Why is Studying the Brain Important for Understanding Autism?

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What causes autism?

Autism is clearly an alteration of brain function that leads to altered behavior.

What is known about brain development and how it is different in autism?
Brain Development

The human brain has about 100 billion neurons.

And at least 100 trillion synapses.
The cerebral cortex has about 20 billion neurons.

During the peak of cortical neuron production (between the 13\textsuperscript{th} and 20\textsuperscript{th} week of pregnancy), cells are generated at the pace of around 2500/second.
Brain Development

It is not surprising that there are missteps in how the brain develops.

What is surprising, is that it ever develops normally!
The brain is about 25% of adult size at birth and grows to 95% of its adult size by age 6.
How the Brain Develops

MRI scans of human brain development
15% of the brains of boys with autism spectrum disorder are larger than expected.

Typical Child  
Age 31 months  
TCV 981.96

Child with ASD  
Age 32 months  
TCV 984.57

Child with ASD  
Age 30 months  
TCV 1180.98
Resolution of MRI is too low to see neurons and networks.

Voxel = 1 mm³

Voxel = 50,000 neurons

Voxel = 100-300 million synapses
How the Brain Develops

Conel, J.L. (1939-1963)  
The postnatal development of the cerebral cortex (Vols 1-6)  
Harvard University Press
Alois Alzheimer

Augusta D 1907
Alois Alzheimer
The first neuropathological studies of autism were carried out in the mid 1980’s.

No consistent sign of disease, like plaques and tangles, have yet been found.

However, new research is providing new insights into brain alterations associated with autism.
Examples of autism research based on postmortem brain donations
T-lymphocytes and Cytotoxic Astrocyte Blebs Correlate Across Autism Brains

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UC-eLinks | UCD-eLinks

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Somatic mosaicism and neurodevelopmental disease

Alissa M. D’Gama\textsuperscript{1,2,3} and Christopher A. Walsh\textsuperscript{1,2,3}\textsuperscript{*}

Traditionally, we have considered genetic mutations that cause neurodevelopmental diseases to be inherited or de novo germ-line mutations. Recently, we have come to appreciate the importance of de novo somatic mutations, which occur postzygotically and are thus present in only a subset of the cells of an affected individual. The advent of next-generation sequencing and single-cell sequencing technologies has shown that somatic mutations contribute to normal and abnormal human brain development. Somatic mutations are one important cause of neuronal migration and brain overgrowth disorders, as suggested by visible focal lesions. In addition, somatic mutations contribute to neurodevelopmental diseases without visible lesions, including epileptic encephalopathies, intellectual disability, and autism spectrum disorder, and may contribute to a broad range of neuropsychiatric diseases. Studying somatic mutations provides insight into the mechanisms underlying human brain development and neurodevelopmental diseases and has important implications for diagnosis and treatment.
Transcriptomic and morphophysiological evidence for a specialized human cortical GABAergic cell type


https://doi.org/10.1038/s41593-018-0205-2
Neuropathology
Genetics
Neurochemistry
Based on findings from MRI and genetic research, postmortem studies will require:

• A large number of clinically and genetically well-characterized brains for analysis
• Appropriate control brains for comparison
Mission

Autism BrainNet is a collaborative network for the acquisition and distribution of postmortem brain tissue and other biologic samples for research on autism spectrum disorder and related neuro-developmental disorders.
Launched May 2014
Promoting Research into the Causes of Autism Spectrum Disorder

Although there is substantial evidence from neuroimaging studies that the brain of a child with autism is undergoing abnormal development, little is known about the underlying cellular, molecular and genetic mechanisms that lead to the onset of autistic symptoms.

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Outreach Manager

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PLEASE REGISTER at TakesBrains.org

Join Autism BrainNet

Donor Registry: Your Information

By signing up as a participant in the Autism BrainNet donor registry, you will receive information on the value of making a brain donation to support research on autism spectrum disorder. This is not a consent form and you are under no obligation to ever make a donation.

* indicates required field.

First Name
Middle Name
Last Name
Address
Apt/Ste/Unit
City
State
Zip Code
Email
Phone
How did you hear about us?

Submit Your Registration

This initiative is guided by:

[Logos of Autism Research Foundation, UC Davis Mind Institute, SFARI (Simons Foundation Autism Research Initiative)]
Anxiety in the Brain:

Regions of the brain responsible for fear and anxiety continue to develop into adulthood.

These regions develop on a different trajectory in people with ASD.

Goal: understand how the brain is changing throughout life in order to look for treatments and interventions.
Anxiety in the Brain:
The Amygdala
The Amygdala: Danger Detector

- Looks for clues of potential threat
- Links information with previous knowledge
- Tells other brain regions what to do
- Enhances memory for highly emotional events
Does the amygdala develop differently in people with ASD?

Measure size of the Amygdala on MRI
Amygdala continues to grow in typical development

Schumann et al., 2004, 2009, Nordahl et al., 2012
Amygdala grows too large too quickly in ASD

Schumann et al., 2004, 2009, Nordahl et al., 2012
What makes the Amygdala bigger?

Number of cells?

Number of connections?
How do the number of neurons change throughout the human lifespan? How is it different in ASD?

Neurons: Primary cells underlying brain function
The number of amygdala neurons increases in typical development by 30% from youth to adulthood.
The number of amygdala neurons continues to increase in typical development.
There are more amygdala neurons in children with ASD, but fewer amygdala neurons in adults with ASD

Avino et al., 2018 PNAS
Too many amygdala neurons in children with ASD

Loss of neurons into adulthood

Avino et al., 2018 PNAS
Neuron numbers increase in the human amygdala from birth to adulthood, but not in autism

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Why are there more amygdala neurons in children with ASD?

Why are people with ASD losing neurons as they get older?
Do amygdala neurons continue to grow fibers into adulthood?

Do amygdala neurons grow fibers differently in people with ASD?
Amygdala neurons continue to grow connections into adulthood
Amygdala neurons continue to grow connections into adulthood
Spines: small spots on neurons where other neurons connect to transmit signals

- **Too many Spines**: too much communication between neurons
  (examples: overactive amygdala leading to anxiety, seizures)

- **Too few Spines**: too little communication between neurons
  (example: loss of spines may be due to overactive amygdala)

Do people with ASD have a different number of neuronal spines in the amygdala?
Children with ASD have more spines on amygdala neurons

Too much communication between neurons in people with ASD may lead to an overactive amygdala and anxiety.
Adults with ASD have fewer spines on amygdala neurons.

Loss of spines may be due to stress, anxiety, and an overactive amygdala.
Amygdala in ASD: Too much too early, then loss

Volume
Neuron #
Spine #

Neurotypical

Autism

Avino et al., 2018 PNAS
The amygdala...

- undergoes substantial changes in typical development and in people with ASD throughout life
- grows too large with too many neurons and spines early in children with ASD, which may contribute to anxiety and social impairments
- potentially loses neurons and spines as people with ASD become adults

Take home message:
If we understand how the brain is changing throughout life, we have the opportunity to change course and find treatments
CONCLUSIONS

• The symptoms of autism are due to altered brain development.

• One way to understand autism at a cellular and molecular level is to study the postmortem human brain.

• Understanding the alterations in brain development and functional neural systems can lead to more effective targeted treatments for the disabilities associated with autism.

• Analyzing the autistic brain provides insight into the way the most sophisticated human behaviors and emotions are produced.
The M.I.N.D. Institute

THANK YOU!