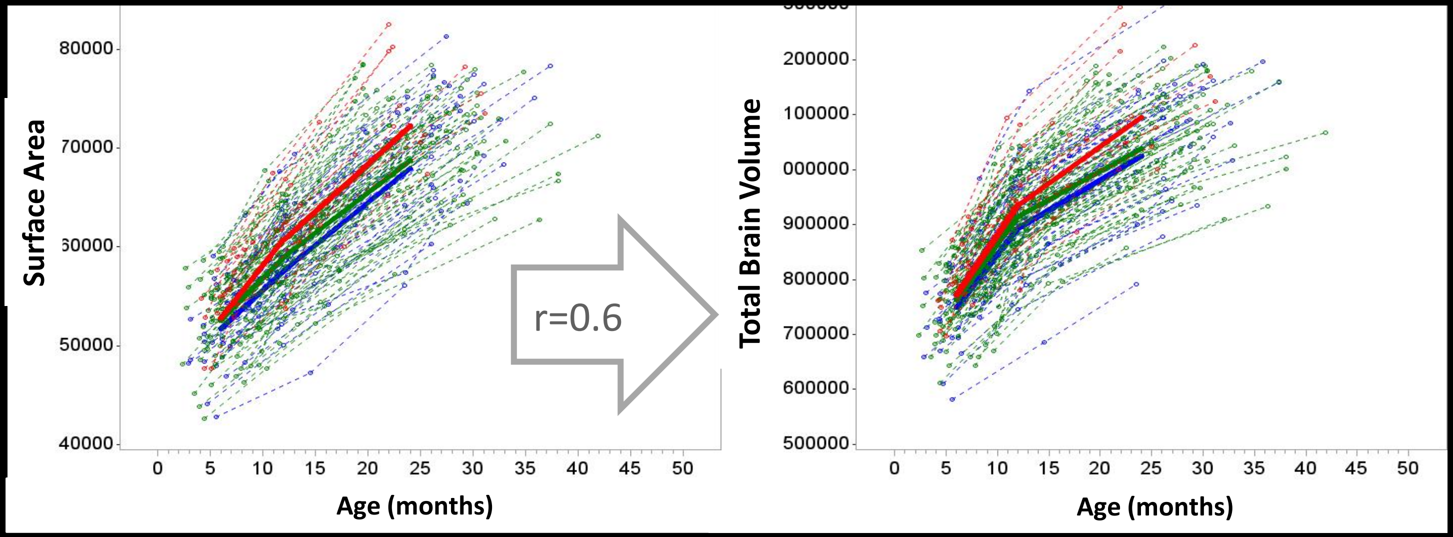
surface area growth rate most robust in regions of visual cortex



R Middle Occipital Gyrus
L Cuneus

Hyper-Expansion of Cortical Surface Area from 6-12 Months

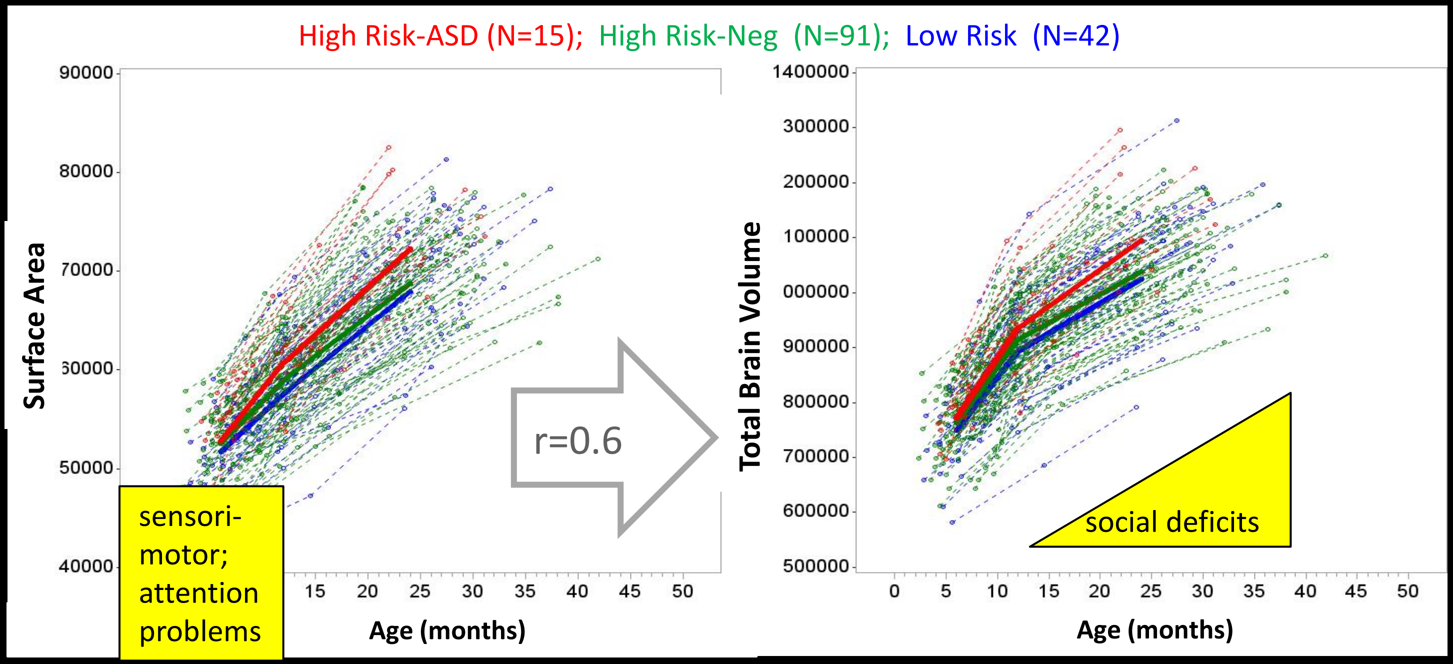
Increased Brain Growth Rate from 12-24 Months



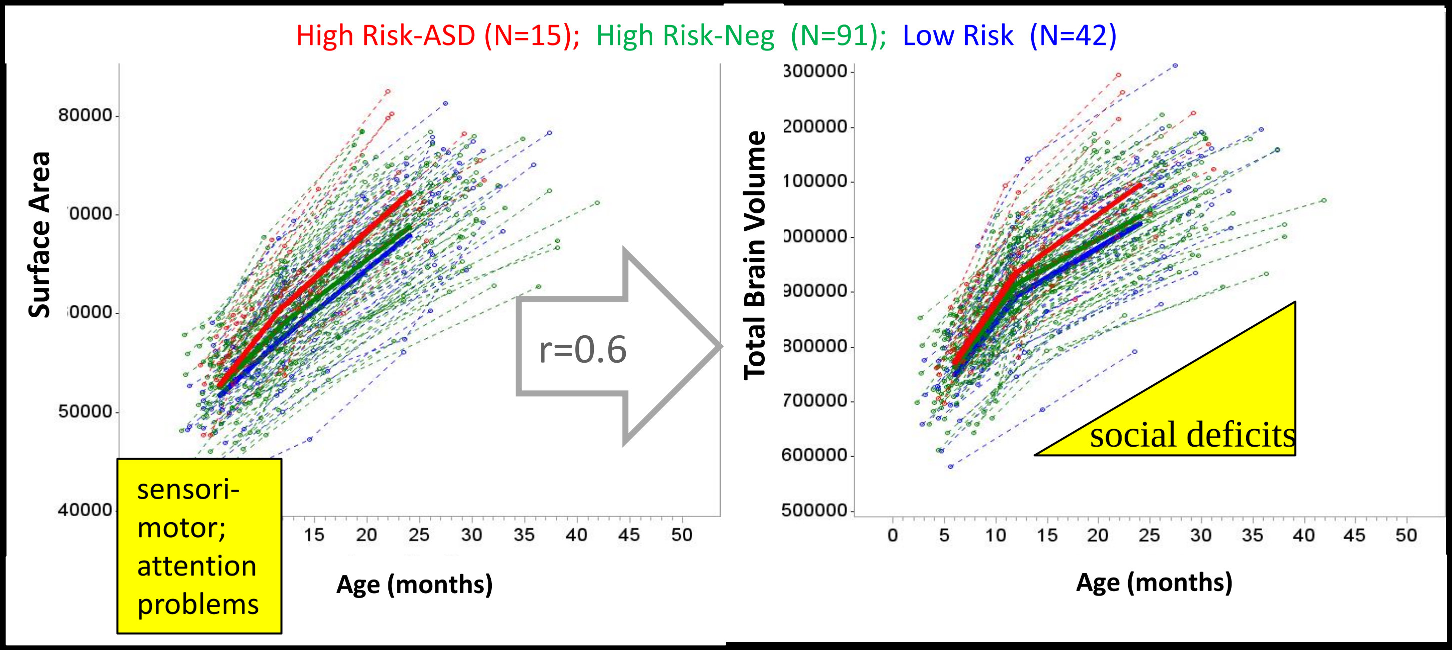
surface area growth rate (6-12 months of age) is significantly associated with brain volume growth rate (12-24 months of age)

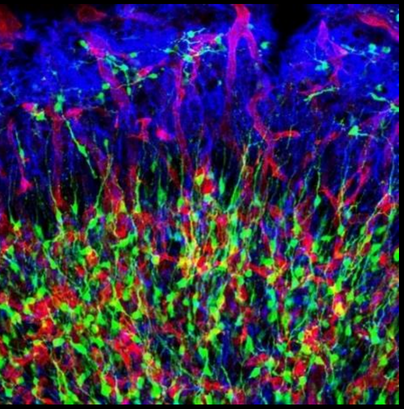
Hazlett et al., Nature (2017)

Sequential Changes in Brain and Behavior from 6-12 and 12-24 Months of Age



Hyper-expansion of cortical surface area from 6-12 Months of Age is a Result of Earlier Changes in Development of Immature Nerve Cells





before birth

cortical surface area expansion is due to development of early (prenatal) neurons (nerve cells or neural progenitor calls) in the brain

P. Rakic; Nat Rev Neurosci (2009)

Marchetto et al., Mol Psychiat. (2017)

When does autism begin ?

The Example of Schizophrenia

Prodrome

10 year old

- attention deficit hyperactivity
- learning problems
- schizoid/schizotypal personality

Diagnosis

18 year old (schizophrenia)

- hallucinations
- delusions

AGE

Cascading Series of Brain and Behavior Changes Leading to Autism

increased proliferation of neural progenitor cells

⇩

expansion of cortical surface area (sensory regions)

⇩

disruption of sensory experiences \ attention

⇩

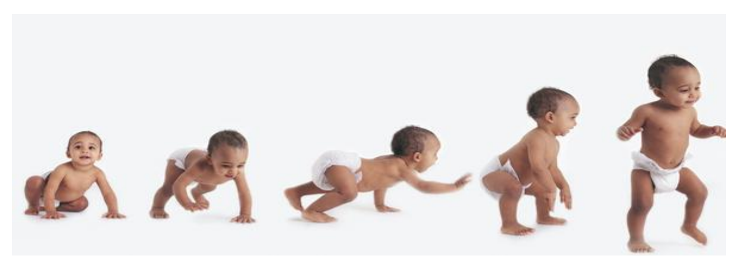
altered experience dependent development ?

⇩

cortical overgrowth

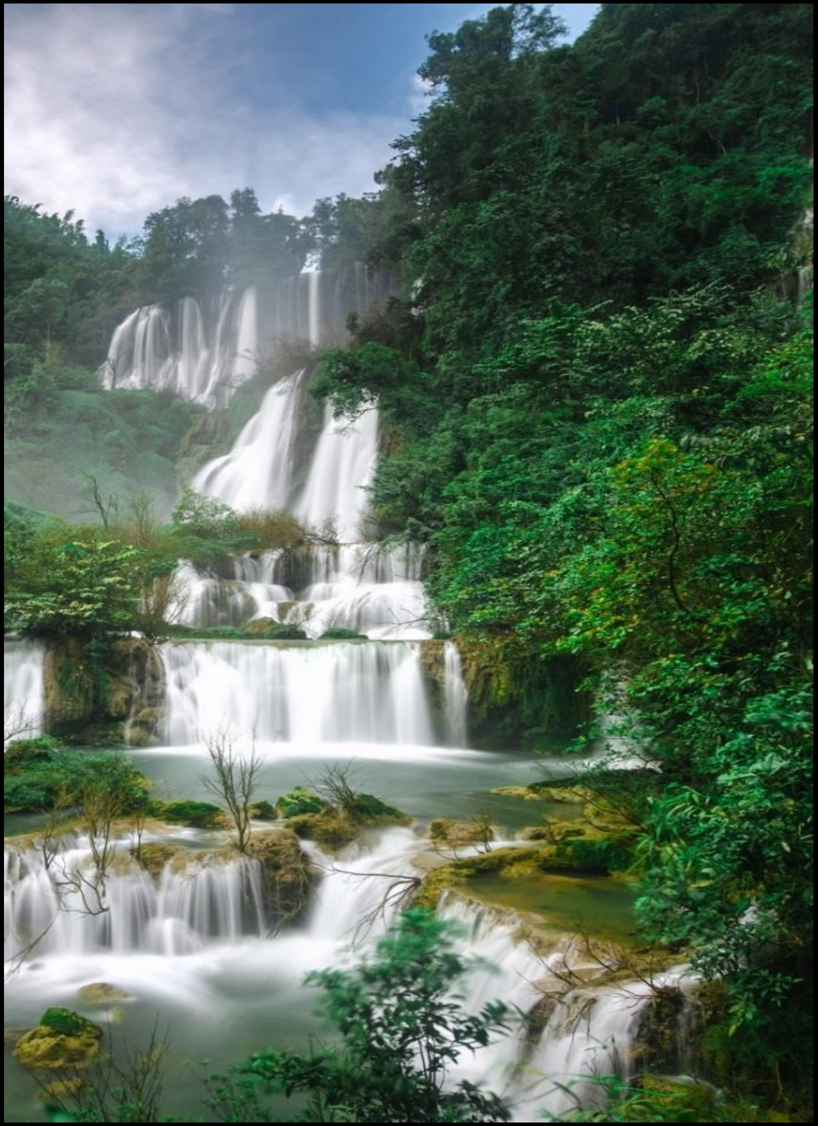
⇩

emergence of autistic social deficits



Piven, Elison, Zylka; Molecular Psychiatry (2018)

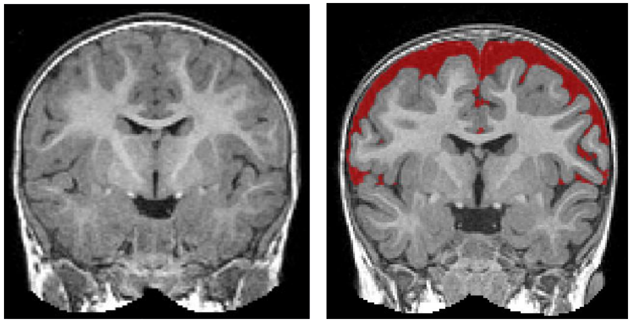
Cascading Events Leading to Autism



Hypothesis: autism may be primarily a disorder of sensorimotor-attention systems in infancy, with the defining features of the disorder emerging secondarily in the 2nd year of life

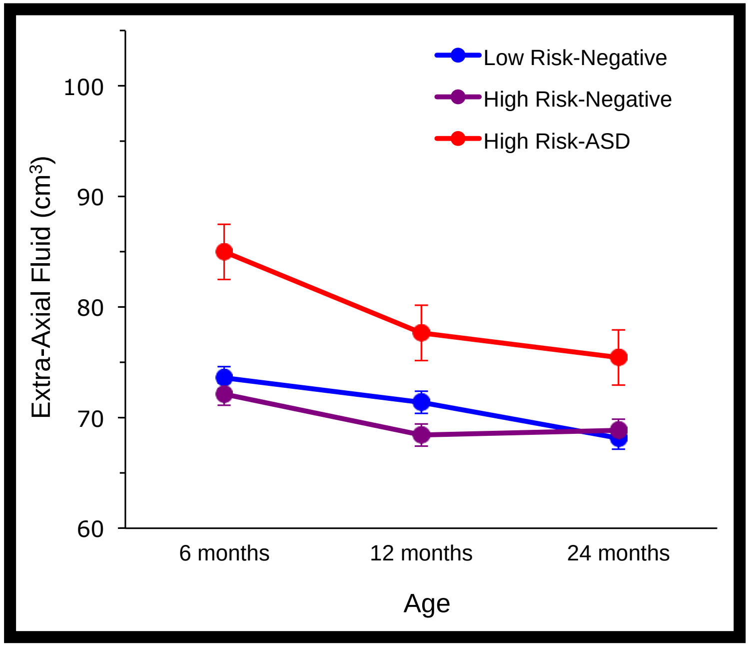
Piven, Elison, Zylka; Molecular Psychiatry (2018)

Increased Extra-axial CSF by Six Months of Age in ASD



Shen et al., Brain 2013

(ASD: N=10)



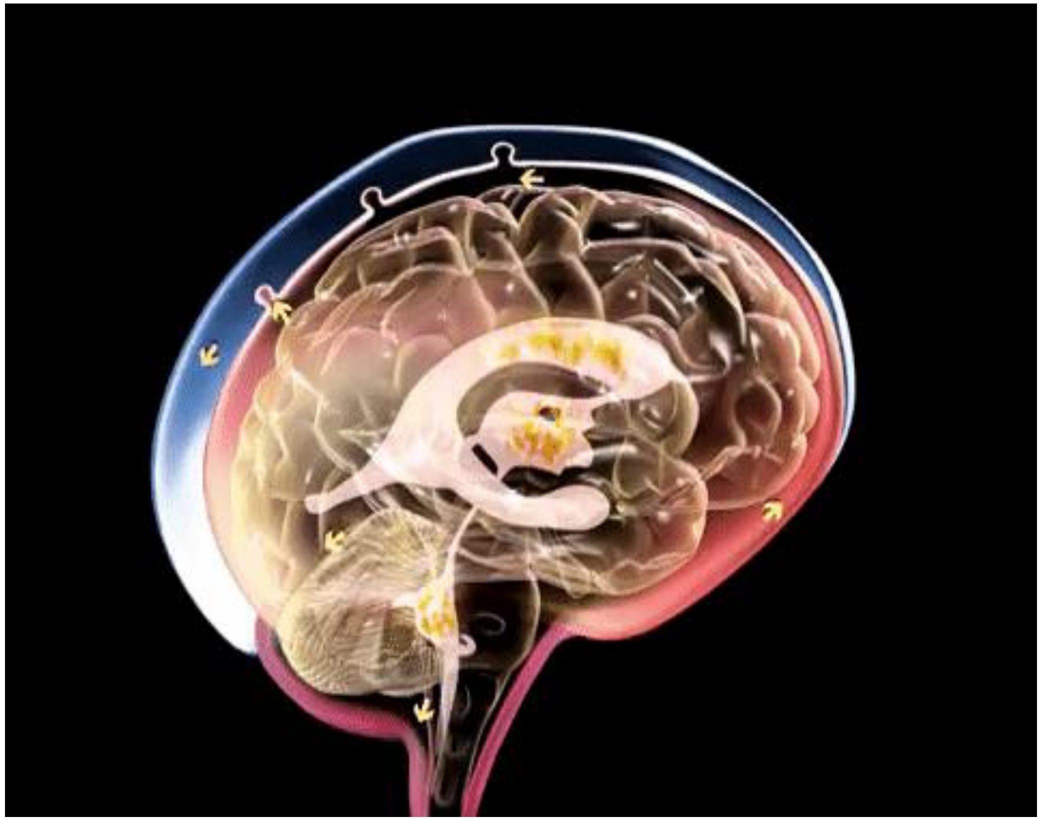
Shen et al., Biological Psychiatry 2017

(ASD: N=47)

Mark Shen

Linking Aberrant CSF Volume to Underlying Mechanisms

continously produced (delivering growth factors) and reabsorbed into brain parenchyma filtering inflammatory cytokines and metabolic byproducts (e.g., β-amyloid)



impact of early CSF physiology on **downstream** brain development

Xie (2013) Science;   Iliff (2012) Sci Transl Med;   Louveau (2015) Nature; Mesquita (2018) Nature; Lehtinen (2011) Neuron

Linking Aberrant CSF Volume to Underlying Mechanisms

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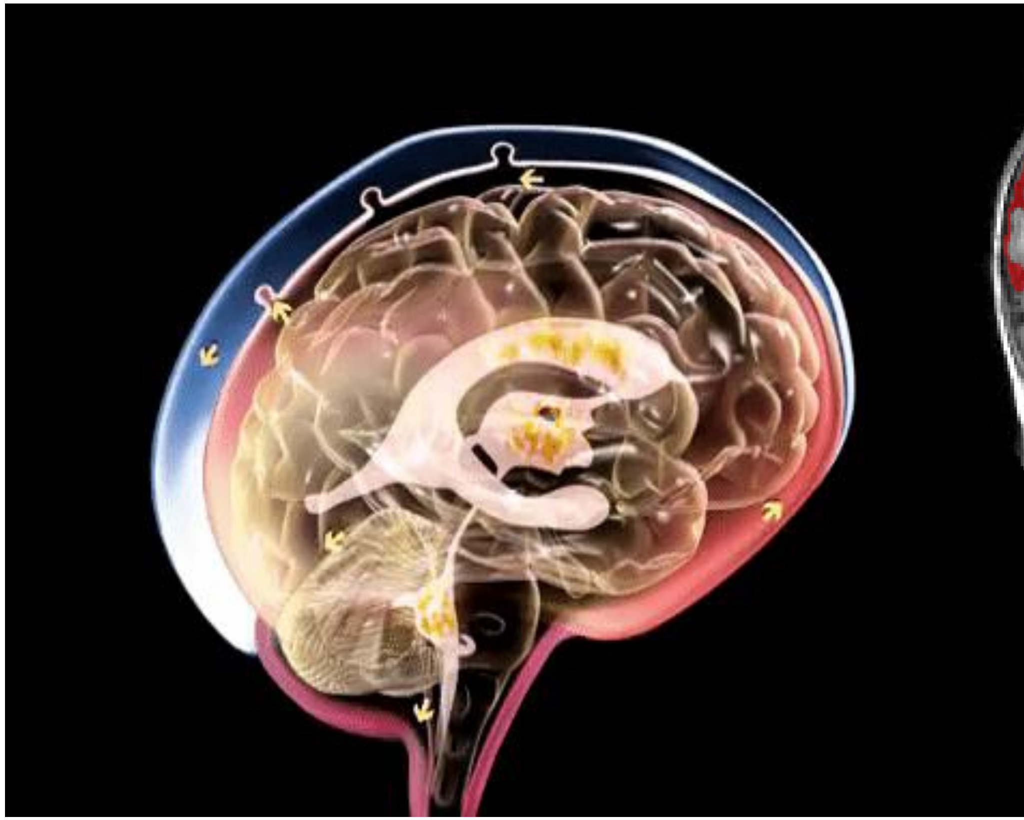

Mark Shen et al.

impact of early CSF physiology on **downstream** brain development

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Earlier and Earlier Identification

DIAGNOSIS/TREATMENT

autism spectrum disorder

social-communication deficits
ritualistic-repetitive behavior

2 years

Presymptomatic Detection: Behavioral Markers

18-Month Predictors of Later Outcomes in Younger Siblings of Children With Autism Spectrum Disorder: A Baby Siblings Research Consortium Study

Katarzyna Chawarska, PhD, Frederick Shic, PhD, Suzanne Macari, PhD, Daniel J. Campbell, PhD, Jessica Brian, PhD, Rebecca Landa, PhD, Ted Hutman, PhD, Charles A. Nelson, PhD, Sally Ozonoff, PhD, Helen Tager-Flusberg, PhD, Gregory S. Young, PhD, Lonnie Zwaigenbaum, MD, Ira L. Cohen, PhD, Tony Charman, PhD, Daniel S. Messinger, PhD, Ami Klin, PhD, Scott Johnson, PhD, Susan Bryson, PhD

PPV = .50

1

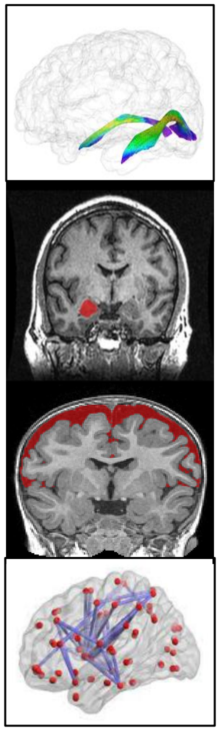
2 years

DIAGNOSIS/TREATMENT

autism spectrum disorder

social-communication deficits
ritualistic-repetitive behavior

Brain Changes in the First Year: Pre-symptomatic Detection ?



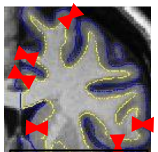
DIAGNOSIS/TREATMENT

autism spectrum disorder

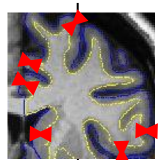
social-communication deficits
ritualistic-repetitive behavior

birth | 6 months | 1 | 2 years

Heather Hazlett et al., (Nature, 2017) : early surface area change predict later autism



sMRI



sMRI

accuracy:	94%
sensitivity	88%
specificity	95%
PPV:	81%

Prediction

birth

12 months

24 months

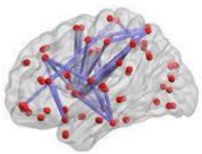
DIAGNOSIS/TREATMENT

autism spectrum disorder

social-communication deficits
ritualistic-repetitive behavior

A positive predictive value (PPV) of 81% means that of those who are positive on the test (brain scan) in the first year, 80% will later meet criteria for ASD

Robert Emerson et al., (Sci Transl Med , 2017): early connectivity predicts later autism



fcMRI

accuracy:	97%
sensitivity	82%
specificity	100%
PPV:	100%

N=59 HR (11 ASD+)

Prediction

birth

6 months

2 years

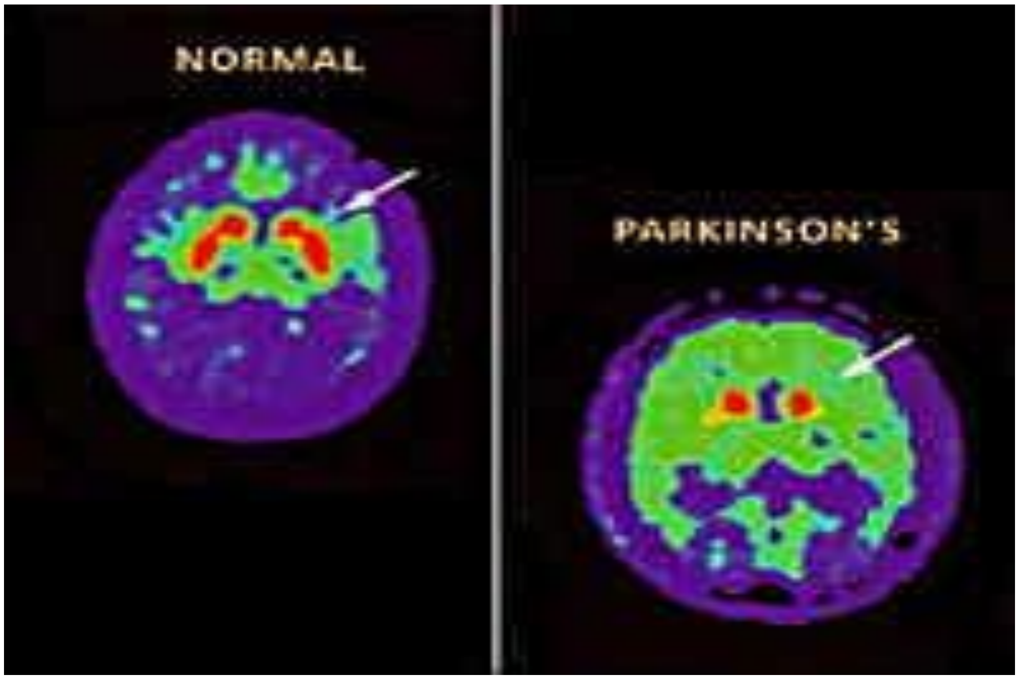
DIAGNOSIS/TREATMENT

autism spectrum disorder

social-communication deficits
ritualistic-repetitive behavior

unpublished data, slide not included

Brain Changes Known to Precede Behavior Change in Other Conditions



~ 50 percent loss of dopamine neurons of the brain in Parkinson's Disease before clinical features are reported

Three distinct approaches have revealed that brain characteristics detectable on MRI, in the first year of life, accurately predict which individuals will meet criteria for autism at 24 months of age

- While we have not yet replicated a specific method …

- we have demonstrated 'proof of principle':
  i.e., replication that early brain features predict later diagnosis

IBIS Early Prediction Study

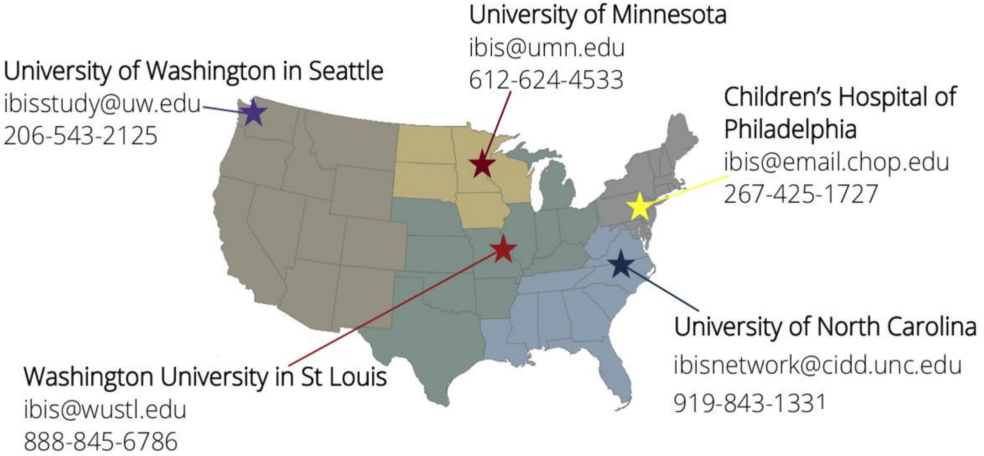
- NIMH
- 250 high risk infants
- 6 → 24 months of age
- 5 sites just started
- www.ibis-network.org

INFANT BRAIN IMAGING STUDY

Have a child with autism <u>and</u> a new baby?
Get paid to participate in research from home!

Who do we need?	• Families who have a child or children with autism *and* a new baby 6-months of age or younger • Infants and child with autism must share same mom and dad
What do you get?	• $50 compensation for completion of remote data collection for each timepoint • A detailed results report of your infant's development
What's the point?	• Identify autism earlier • Earlier identification means earlier intervention and improved out-comes

www.ibis-network.org



Current Practice: Treatment after Diagnosis

DIAGNOSIS/TREATMENT

autism spectrum disorder

social-communication deficits
ritualistic-repetitive behavior

birth

1

2 years

Pre-symptomatic Detection

birth

1

Pre-symptomatic Detection and Intervention

birth

1

- earlier is better
  - plasticity

brain doubles in size from 2 to 52 weeks

Knickmeyer et al (2008)

Pre-symptomatic Detection <u>and Intervention</u>

- earlier is better
    - plasticity
    - general rule: hypertension → stroke

birth

1

Effectiveness of community-based early intervention for children with autism spectrum disorder: a meta-analysis

Allison S. Nahmias,[1] Melanie Pellecchia,[2] Aubyn C. Stahmer,[1] and David S. Mandell[2]

Journal of Child Psychology and Psychiatry (2019)

*There were **small** but statistically significant **gains**, ranging from effect sizes of 0.21 for adaptive behavior to 0.32 for communication. These results are in stark contrast to those reported in prior meta-analyses of university-based clinical trials.*

.

Pre-symptomatic Detection and Intervention

birth

1

- earlier is better
  - plasticity
  - general rule
  - ASD treatment

Outcome for Children Receiving the Early Start Denver Model Before and After 48 Months

Giacomo Vivanti[1,2] · Cheryl Dissanayake[2] · The Victorian ASELCC Team[3]

Pre-symptomatic Detection and Intervention

birth 1

- earlier is better
  - plasticity
  - general rule
  - ASD treatment
  - preclinical studies

JCI The Journal of Clinical Investigation

***Ube3a* reinstatement identifies distinct developmental windows in a murine Angelman syndrome model**

Sara Silva-Santos, … , Steven A. Kushner, Ype Elgersma

J Clin Invest. 2015;125(5):2069-2076. https://doi.org/10.1172/JCI80554.

Pre-symptomatic Intervention ?


Training Attentional Control in Infancy

Current Biology 21, 1543–1547, September 27, 2011

Sam Wass,[1,2,*] Kaska Porayska-Pomsta,[2] and Mark H. Johnson[1]
[1]Centre for Brain and Cognitive Development, Department of Psychological Sciences, Birkbeck, University of London, London WC1E 7HX, UK
[2]London Knowledge Lab, Institute of Education, London WC1N 3QS, UK

appropriate televisior
amount of time.

Training Results
Outcome measures w
difficulty level during
adaptively during trai
mance according to r

Language outcome in autism: Randomized comparison of joint attention and play interventions.

Connie Kasari et al. (JCCP, 2008)

birth

1

Pre-symptomatic Intervention ?


Training Attentional Control in Infancy

Current Biology 21, 1543–1547, September 27, 2011

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and Mark H. Johnson[1]
[1]Centre for Brain and Cognitive Development,
Department of Psychological Sciences, Birkbeck,
University of London, London WC1E 7HX, UK
[2]London Knowledge Lab, Institute of Education,
London WC1N 3QS, UK

appropriate television
amount of time.

Training Results
Outcome measures w
difficulty level during
adaptively during trai

Language outcome in autism: Randomized comparison of joint attention and play interventions.

Connie Kasari et al. (JCCP, 2008)

birth

1

Pre-symptomatic Detection and Intervention: Scalability

birth

1

- population screening ?

phase I screen → phase II MRI

- behavior questionnaire
- eye tracking (Jones and Klin, 2013)
- polygenic risk score ?
- EEG (Gabard-Durnam et al., 2019 – Nelson Lab)
- multi-modal

unpublished data, slide not included

Future Directions

- **replicate MRI early prediction** (→ future presymptomatic treatment studies)
- **infancy → school age**
  John Pruett (Wash U St Louis), Joe Piven (UNC)
- **contrasting disorders** (Fragile X, Down Syndrome)
  Kelly Botteron (Wash U St Louis), Heather Hazlett (UNC)
- **cost effective markers** (population): EEG, eye tracking
  Shafali Jeste (UCLA, Jed Elison (U Minnesota)
- **molecular/cellular underpinnings** (genetics, induced pluripotent stem cells)
  Dani Fallin (Johns Hopkins), Jason Stein (UNC)
- **environmental exposures** (air pollution, metals)
  Heather Volk (Johns Hopkins)
- **ethical-legal-social implications** of pre-symptomatic detection
  Kate McDuffie (U Washington)

Infant Brain Imaging Study (IBIS)

University of North Carolina
Heather Cody Hazlett
Martin Styner
Mark Shen
Jessica Girault
Becca Gradzinski
Brent Munsell
Mahmoud Mostapha

Ben Philpot
Bin Gu
Jason Stein
Rose Glass

Univ of Washington
Annette Estes
Stephen Dager
Kate MacDuffie

Annual IBIS Meeting; NYC, 2017

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Julia Parrish-Morris

University of Minn
Jed Elison
Jason Wolff

University of Alberta
Lonnie Zwaigenbaum

New York University
Guido Gerig

Washington Univ. in St Louis
Kelly Botteron
John Constantino
Bob McKinstry
John Pruett
Natasha Marrus
Adam Eggebrecht

Johns Hopkins
Danielle Fallin
Heather Volk

NIMHANS
Shoba Meera

UT Dallas
Meghan Swanson

UCLA
Shafali Jeste

McGill University
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John Lewis
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Samir Das

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