Differences in early brain development predict ASD outcome in high risk infants

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Bethesda, MD April 2017

Conflicts of Interest

No conflicts of interest

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Turning Discovery Into Health

AUTISM SPEAKS®

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Why study early brain development in autism?

Early brain overgrowth

‘infantile autism’
Leo Kanner (1943)

He reported that 5 of the original 11 cases had ‘relatively large heads’

Kanner

Head Circumference

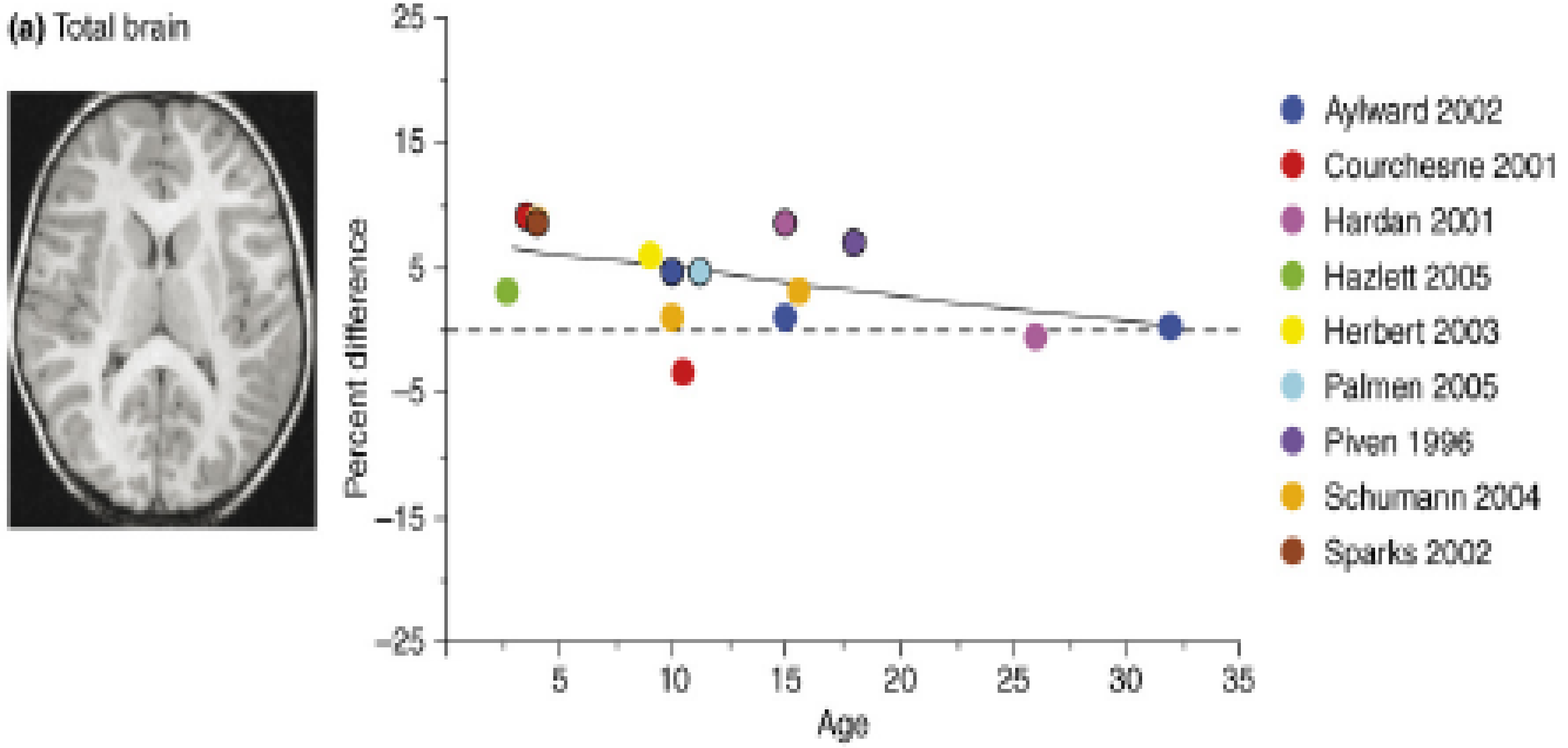
- Indirect measure of brain

- Increased head circumference in ASD, present during the first 3 years

- Methodological differences in studies

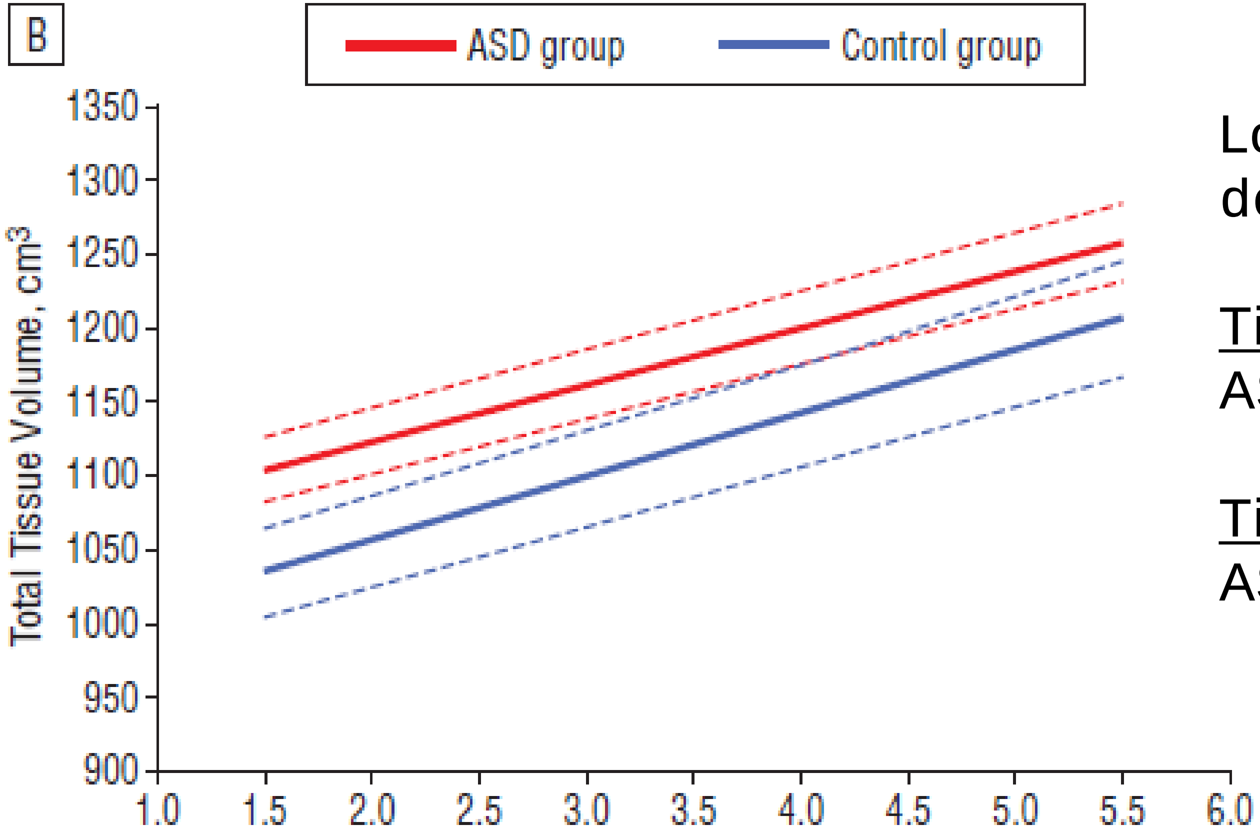
  Prospective/retrospective
  Samples included/diagnostic criteria
  Accuracy of measures/QC
  Normative data

Brain volume increased early in autism



Amaral, Schumann, & Nordahl, 2008

Brain development present in toddlers with ASD



Longitudinal design:

<u>Time1(~ 2 yrs)</u>
ASD=59,TD=38

<u>Time (~ 4-5 yrs)</u>
ASD=36,TD=21

Hazlett et al., Am J Psych, 2011

Increased surface area, but not cortical thickness, in a subset of young boys with autism spectrum disorder.

Ohta, Nordahl, Iosif, Lee, Rogers, & Amaral. Autism Res, 2015.

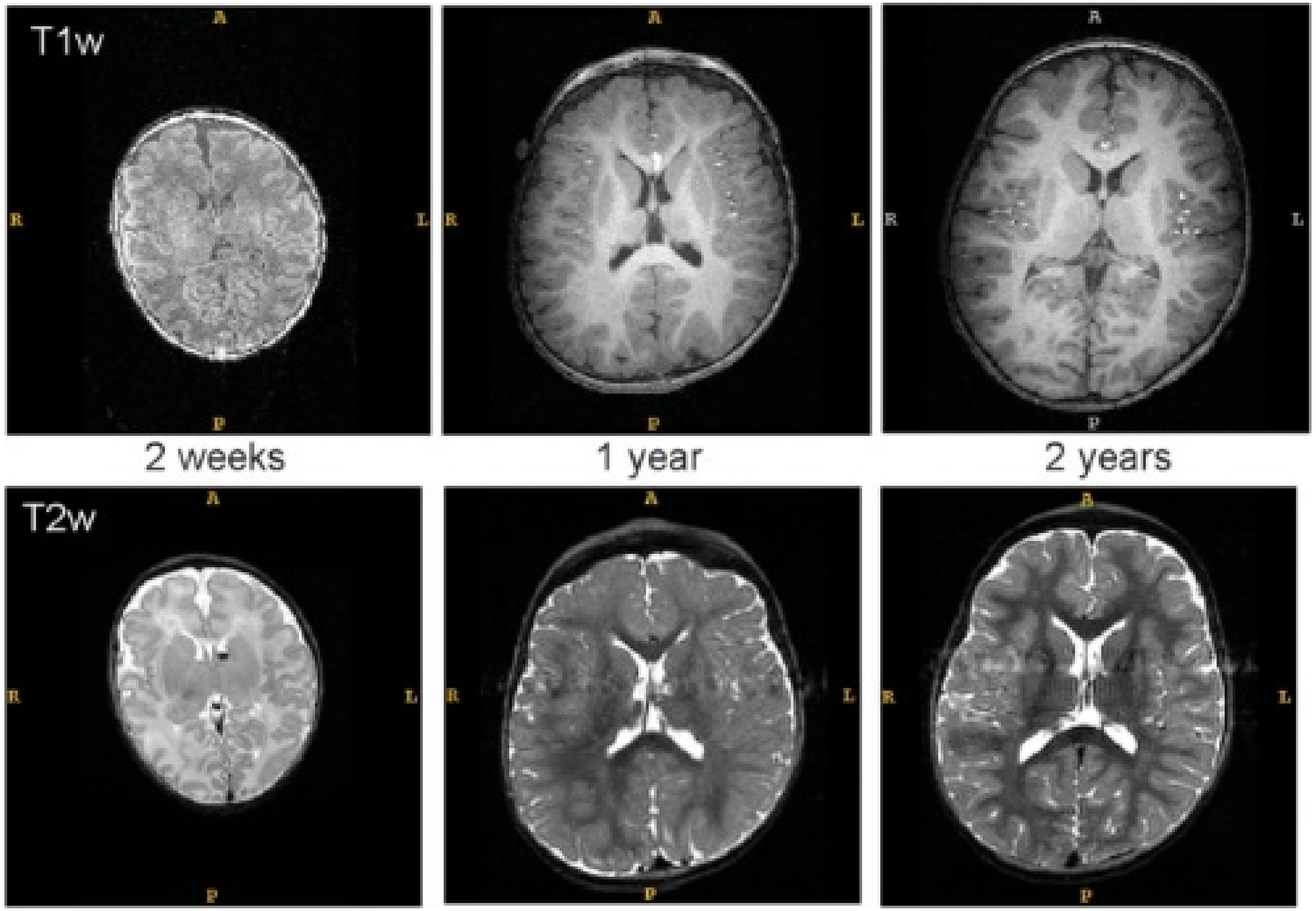
- Autism Phenome Project
- 115 ASD boys (15% DM), 50 TD boys
- Scanned at age 3

- Found ASD group had greater surface area than TD but not in cortical thickness

Birth to Three

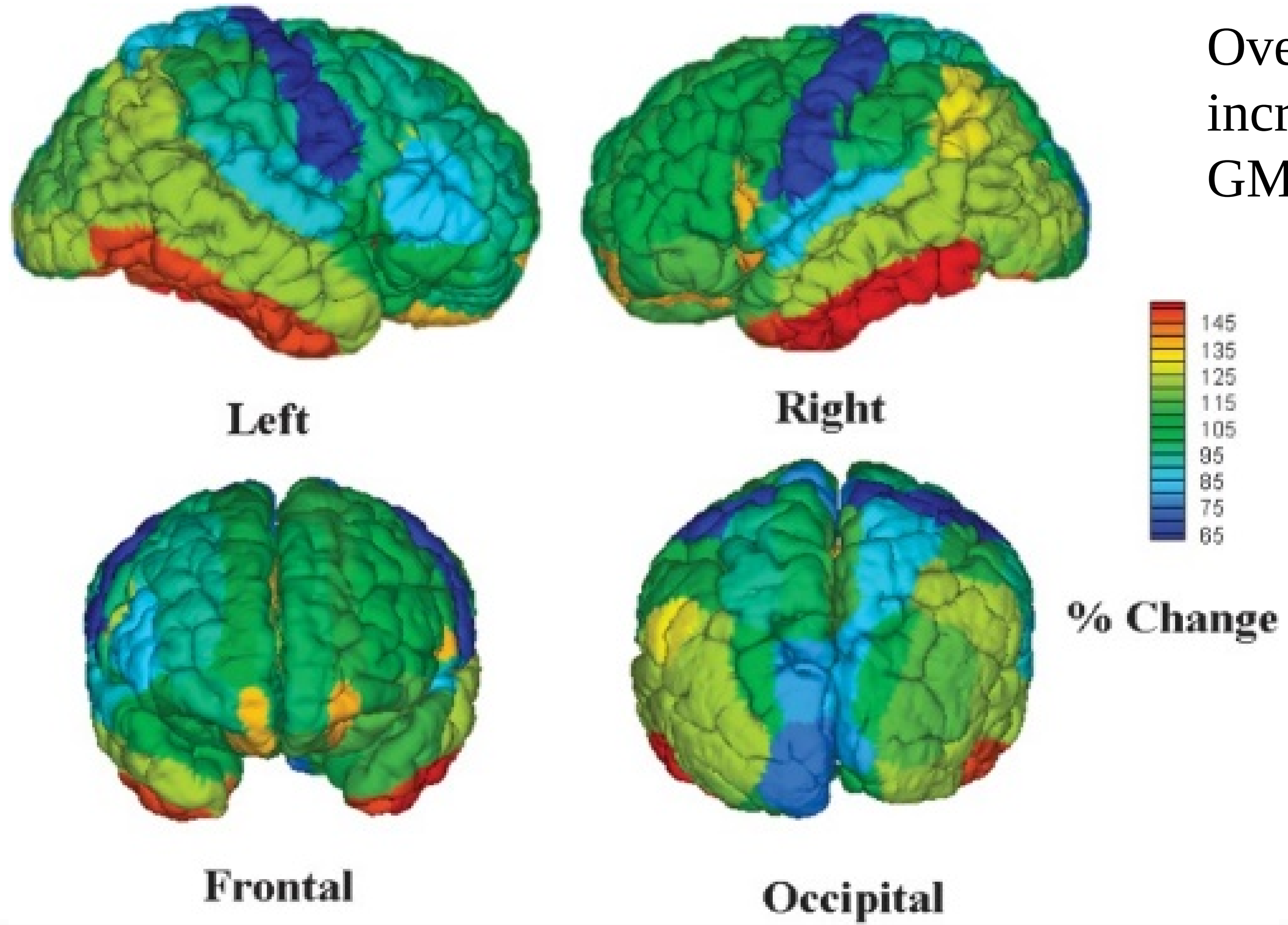
- The first two years of life involve rapid brain growth and development
- Brain development is 'activity dependent'
- Critical periods for development

Typical brain development



Gilmore et al., 2012

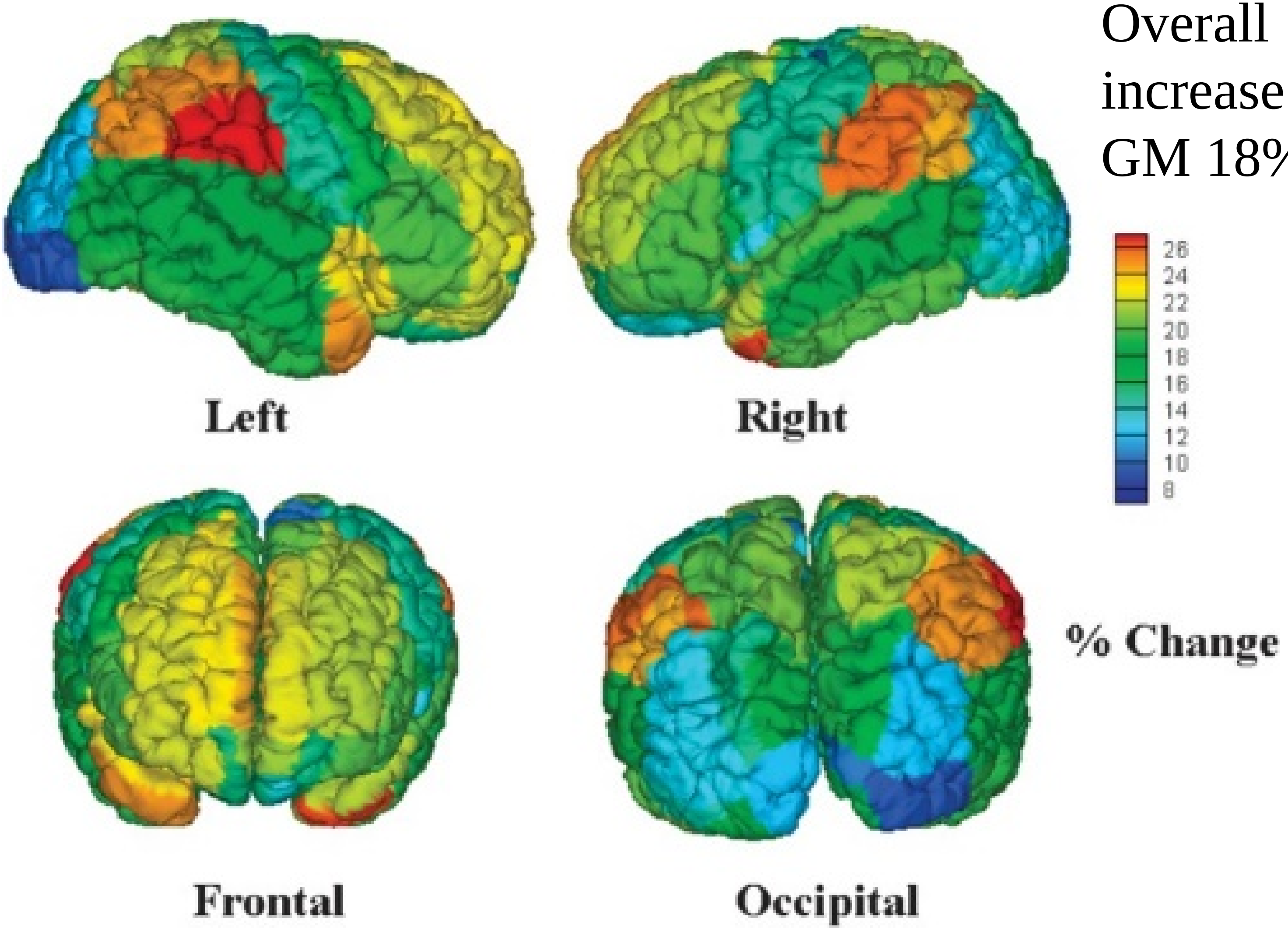
Gray matter maturation in 1st year



Overall increase in GM 106%

Gilmore et al., 2012

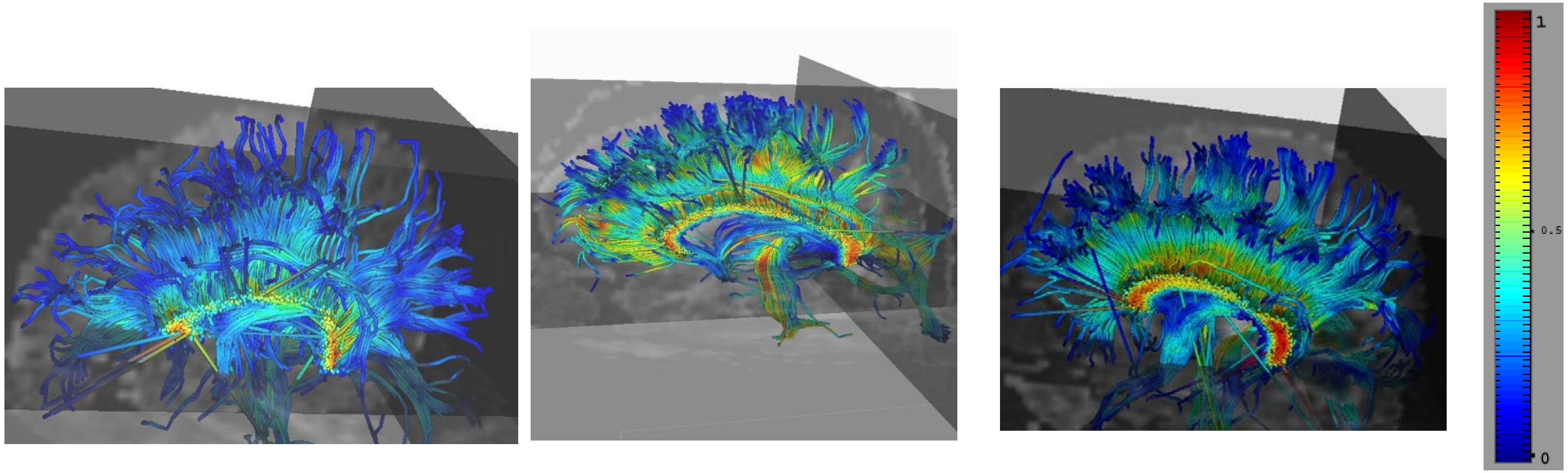
Gray matter maturation in 2nd year



Overall increase in GM 18%

Gilmore et al., 2012

White matter maturation



Neonate (2 wks) **Infant (1 year)** **Adult**

Corpus callosum: DTI (FA) along commissural bundles

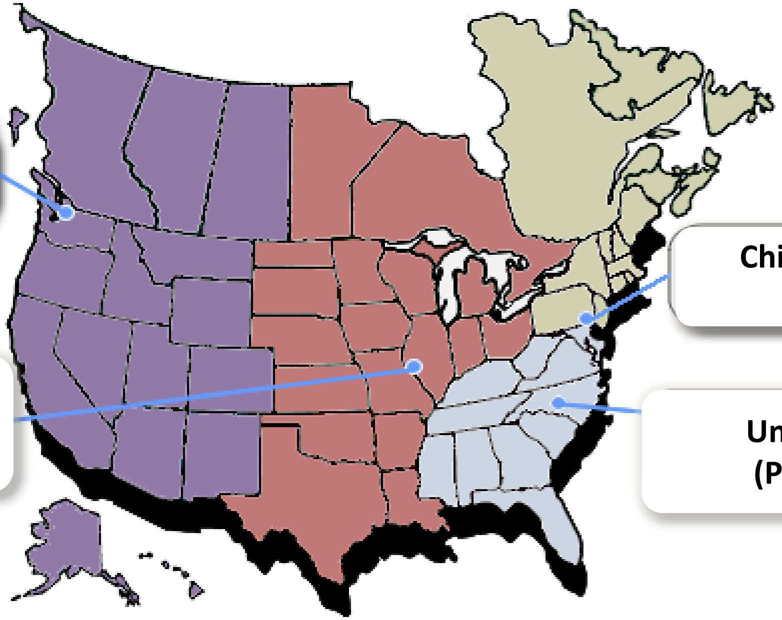
Can brain differences be used to detect ASD?

IBIS (Infant Brain Imaging Study) Network

NIH Autism Center of Excellence (PI: Joseph Piven)

University of Washington
(Dager, Estes)

Washington University
(Botteron, McKinstry, Constantino)



Children's Hospital of Philadelphia
(Schultz, Pandey, Paterson)

University of North Carolina
(Piven, Hazlett, Styner, Gu)

Alberta University
(Zwaigenbaum)

Montreal Neurological Institute
DCC (Evans, Collins, Pike)

New York University
(Gerig)

University of Minnesota
(Elison, Wolff)

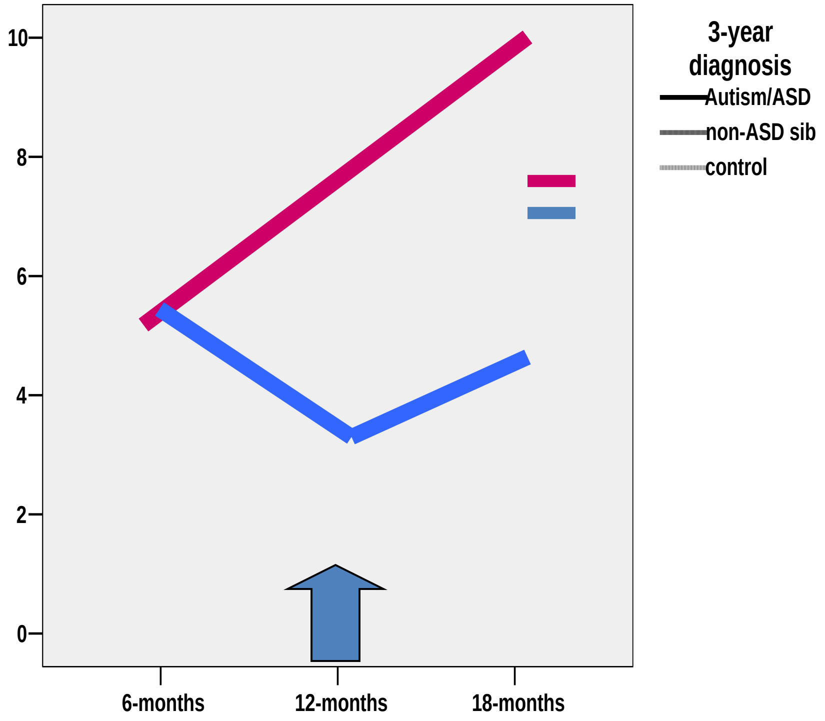
Johns Hopkins University
(Fallin, Volk)

Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

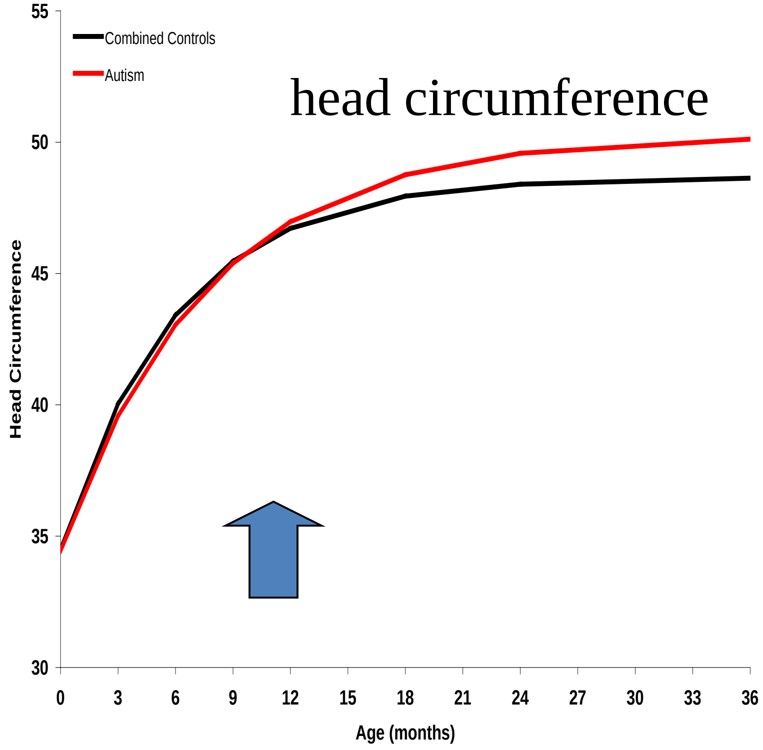
Onset of Brain Enlargement in Autistic Children before 12 mo.

Zwaigenbaum et al 2005



AOSI

Hazlett et al 2005



IBIS Network

- Infants at high-risk for autism (“baby sibs”) – younger sibling at increased risk (~20%)
- Seen longitudinally at 3, 6, 12, and 24 months with follow up at 36 m
- Developmental & behavioral assessments and MRI

LETTER RESEARCH

Nature 2017

Early brain development in infants at high risk for autism spectrum disorder

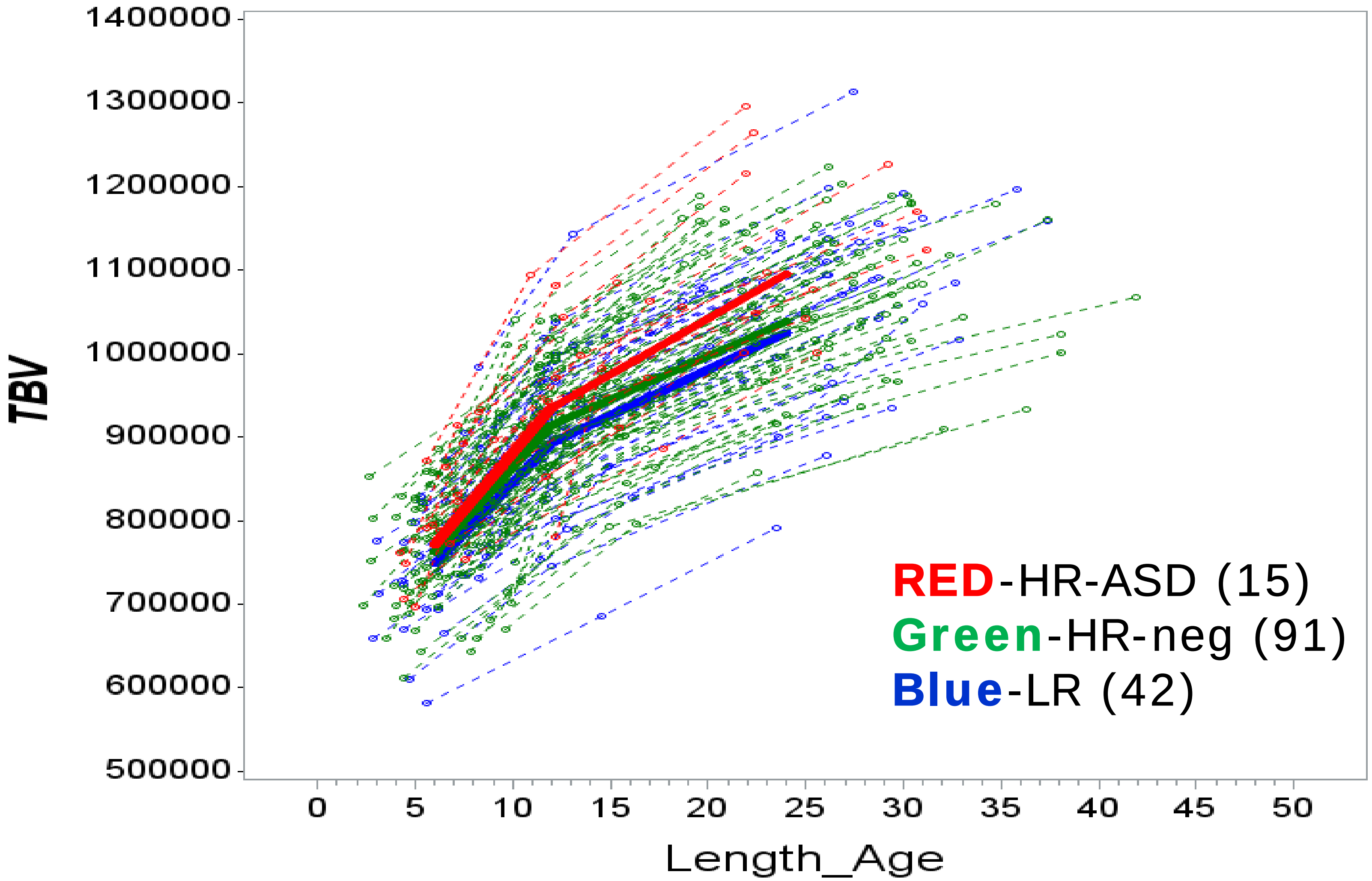
Heather Cody Hazlett[1,2], Hongbin Gu[1], Brent C. Munsell[3], Sun Hyung Kim[1], Martin Styner[1], Jason J. Wolff[4], Jed T. Elison[5], Meghan R. Swanson[2], Hongtu Zhu[6], Kelly N. Botteron[7,8], D. Louis Collins[11], John N. Constantino[7], Stephen R. Dager[8,9], Annette M. Estes[9,10], Alan C. Evans[11], Vladimir S. Fonov[11], Guido Gerig[12], Penelope Kostopoulos[11], Robert C. McKinstry[13], Juhi Pandey[14], Sarah Paterson[15], John R. Pruett Jr[7], Robert T. Schultz[14], Dennis W. Shaw[8,9], Lonnie Zwaigenbaum[16], Joseph Piven[1,2] & the IBIS Network*

Sample

	LR	HR-neg	HR-ASD	
N	117	248	70	
% males	59%	57%	83%	*
Maternal age (yrs)	33.2	33.2	33.3	
Birth weight (lbs)	8.0	7.9	7.9	
Gestational age (wks)	39.3	39.1	38.9	
Age at visit				
6m	6.7	6.6	6.6	
12m	12.7	12.7	12.7	
24m	24.6	24.7	24.6	
Mullen ELC at 24m	109.7	101.8	79.3	*
Vineland ABC at 24m	105.0	101.0	88.1	*

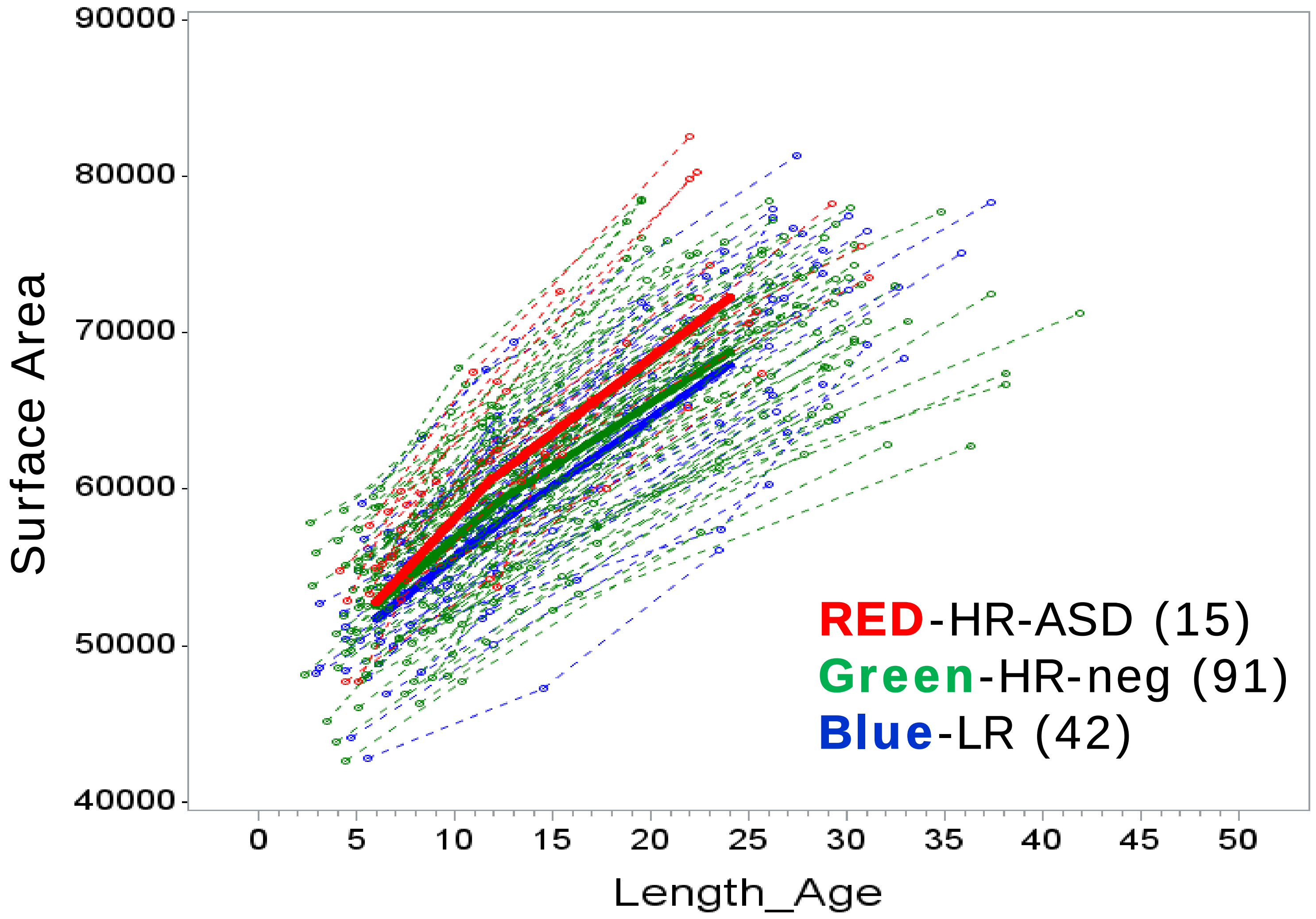
Note: also saw difference in maternal education

Brain overgrowth in HR-ASD



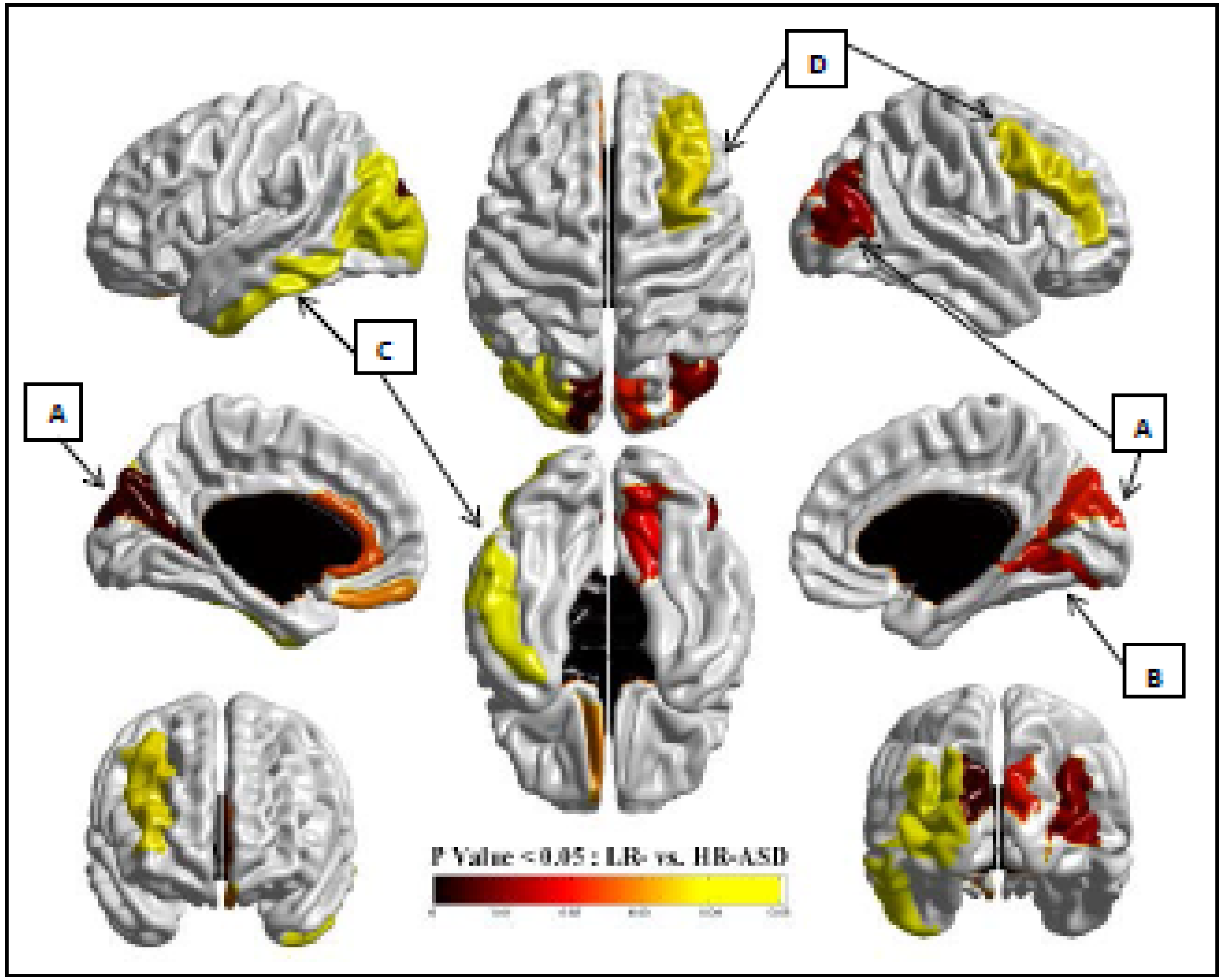
Hazlett et al., Nature 2017

Trajectory of surface area 6-24m



Hazlett et al., Nature 2017

Regions of SA expansion in HR-ASD



A=middle occipital gyrus & cuneus, B=lingual gyrus, C=inferior temporal gyrus, D = middle frontal gyrus

Hazlett et al., Nature 2017

Brain enlargement associated with behavioral features

TBV growth rate & ADOS severity score

- no relationship at 6-12 month interval
- significant (positive) relationship at 12-24 months (p=0.06)
- relationship with social affect score, not repetitive behavior

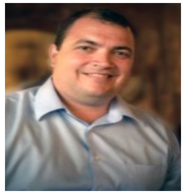
Relationship to social behaviors also seen in CSBS

- Social deficits at 24 months related to increased growth rate in TBV from 12-24 months

Could early surface area be a biomarker?

Deep Learning Classification of Cortical Data

Martin Styner, Ph.D. & Brent Munsell, Ph.D.
UNC **College of Charleston**



- predicting clinical best estimate diagnosis at 24 months:
  high risk–ASD versus high risk-negative
- 6 and 12 month scans
- cortical thickness & surface area; sex, total brain volume
- 78 ROI’s x 2 hemispheres x 2 time points = 608 data points
- divide 179 (34 HR-ASD, 145 HR-neg) into 10 equal parts (folds) each with a HR-ASD/AR-Neg ratio ~ to total sample
- train on 9 parts/folds and test on 1 part/fold; average correct vs incorrect across all 10 folds

Hazlett et al., Nature 2017

Predicting 24 Month Diagnostic Outcome from 6-12 Month Surface Area

	ASD (n=34)	Non-ASD (n=145)	
Positive Test (ASD)	True Positive (TP) N=30	False Positive (FP) N=7	**PPV = 81%** **TP / (TP + FP)**
Negative Test (Non-ASD)	False Negative (FN) N=4	True Negative (TN) N=138	**NPV = 97%** **TN / (FN + TN)**
	Total ASD	Total non-ASD	
	sensitivity = 88% **TP / ASD**	**specificity = 95%** **TN / non-ASD**	

features correctly classify ~ 8 of 10 (81%) of infants as ASD

Predicting Later Autism from Early Behavior?

autism

Article

The First Year Inventory: a longitudinal follow-up of 12-month-old to 3-year-old children

Autism
17(5) 527–540
© The Author(s) 2012
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sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1362361312439633
aut.sagepub.com
SAGE

Autism; 2013

PPV = .14
no validation sample

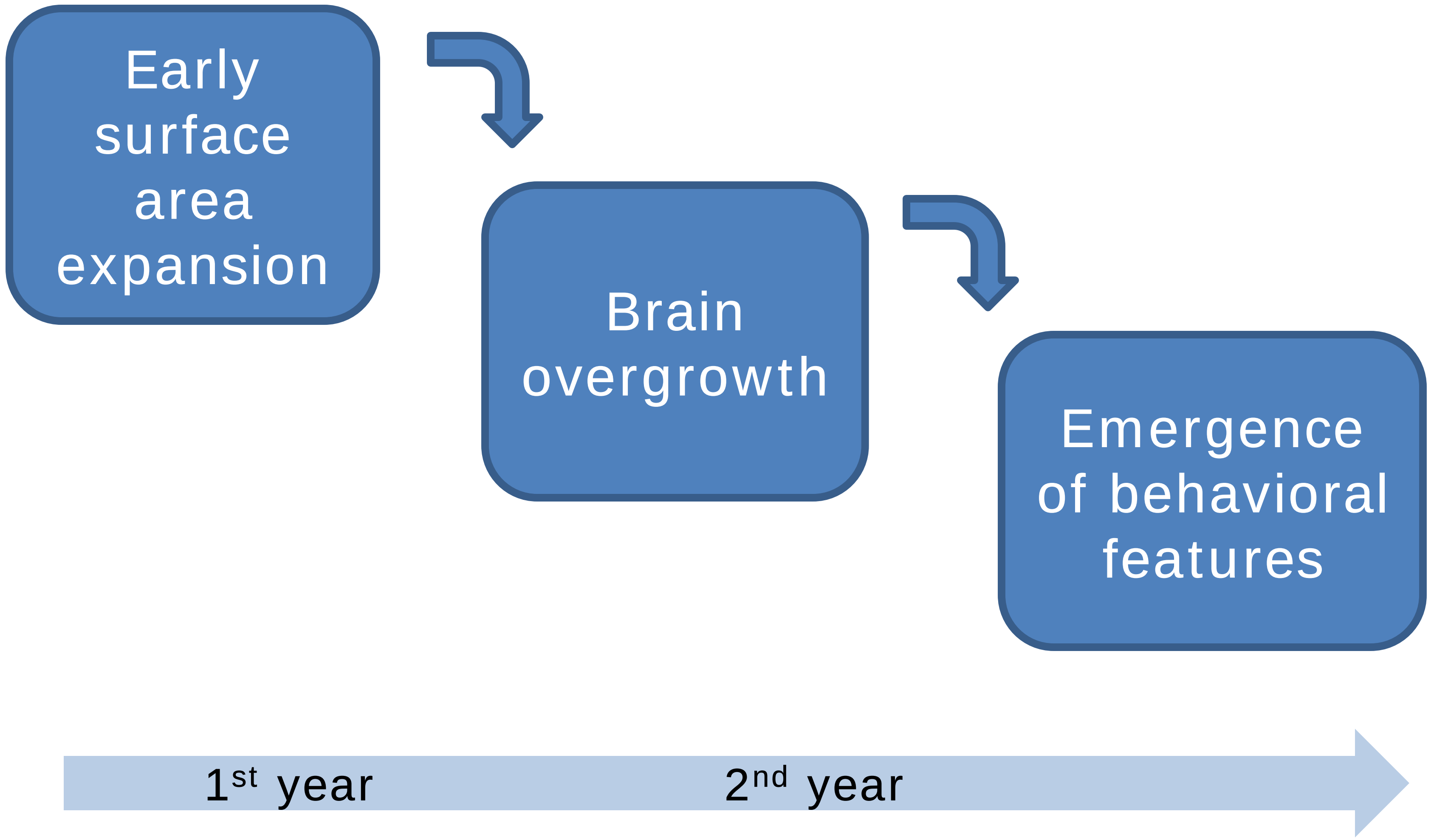
Lauren M Turner-Brown
University of North Carolina at Chapel Hill, USA

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

JAACAP 2014

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
in a validation sample



Early surface area expansion
Brain overgrowth
Emergence of behavioral features
1st year
2nd year

Summary of findings

brain changes are present as early as **6 months of age** (before the appearance of the defining features of autism)

the brain in autism **changes over time** (age 6 – 24 months) ... during a critical period when autistic behavior is first unfolding

Clues to mechanisms?

Neocortical neurogenesis and the etiology of autism spectrum disorder (2016). Alan Packer (SFARI)

Some ASD risk genes have role in neurodevelopment

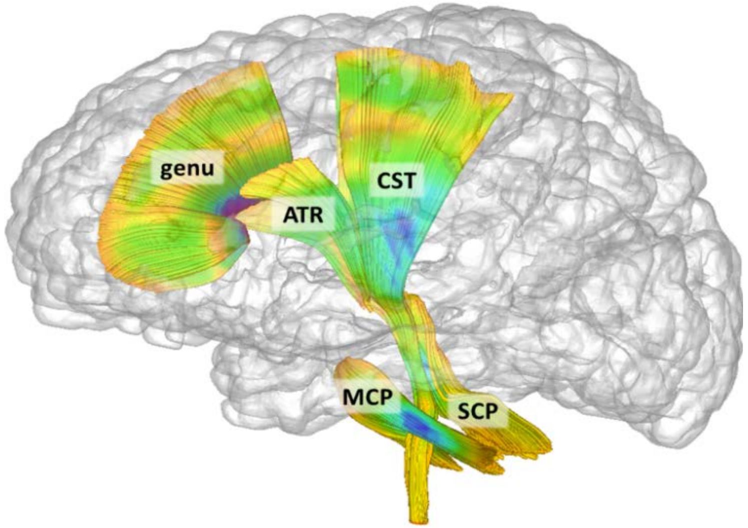
Altered neurogenesis?

Neural progenitor cell proliferation?

Other evidence for early brain differences and ASD outcomes?

Neural circuitry at age 6 months associated with later repetitive behavior and sensory features in autism

JasonWolff



ATR = anterior thalamic radiation; **CST** = cortico-spinal tract; **genu** = genu of corpus callosum; **MCP** = mid-cerebellar peduncle; **SCP** = superior cerebellar peduncle

HR-ASD (N=44); **HR-NEG** (N=173)

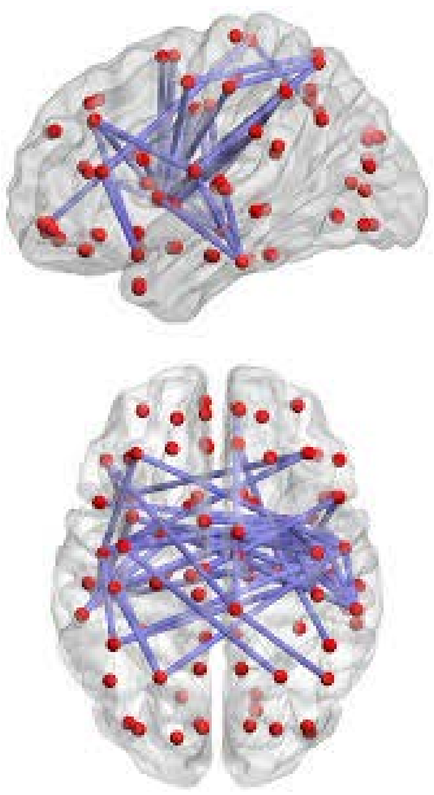
- DTI tracts at 6, 12 and 24 months
- Behavior: RBS-R, SEQ

Genu FA & Cerebellar pathways at <u>6 months</u> → Repetitive behavior & sensory features at <u>24 months</u>

- **no association** between genu/cerebellar tracts and ADOS **social affect** score

Wolff et al, <u>Mol Autism</u> 2017

Examining brain networks



functional connectivity
networks from rsMRI

Robert Emerson

6 Months of Age

Using functional connectivity at 6 months to predict ASD outcomes at 24 months

Future directions and next steps

- Explore brain-behavior relationships in cortical and subcortical data
- Multi-modal analyses (e.g, sMRI, DTI, bx)
- Individual profiles and domain based trajectories (e.g., RDoC)
- Incorporate genetics and environmental risk data

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Infant Brain Imaging Study (IBIS) NIH ACE Network

Acknowledgements

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