The need for nonhuman primate models of neurodevelopmental disorders - Autism

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Brain Development in ASD

Magnetic resonance imaging provides evidence of different types of ASD
Child-friendly scanning environment

Before

After
Total Brain Measurements
Total brain size is on average larger but extremely variable in ASD.
Total brain size is on average larger but extremely variable in ASD.
Distribution of Brain Size/Height for Boys in APP

![Graph showing the distribution of total cerebral volume in cubic centimeters (cm³) against height in inches, with different colors representing different groups: ASD-DM, ASD-N, and TD.]
Disproportionate Megalencephaly (ASD-DM)

i.e. the ratio of brain volume to height is 1.5 standard deviations above control mean
Disproportionate Megalencephaly (ASD-DM)

Boys

85% 15%

Typical Child
Age  31 months
TCV 981.96

Autism
Normal brain size
Age  32 months
TCV 984.57

Autism
Megalencephaly
Age  30 months
TCV 1180.98
More surface area of the cortex
But not thicker cortex

Typical Child
Age 31 months
TCV 981.96

Autism
Normal brain size
Age 32 months
TCV 984.57

Autism
Megalencephaly
Age 30 months
TCV 1180.98
Are there behavioral, cognitive or biomedical differences between ASD-N and ASD-DM?

COMMENTARY

In Pursuit of Neurophenotypes: The Consequences of Having Autism and a Big Brain

David G. Amaral, Deana Li, Lauren Libero, Marjorie Solomon, Judy Van de Water, Ann Mastergeorge, Letitia Naigles, Sally Rogers, and Christine Wu Nordahl

<table>
<thead>
<tr>
<th></th>
<th>Time 1 (~3 years)</th>
<th>Time 3 (~6 years)</th>
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<tbody>
<tr>
<td>ASD-N</td>
<td>63.8 (21.3)</td>
<td>84.2 (22.0)</td>
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<tr>
<td>ASD-DM</td>
<td>56.5 (22.4)</td>
<td>68.4 (26.1)</td>
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Relationship between language and brain size in ASD-DM and ASD-N Boys
Disruptive CHD8 Mutations Define a Subtype of Autism Early in Development
Macrocephaly – 80%
Autism – 87%
Need for nonhuman primate model of autism

• We do not understand the neurobiology of megalencephaly in autism – and these children have a poorer prognosis.

• The behavioral impairments and megalencephaly of autism primarily involve the prefrontal cortex which is primitive in rodents.

• Manipulations of CHD8 in rodents produces megalencephaly but not the behavioral characteristics typical of autism.
Need for nonhuman primate model of autism

• Nonhuman primates have brain organization and social behavior much more like that of humans.

• Manipulations of genes in NHP that produce autism with megalencephaly in humans (eg. CHD8) would provide the substrate for understanding and for developing targeted treatments.

• It is in our national interest to develop the capacity to produce genetically modified