Neuroimaging the Full Spectrum of Autism

David G. Amaral, Ph.D.
dgamaral@ucdavis.edu

The M.I.N.D. Institute,
Dept. of Psychiatry and Behavioral Sciences,
California National Primate Research Center (CNPRC)
UC Davis
Genes
\(G_1, G_2, G_3, \ldots, G_n\)

Environment
Factor 1, Factor 2, \ldots, Factor \(n\)

Autism Type A
Autism Type B
Autism Type C

Heterogeneity of Causes?
There are many causes of autism and many types of autism?

AutismS not Autism
Magnetic resonance imaging may provide evidence to help define different types of ASD
MRI of Autism Spectrum Disorder

Weaknesses of Earlier Studies

- Small sample sizes (dozens instead of hundreds)
- Heterogeneous samples
- Cross-sectional
- Focus on older and higher functioning individuals
There is a scarcity of large-scale, longitudinal neuroimaging studies of infants at all severity levels of autism spectrum disorder.
Autism is a neurodevelopmental disorder

Only a small number of papers have focused on children under age 5
Overarching Hypothesis:

When you study the brains of young children with ASD using MRI, you will see different neurophenotypes.
Autism Phenome Project
Large-scale multidisciplinary project aimed at identifying subtypes of autism 2 to 3.5 year old children, longitudinal assessments
The MIND Institute
Autism Phenome Project (APP)

• Children are recruited between 2 and 3 1/2 years of age.

• Study includes all children with autism with very few exclusions.

• Both boys and girls are included.

• Age-matched typically developing children serve as controls.
The MIND Institute Autism Phenome Project (APP)

• The study is longitudinal - children return to the MIND Institute annually for further testing.

• Blood samples are obtained from subjects, siblings and from parents.
Visit 1: Diagnostic Confirmation, Cognitive Testing

Visit 2: Language Assessment, Imitation, Handedness

Visit 3: Medical Exam, 3-D Photgraph, Vitals Measurement and Blood Draw

Visit 4: Nighttime MRI

Visit 5: EEG/ERP
Autism Phenome Project Background

Number of Families Participating

- **ASD**
  - 2006: 28
  - 2007: 79
  - 2008: 156
  - 2009: 234
  - 2010: 324
  - 2011: 366

- **TD**

- **Cumulative**

Autism Phenome Project Background
Male and Female Participants

- Female: 35 TD, 42 ASD
- Male: 80 TD, 209 ASD
## Autism Phenome Project Background

### Age at Entry into Study

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASD</td>
<td>TD</td>
</tr>
<tr>
<td>N</td>
<td>209</td>
<td>80</td>
</tr>
<tr>
<td>Average Age (yrs)</td>
<td>2.97</td>
<td>2.86</td>
</tr>
<tr>
<td>Std Dev</td>
<td>0.50</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Autism Phenome Project Background

**Race**
- 66% White
- 13% Asian
- 10% Black
- 7% Mixed
- 5% Am. Indian
- 5% Unknown
- 1% Non-Hispanic
- 75% Hispanic
- 7% Unknown

**Ethnicity**
Developmental Quotient

Verbal DQ

Non-Verbal DQ
MRI of Young Children

Thomas the Train Mock Session

MRI Practice Kit
MRI of Young Children

MRI Practice Kit
Child-friendly scanning environment

Before

After
Christine Nordahl, Ph.D.
and
MRI Team
<table>
<thead>
<tr>
<th>Subjects and Success</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Time 1</td>
</tr>
<tr>
<td>38 months</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>Time 2</td>
</tr>
<tr>
<td>51 months</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>Time 3</td>
</tr>
<tr>
<td>64 months</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>279</td>
</tr>
<tr>
<td>191</td>
</tr>
<tr>
<td>142</td>
</tr>
<tr>
<td>Success Rate</td>
</tr>
<tr>
<td>88%</td>
</tr>
<tr>
<td>91%</td>
</tr>
<tr>
<td>88%</td>
</tr>
<tr>
<td>Attrition</td>
</tr>
<tr>
<td>19%</td>
</tr>
<tr>
<td>21%</td>
</tr>
</tbody>
</table>
Total Brain Measurements

- Frontal
- Parietal
- Temporal
- Frontal
Total cerebral volume (TCV) is enlarged by 6% in boys with ASD.

** BOYS

** p < .001

Volume (cm³)

** GIRLS

no difference

Volume (cm³)

** p < .001
Total brain size is extremely variable in ASD
Autism Onset and Brain Size

Onset status is based on parent report on ADI-R

Early Onset = 47%

Regression = 53%
ASD children who regressed have enlarged brains

** ASD-EO             ASD-Reg                 TD **

** ANCOVA – age, DQ, gender as covariates
** p < .01 ASD-Reg > TD & ASD-EO **

ANCOVA – age as covariate

** p < .01 ASD-Reg > TD & ASD-EO **
Retrospective head circumference shows divergence at 4-6 months.
Surface rendering of children’s brains

Typical Child
Age 31 months
TCV 981.96

Autism Early Onset
Age 32 months
TCV 984.57

Autism Regression
Age 30 months
TCV 1180.98
Relationship of Total Cerebral Volume to Height

On average, ASD kids are not taller than Typical kids.
Relationship of Total Cerebral Volume to Height

ASD only

- illustrates where the Mega subgroups fall on height and TCV
One clear neurophenotype is Disproportionate Megalencephaly (ASD-DM)
i.e. the ratio of brain volume to height is 1.5 standard deviations above control mean

This accounts for 15% of our male, ASD cohort
Is the cortex of the brain thicker?

or

Is there more surface area?
Visualization in Freesurfer

dark grey = sulci; light grey = gyri
Average of cortical thickness of whole brain

Cortical surface area of whole brain

P < 0.01
Average of cortical thickness of whole brain

Cortical surface area of whole brain

P < 0.01

P < 0.01
Is there evidence for different fiber connection alterations in the megalencephalic brains?
DTI Tractography

- Parallel bundles of fibers have high anisotropy
- White-matter can be isolated and investigated
- Fiber pathways can be reconstructed with good anatomic validity
Diffusion properties of major white matter tracts in young, typically developing children

Ryan T. Johnson\textsuperscript{a}, Jason D. Yeatman\textsuperscript{b}, Brian A. Wandell\textsuperscript{b}, Michael H. Buonocore\textsuperscript{c}, David G. Amaral\textsuperscript{a}, Christine Wu Nordahl\textsuperscript{a,*}

\textsuperscript{a} M.I.N.D. Institute, Department of Psychiatry and Behavioral Sciences, University of California at Davis, 2825 50th Street, Sacramento, CA 95817, USA
\textsuperscript{b} Department of Psychology, Jordan Hall, Stanford University, 450 Serra Mall, Stanford, CA 94305, USA
\textsuperscript{c} Department of Radiology, UC Davis School of Medicine, University of California, Sacramento, CA 95817, USA
White Matter Abnormalities in Boys with ASD
Anterior Thalamic Radiation
### Fiber Tract Abnormalities in ASD males

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tracts Implicated</th>
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<tbody>
<tr>
<td>Social Communication</td>
<td></td>
</tr>
<tr>
<td>Reception of Facial Communication</td>
<td>Uncinate fasciculus</td>
</tr>
<tr>
<td>Reception of Non-Facial Communication</td>
<td>Inferior longitudinal fasciculus</td>
</tr>
<tr>
<td>Production of Non-Facial Communication</td>
<td>Arcuate fasciculus, Inferior longitudinal fasciculus</td>
</tr>
<tr>
<td>Perception and Understanding of Self</td>
<td></td>
</tr>
<tr>
<td>Agency</td>
<td>Inferior longitudinal fasciculi, Corticospinal tract</td>
</tr>
<tr>
<td>Self-Knowledge</td>
<td>Uncinate fasciculus</td>
</tr>
<tr>
<td>Perception and Understanding of Others</td>
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</tr>
<tr>
<td>Animacy Perception</td>
<td>Inferior longitudinal fasciculus</td>
</tr>
<tr>
<td>Action Perception</td>
<td>Corticospinal tract</td>
</tr>
<tr>
<td>Understanding Mental States</td>
<td>Uncinate fasciculus, Inferior longitudinal fasciculus</td>
</tr>
<tr>
<td>Positive Valence Systems</td>
<td></td>
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<tr>
<td>Repetitive/Stereotypic/Compulsive Behaviors</td>
<td>Uncinate fasciculus</td>
</tr>
<tr>
<td>Cognitive Systems</td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td>Arcuate fasciculus</td>
</tr>
</tbody>
</table>
The Amygdala
Amygdala growth relative to TCV

• 40% of boys with ASD have an abnormally rapid growth of the amygdala

• 20% of boys with ASD have an abnormally slow growth of the amygdala

• 40% of boys with ASD have a normal growth rate of the amygdala
Questions Related to Outcome

• Do early neurophenotypes persist into middle childhood?

• Do early neurophenotypes predict different patterns of autism severity, cognitive function and co-morbid syndromes?

• Is there a pattern of early brain organization that is associated with optimal outcome?
Figure 1 HC and MRI percent difference (%Diff) by age. %Diff values from all HC and MRI studies are plotted by the mean age of the study. The best fitted curve shows the most rapid rates of increased deviation from normal brain size in autism within first ...

Elizabeth Redcay, Eric Courchesne

When Is the Brain Enlarged in Autism? A Meta-Analysis of All Brain Size Reports

Biological Psychiatry, Volume 58, Issue 1, 2005, 1 - 9
Some low IQ  Few low IQ

Figure 1 HC and MRI percent difference (%Diff) by age. %Diff values from all HC and MRI studies are plotted by the mean age of the study. The best fitted curve shows the most rapid rates of increased deviation from normal brain size in autism within first ...

Elizabeth Redcay, Eric Courchesne

When Is the Brain Enlarged in Autism? A Meta-Analysis of All Brain Size Reports

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Mean Total Cerebral Volume: 3-6 years

- ASD-DM
- ASD-norm
- TD

Total Cerebral Volume, cm³

Time 1 | Time 2 | Time 3
---|---|---
850 | 900 | 950
900 | 950 | 1000
950 | 1000 | 1050
1000 | 1050 | 1100
1050 | 1100 | 1150
1100 | 1150 | 1200
1150 | 1200 | 1250
1200 | 1250 | 1300
1250 | 1300 | 1350
IACC 2009 Strategic Plan

Question 2: How Can I Understand What is Happening?

Research Opportunity

Multi-disciplinary, longitudinal, biobehavioral studies of children, youths, and adults beginning during infancy that characterize neurodevelopmental and medical developmental trajectories across the multiple axes of ASD phenotype and identify ASD risk factors, subgroups, co-occurring symptoms, and potential biological targets for intervention.
Subject NB

- 9 year old male
- I.Q. 41
- ADOS Total Score 19
- Non-verbal
- Self injurious behavior
- Aggression
NB scans

Time 1
Age 3.7 years

Time 2
Age 4.7 years

Time 4
Age 9.7 years
Acknowledgments

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• The MIND Institute faculty and staff that have participated in the Autism Phenome Project
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  • The MIND Institute
  • The NIH
  • Many donors including the family of Peter Bell.