



Neuroanatomy of autism

Amaral D, Schumann C, Nordahl C,
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Overview

- What are autism spectrum disorders? What are its types?
- Which are the brain regions involved in autism spectrum disorders?
- What are the techniques used to study the neuroanatomical and neuropathological changes in these disorders?
- What are the limitations of these techniques and how can they be solved?
- What are clinical correlations of these neuroanatomical abnormalities?

Autism Spectrum Disorders (ASDs)

- Disorders characterized by varying degrees of impairment in communication skills, social interactions and restricted, repetitive and stereotyped patterns of behavior
- Detected reliably at 3 years of age but in some cases as early as 18 m
- Co-morbid features: mental retardation, epilepsy, anxiety and mood disorders



Classification of ASDs



Classification of ASDs



- Autistic disorder: qualitative impairments in social interaction, communication and restricted, repetitive and stereotypical patterns of interests, activities and behaviors
- Aspergers syndrome: qualitative impairment in social interactions, repetitive behaviors but no significant delays in cognitive or language development
- Childhood disintegrative disorder: normal development of communication, play and social interactions for the first 2 years of life followed by loss of previously acquired skills (by age of 10 years)

Classification of ASDs

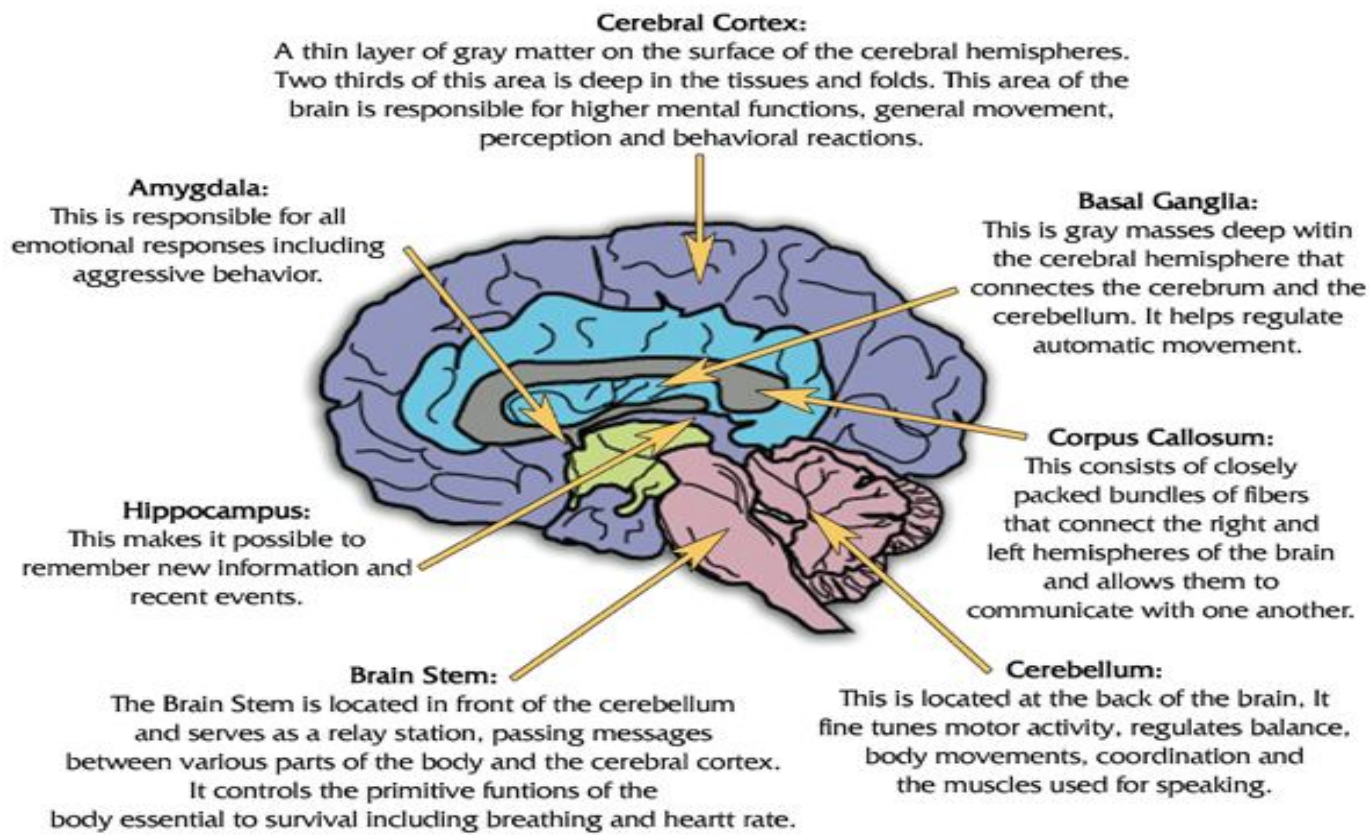


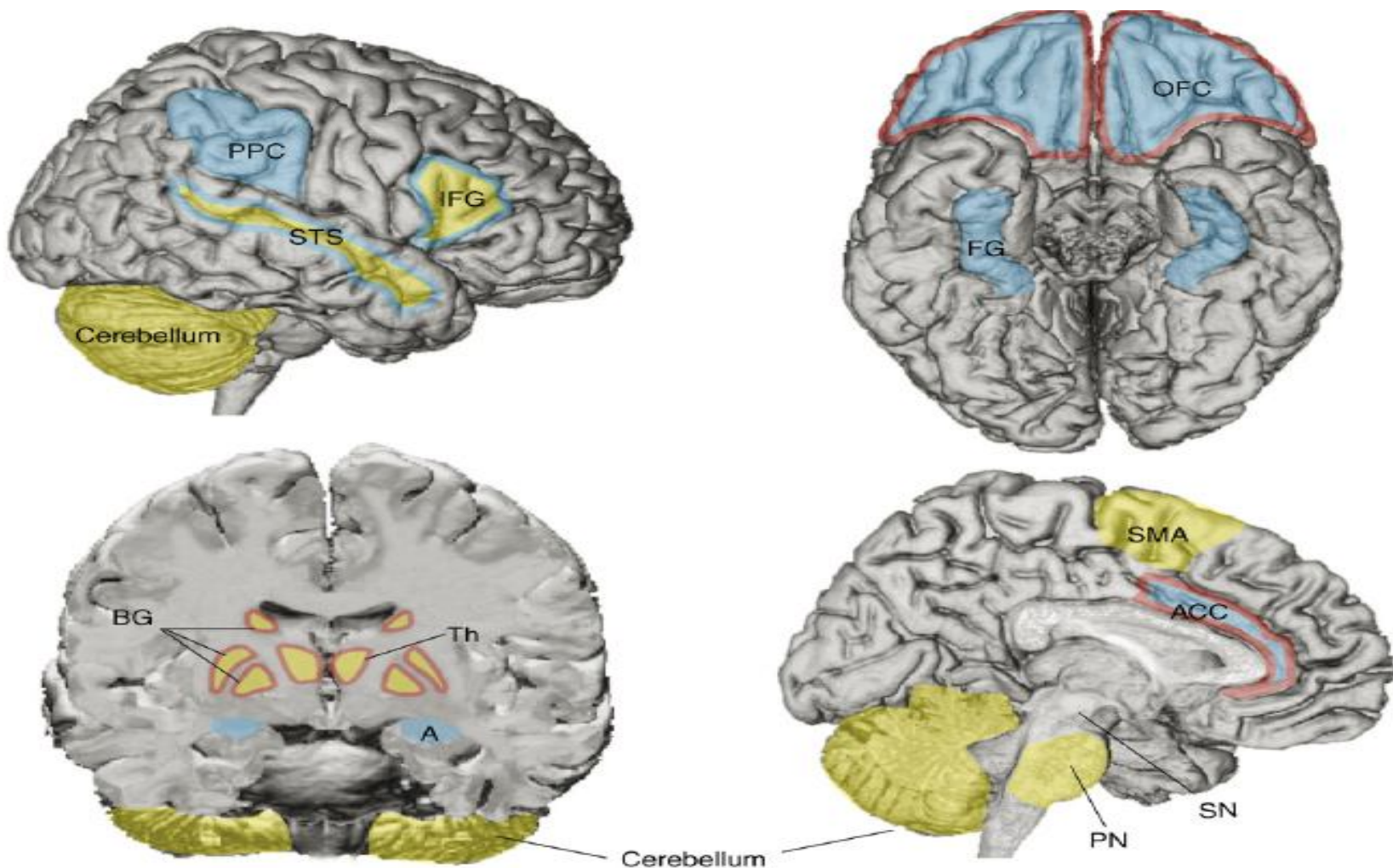
- Rett's syndrome: normal prenatal, perinatal and early postnatal development up to about 5 m of age followed by progressive loss of gross and finemotor skills, loss of social engagement, severely impaired receptive and expressive language and psychomotor retardation
- PDD-NOS: significant impairments in social interactions, communication and presence of repetitive behaviors, but criteria are not met for a specific disorder. Includes cases of atypical or subclinical symptomatology or late age of onset

(DSM-IV 2000– Criteria for autism)

Brain areas implicated in autism

Parts of the Brain Affected by Autism





Social impairment	Communication deficits	Repetitive behaviors
<p>OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex FG – Fusiform gyrus STS – Superior temporal sulcus A – Amygdala mirror neuron regions IFG – Inferior frontal gyrus PPC – Posterior parietal cortex</p>	<p>IFG- Inferior frontal gyrus (Broca's area) STS – Superior temporal sulcus SMA – Supplementary motor area BG – Basal ganglia SN – Substantia nigra Th – Thalamus PN – Pontine nuclei cerebellum</p>	<p>OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex BG – Basal ganglia Th – Thalamus</p>

Techniques to study the neuroanatomy of autism

- MRI –
 - safe, non-invasive tool
 - Helps to study gross neuropathology
- Postmortem studies-
 - Understanding the neurobiology of the abnormalities



Neuroanatomical abnormalities

1. Differences in total brain volume:

- Precocious growth during early postnatal life followed by a deceleration in age related growth
- At birth normal or smaller head circumference followed by an increase in rate of growth at 12 m of age
- This enlargement persists through early childhood

(Courschesne et al 2001, 2003, Dawson et al 2007, Hazlett et al 2005, Dementieva et al 2005, Sparks et al 2002, Aylward et al 2002)

Neuroanatomical abnormalities

2. Changes in gray and white matter volumes:

- Increased white matter accounts for brain enlargement more than gray matter increases
- Gray matter enlargement is smaller but may persist into adulthood
- Reductions in FA in cerebral white matter in & near the genu of the corpus callosum. 14 % reduction in size of corpus callosum

(Courschesne et al 2001, Hazlett et al 2005, Keller et al 2007, Barnea-Goraly et al 2004)

Neuroanatomical abnormalities

3. Regional specificity of gray and white matter differences:

- Frontal lobes – increases in dorsolateral prefrontal cortex and medial frontal cortex and decreases in orbitofrontal cortex
- Changes in cortical shape: sylvian fissure, superior temporal sulcus, intraparietal sulcus and inferior frontal gyrus

(Herbert et al 2004, Carper & Courchesne 2005, Levitt et al 2003, Nordahl et al 2007)

Neuropathological abnormalities

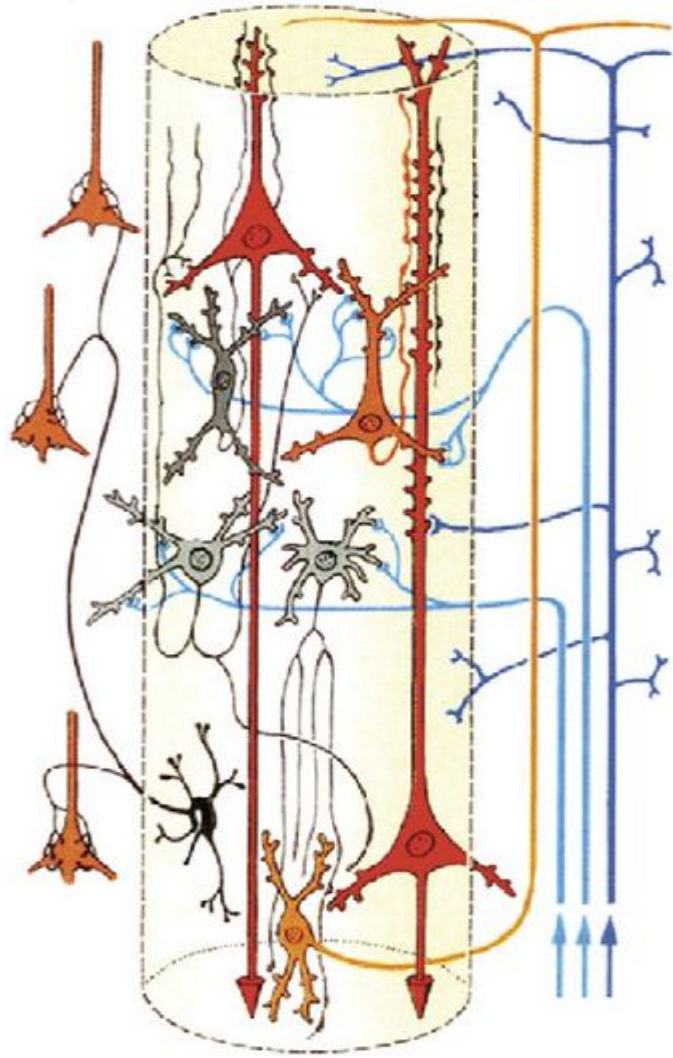
- 6 cases of autism (4 had seizures, 5 with mental retardation)-
 - Anterior cingulate cortex coarse and poorly laminated (Kemper and Bauman 2003)
- 6 cases with autism and mental retardation (4 cases with seizures)-
 - Cortical dysgenesis- Increased cortical thickness, high neuronal density, irregular laminar patterns, ectopic gray matter, increased number of neurons in the white matter (Bailey et al 1998)

Alterations of the columnar structure of the neocortex

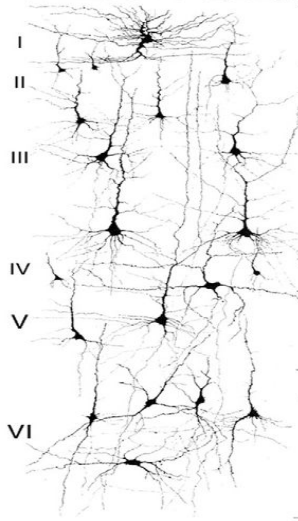
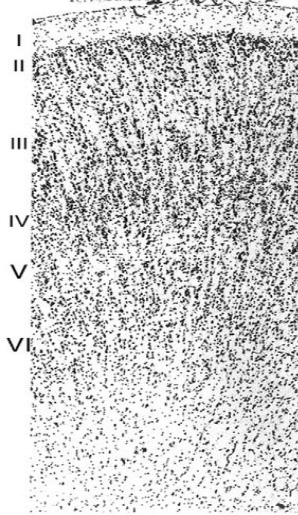
- Minicolumn is the basic unit of the mature neocortex containing 80 -100 neurons
- It contains a narrow chain of neurons extending vertically along layers II-VI perpendicular to the pial surface. Each minicolumn is responsible for a receptive field
- Column contains neurons, apical dendrites, myelinated fibres of the thalamus, cortical efferents and corticocortical fibres and unmyelinated axons and synapses

(Jones 2000. Mountcastle 1997, Buxhoeveden & Casanova 2002)

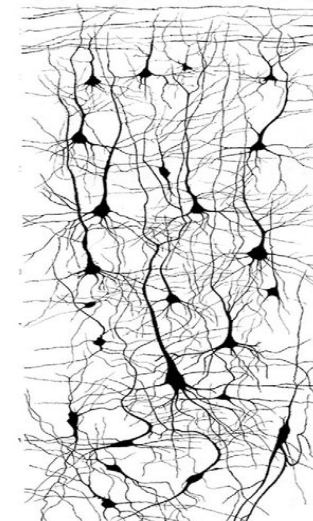
Normal cortical minicolumns



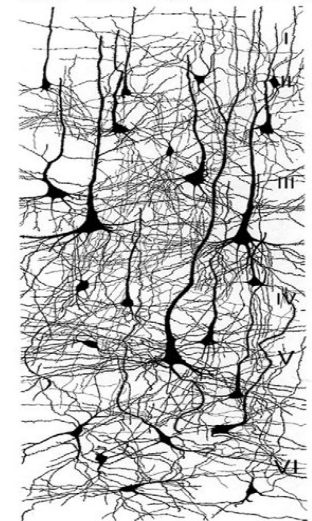
(a) One month old



(b) Six month old



(c) 24 month old



Alterations in minicolumns

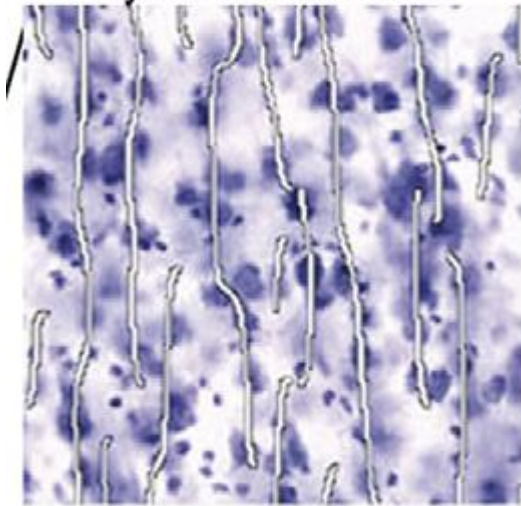
With development:

- ↓ neuronal density
- ↑ intercolumnar width
- ↑ dendritic arborization

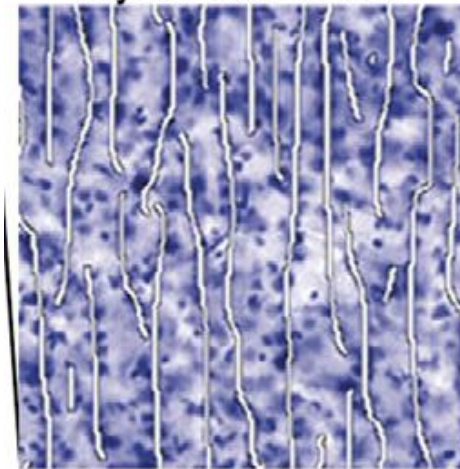
In autism:

- ↑ neuronal density in BA 9
- ↓ intercolumnar width
- ↓ dendritic arborization

4 year old Control



5 year old Autism



Neuropathological changes in brain areas

- Cerebellum – modulation of cognitive and motor functions
 - enlarged relative to controls (proportional to total brain volume) based on MRI studies
 - Smaller or larger autistic vermis based on phenotype- emotion, arousal, sensory responsiveness
 - Decreased Purkinje cell number & density (subjects with epilepsy and MR) based on postmortem studies

(Hardan et al 2001, Kaufmann et al 2003, Okugawa et al 2003, Courchesne et al 1994)

Neuropathological changes in brain areas

- Amygdala- emotion, memory and learning
 - Precocious enlargement persisting into late childhood -severe anxiety and worse social and communication skills
 - 13-16% enlargement in children (36-56m of age)
 - 15% enlargement in 8-12 yr olds compared to controls.
 - Did not differ in 13-18 yr olds
 - No difference or smaller amygdala in autistic adults as compared to controls
 - Microscopically- neurons in certain nuclei smaller and more densely packed and fewer total number of neurons

(Sparks et al 2002, Juranek et al 2006, Munson et al 2006, Schumann et al 2004, Kemper and Bauman 1993)

Neuropathological changes in brain areas

- Enlargement of caudate – repetitive behaviors
- Abnormalities in shape and volume of the hippocampus – increased density and smaller neurons – memory and learning

(Kemper & Bauman 1993, Schumann et al 2004, Sears et al 1999, Holander et al 2005, Nicolson et al 2006, Daeger et al 2007)

Future directions



- Imaging studies:
 - should be starting at early ages & should be longitudinal
 - should look at brain connectivity as well
 - should be applied to larger populations of better phenotyped individuals
- Postmortem studies:
 - Techniques like in-situ hybridization and single cell PCR applied in specific phenotypes

Clinical correlates of neuroanatomical abnormalities

- Negative correlation between white matter volume in left hemisphere and scores on PANESS (Mostofsky et al 2007)
- Finger sequencing task in children with HFA leads to:
 - a.increased activation of supplementary motor cortex
 - b.inability to shift from effortful to habitual control
 - c.deficits in automatization and motor sequence learning(Mostofsky et al 2009)
- Local over-connectivity and long distance under-connectivity with lesser integration of remote cortical areas. This disrupts development of complex motor skills and social/communicative gestures

Thank you

