Structure & Function of the Brain in Autism Spectrum Disorders: What do we know?

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THE BRAIN IS MISWIRED IN ASD

MYTHS & EVIDENCE

SCULPTURE depicts overhead view of brain's cortex (copper) and white matter core.
Objectives:

1. Symptoms of ASD
2. What is brain wiring?
3. Is the brain miswired in ASD?
   - Post-mortem Findings
   - Structural Neuroimaging
   - Functional Neuroimaging
   - Diffusion Tensor Imaging
Autistic Disorder

- Impaired Social Interaction
  - non-verbal behaviours,
  - peer relationships
  - sharing enjoyment, activities, interests
  - social or emotional reciprocity

- Impaired Communication
  - Delay or lack of language development
  - Conversation
  - Use of language
  - Make believe/social imitative play

Asperger’s Disorder

- Restrictive, repetitive, stereotyped behaviour, interests, activities
  - Intense/circumscribed interest
  - Inflexible adherence to non-functional routines
  - Stereotyped, repetitive motor manoeuvres
  - Persistent preoccupation with parts of objects

PDD-NOS

DSM IV TR (2000)
Autistic Disorder

- Impaired Social Interaction
- Impaired Communication

Restrictive, repetitive, stereotyped behaviour, interests, activities

Delay or abnormal function in:
- social interaction,
- language use for social communication
- or symbolic/imaginative play

Prior to 3 years of age

DSM IV TR (2000)
Impaired Social Interaction

Restrictive, repetitive, stereotyped behaviour, interests, activities

No delay in language
No significant delay in cognitive development, self-help skills or adaptive behaviour (aside from social interaction)

DSM IV TR (2000)
PDD-NOS

Severe and pervasive impairment in development of reciprocal social interaction + Impaired communication OR Stereotyped behaviours, activities, interest

DSM IV TR (2000)
Autism Spectrum Disorders (ASD): Three Diagnostic Symptom Clusters +++

- Savant skills
- GI Problems
- Intelligence/LD
- Sleep D/O

- Impaired communication
- Impaired social interactions
- Stereotyped, Repetitive, Restricted behaviour, interests, & activities

- ADHD Sx
- Aggression
- Self injury
- Anxiety
- Seizures
White matter fills nearly half the brain. It consists of millions of cables (white) that connect individual neurons (gray matter) in different brain regions, like trunk lines connecting telephones across a country.

Corpus callosum, a mass of white matter cables, connects the brain’s left and right hemispheres. On either side, the cables extend up and outward toward the...
THE WIRES

Fields. Scientific American 2008
Neural Networks

Courtesy of Marco Catani
What is the Evidence?

1. Post-mortem Findings
2. Structural MRI
3. Functional MRI
4. Diffusion Tensor Imaging
<table>
<thead>
<tr>
<th>Consistent Post-Mortem Findings in ASD</th>
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<tbody>
<tr>
<td>Increased cell packing density &amp;</td>
<td>9/14 cases studied</td>
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<td>smaller neurons in the limbic system</td>
<td>(8 with MR +/- epilepsy)</td>
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<td>All new cases</td>
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<td>7-29 years</td>
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<td>Reduced Purkinje cell number in</td>
<td>21/29 cases studied</td>
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<tr>
<td>Cerebellum</td>
<td>14 new cases</td>
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<td>(confirmed MR in 19 +/- epilepsy)</td>
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<td>9-29 years</td>
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<tr>
<td>Cortical dysgenesis</td>
<td>4/6 cases studied</td>
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<td>(6 with MR, 3 epilepsy)</td>
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<td>20-27 years</td>
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<td>Abnormal cortical minicolumns</td>
<td>2/2 Asperger’s cases studied</td>
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<td>9/9 Autistic Disorder cases studied</td>
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<td>(7 with MR, 5 epilepsy)</td>
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<td>12-79 years</td>
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Minicolumn Abnormalities in ASD

Control

ASD

Increased number

Casanova et al., Neurology (2002); J of Child Neurology (2002)
Potential effects of network connectivity patterns on brain activation

Local overconnectivity may drive long range underconnectivity
Changes In Prefrontal Axons May Disrupt The Network In Autism

Anterior Cingulate Cortex

![Graphs showing changes in relative density of axons in control and autistic groups.](image)

- **Long-range Axons**
- **Short-Range Axons**

Grey and White Matter Pathology in ASD

Points to abnormal cortical and sub-cortical development

Some evidence that abnormal cortical development may alter white matter development (abnormal wiring)

Signs of local overconnectivity and long-range underconnectivity found in Anterior Cingulate Cortex
What is the Evidence?

1. Post-mortem Findings
   High Functioning Samples

2. Structural MRI

3. Functional MRI

4. Diffusion Tensor Imaging
When Is the Brain Enlarged In Autism? A Meta-Analysis of All Brain Size Reports

Reduced or normal brain size at birth, followed by early overgrowth of the brain and an abrupt and early cessation of brain growth by 2-4 years

Redcay & Courchesne (2005)
Longitudinal Magnetic Resonance Imaging Study of Cortical Development Through Early Childhood Autism
Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys

Herbert et al., Brain (2003)
Localization of White Matter Volume Increase in Autism and Developmental Language Disorder

Voxel-based meta-analysis of regional white matter volume differences in autism spectrum disorder versus healthy controls

Overgrowth of the brain in early childhood ASD (frontal/temporal lobe; grey and white matter)

Effects in white matter may be maintained

Effects may be pronounced in specific regions (i.e., frontal lobe)
What is the Evidence?

1. Post Mortem Findings
2. Structural MRI
3. Functional MRI
4. Diffusion Tensor Imaging
**Trends for studies of Social Cognition:** ASD show decreased probability for activation of social brain structures and increased probability towards activation of somatosensory regions

**Trends for studies of Executive Function:** ASD show decreased probability for activating task relevant higher-order regions and increased probability for activating lower-order
Cortical activation and synchronization during sentence comprehension in high functioning autism: evidence of underconnectivity

Just, Cherkassky, Keller & Minchew, Brain (2004)
Atypical circuit activation
- Use of lower order regions over higher order regions

Underconnectivity between task-relevant structures
What is the Evidence?

1. Post-mortem Findings
2. Structural MRI
3. Functional MRI
4. Diffusion Tensor Imaging
Diffusion Tensor Imaging (DTI)

MRI based imaging method
DTI is sensitive to the microscopic motion of water molecules

Water molecule movement is different in different tissue = different DTI signal

Different Diffusion Ellipsoids

National Alliance for Medical Image Computing (www.na-mic.org)
Tracking White Matter Development with DTI

Increased Fractional Anisotropy (FA)
Decreased Mean Diffusivity
Decreased Axial Diffusivity
Decreased Radial Diffusivity
Deterministic Tractography

National Alliance for Medical Image Computing (www.na-mic.org)
Accelerated Maturation of White Matter in Young Children with Autism

Tract-specific Analysis of Diffusion Tensor Imaging Show Widespread White Matter Compromise in Autism Spectrum Disorder

Impaired Frontal White Matter Connections in Autism Spectrum Disorders: A diffusion tensor imaging study

Ameis, Fan, Anagnostou et al. Under Review
Lower FA in:
Right uncinate fasciculus
Right Cingulum
Corpus callosum
Left arcuate fasciculus

Kumar et al. Cerebral Cortex (2009)
Extended Limbic Pathways in Asperger’s Syndrome

Pugliese, Catani, Ameis et al., NeuroImage (2009)
Abnormal white matter connections in ASD (microstructural and macrostructural differences

Developmental differences

Underconnectivity of long-range white matter tracts suggested
# What Do We Know?

<table>
<thead>
<tr>
<th>Abn. Develop</th>
<th>Post-Mortem</th>
<th>Structure</th>
<th>Function</th>
<th>DTI</th>
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<th>Grey Matter</th>
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<th>Connections</th>
<th>Post-Mortem</th>
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<th>Frontal prominence</th>
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<td>What We Don’t Yet Know</td>
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<td>Developmental trajectories</td>
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<td>Genes x Environment</td>
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<td><strong>What</strong></td>
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<td>Neurons/Axons/Glia/Inflammation</td>
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<td><strong>Behavioural Correlates</strong></td>
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<td>Not well characterized with neuroimaging findings</td>
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<td><strong>Specificity</strong></td>
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<td>What is different in ASD vs. other neuropsychiatric/neurodevelopmental disorders Is miswiring a problem across the spectrum</td>
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<td><strong>Plasticity</strong></td>
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<td>Opportunities for intervention</td>
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Conclusion: abnormal wiring may be an important part of the picture in ASD..... BUT, there is still a lot we don’t know
THANK YOU!

Evdokia Anagnostou
Wendy Roberts
Peter Szatmari
Schachar Lab
Russell Schachar
Abel Ickowicz
Mabbott Lab
Don Mabbott
Conrad Rockel
Marco Catani

Aristotle Voinoskos
Nancy Lobaugh
Jin Fan
Altering Cortical Connectivity: Remediation-Induced Changes in the White Matter of Poor Readers

Keller & Just, Neuron (2009)
Minicolumns are a building block for connectivity