The Neuropathology of Autism Research

May 26, 2012

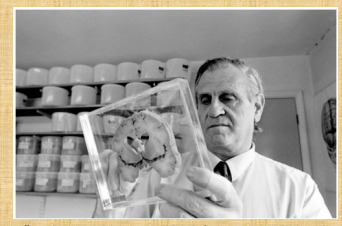
Manuel F. Casanova, M.D.

Neuropathology: the study of diseases of nervous system tissue, usually in the form of either small surgical biopsies or whole autopsy brains.

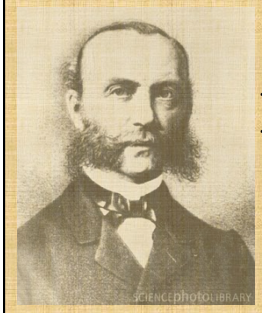
In 1884, Mental Hospital were still referred as Lunatic Asylums

From lunaticus meaning of the moon or moonstruck.

J.A.N. Corsellis (1915-1994)

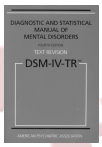


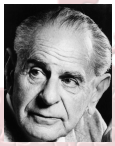
"…when psychiatry stood back from neuropathology it allowed for the recruitment of other disciplines, such as psychoanalysis, in order to better understand mental illnesses."



Wilhelm Griesinger
(1817-1868)

- "Mental diseases are brain diseases."
- Unfortunately, even in Germany, early researchers had to waddle their way through confusing terminology and classification schemes. Published articles variously referred to autism as childhood psychosis, *dementia praecoccisima*, *dementia infantilis*, or childhood schizophrenia.



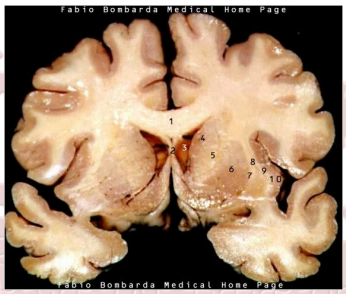


Karl Popper (1902-1994)

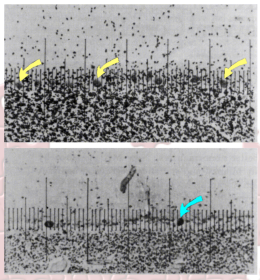
Autism is a severe pervasive developmental disorder of childhood characterized by:

- Disturbances of social interaction
- A delay or failure to acquire verbal and non-verbal communicative skills, and
- Restricted and/or stereotyped patterns of interests, activities, and behaviors.

Coronal Section through the Human Brain



Purkinje Cell Counts

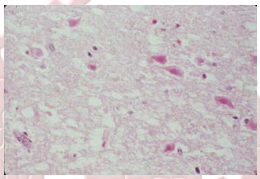


Boy with no CNS pathology

Autistic boy

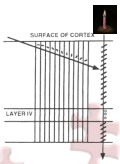
Ritvo et al., *Am J Psychiatry*, 1986

Hippocampus: Acute Infarct



- Note eosinophilic neurons (coagulation necrosis)

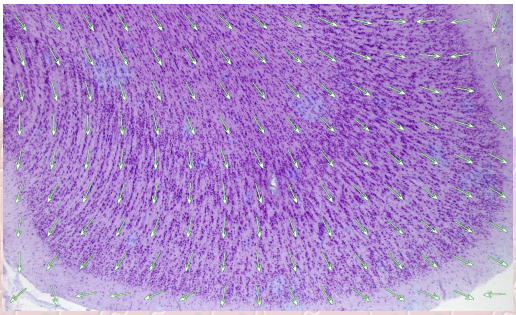
Orientation Preference of Columns



Proposed emergent properties: Thresholding, amplification, derivative functions, feature convergence, distribution functions, coincidence detection, pattern generation, etc.

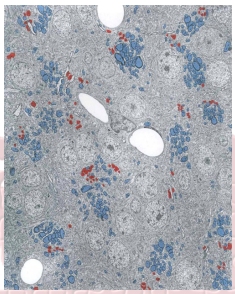
—Mountcastle, 1998

Gyri and Minicolumns



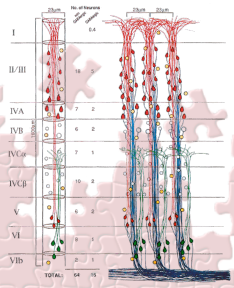
Apical Dendrites

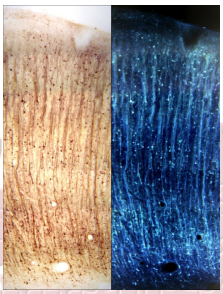
A high-power electromicrograph of a horizontal section taken at the level of layer IV. The apical dendrites in the clusters have been colored red and the myelinated axons blue.



Peters & Sethares, *J Comp Neurol*, 1996

Arrangement of Neurons and Their Processes within Cortical Modules

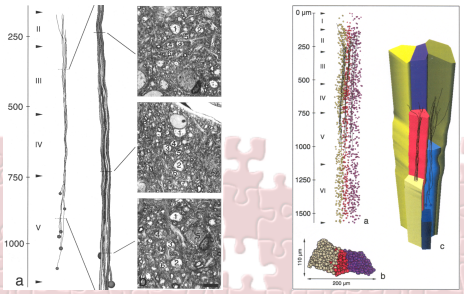




Peters & Sethares, *J Comp Neurol*, 1996

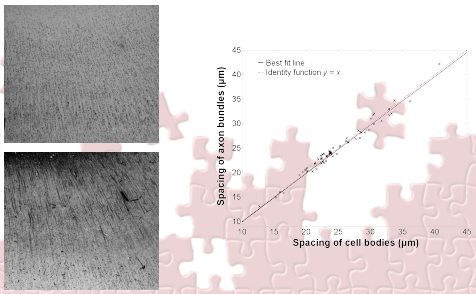
Prieto, 2011

Compartments of the Minicolumn



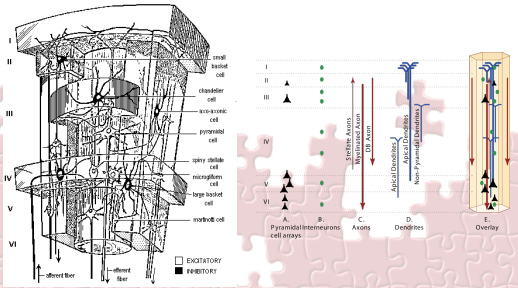
Skoglund et al., *Neurosci Res*, 2004

Correspondence of Myelinated Bundles and Pyramidal Cell Arrays



Casanova et al., *J Neurosci Methods*, 2008

Correspondence of Myelinated Bundles and Pyramidal Cell Arrays

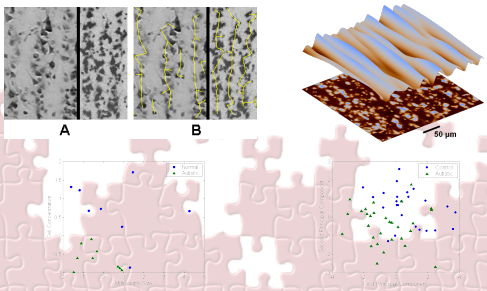


Szentágothai & Arbib, *Neurosci Res Program Bull*, 1974

Casanova et al., *Neuroscientist*, 2003

Minicolumn Method

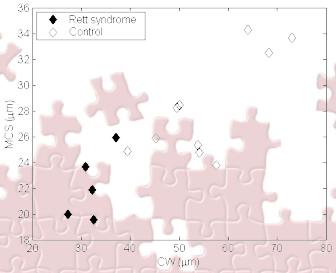
GLI Method



Casanova et al., Neurology, 2002

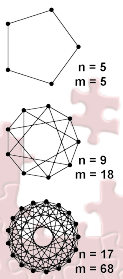
Casanova et al., J Child Neurol, 2002

Rett Syndrome



Casanova et al., *Clin Neuropathol*, 2003

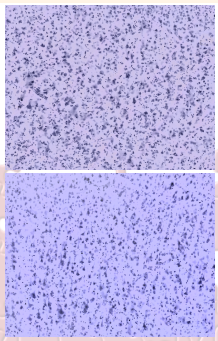
Macroscopic Correlates of a Putative Minicolumnopathy



Casanova, J Child Neurol, 2002

Casanova, Ann Neurol 2004

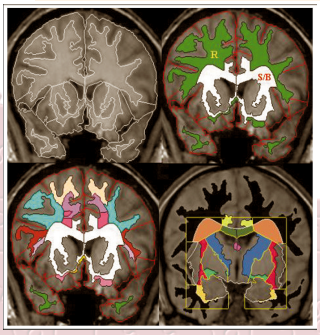
Spatial Statistics: Neuronal Size (Area)



24 year old, autistic male
$\bar{A}$ = 89.1 μm²

25 year old, normal male
$\bar{A}$ = 123.2 μm²

White Matter Abnormalities in Autism

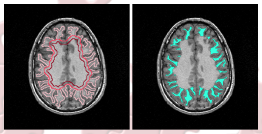


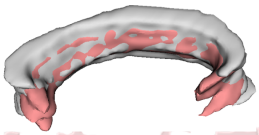
Clockwise from upper left:

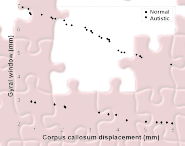
- Gray-white segmentation
- Initial division of white matter into outer and inner zones
- Parcellation of radiate (R) compartment
- Parcellation of sagittal and bridging (S/B) systems compartments.

Source: Herbert et al. *Ann. neurol.* 2004;55:530-540

Ratio of Long to Short Fibers

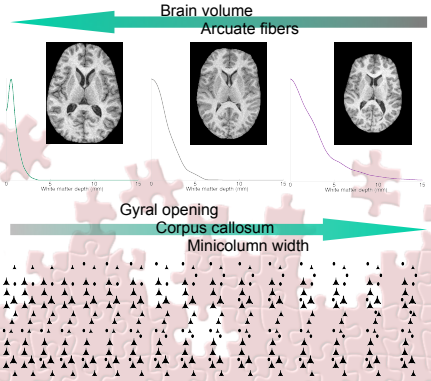




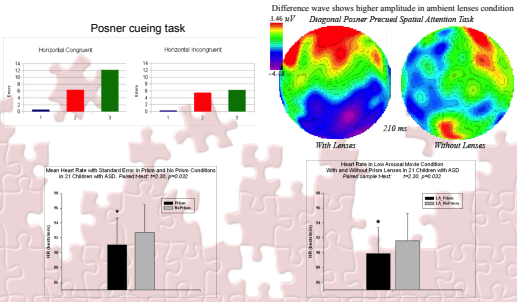


Dombroski et al., *Transl Neurosci*, 2011

Casanova et al., *JADD*, 2009

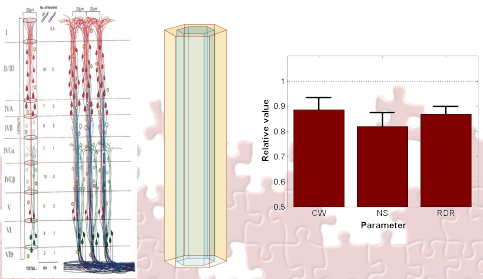


Prism Lenses



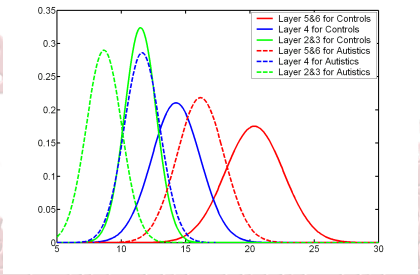
Heart rate differences in prism/no prism conditions during high and low intensity episodes of *The Lion King*

Minicolumns in Autism



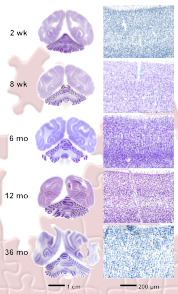
Casanova et al., Neurology, 2002

Minicolumnar Width by Lamina in Autism and Controls



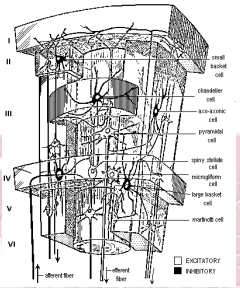
Casanova, Brain Pathology 2008

Minicolumnar Variability



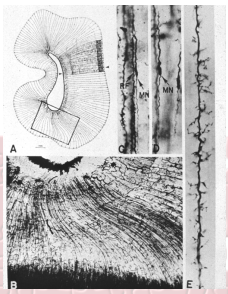
Casanova, Journal of Anatomy, 2009

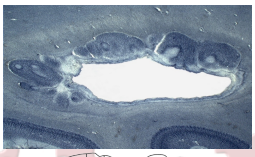
Shower Curtain of Inhibition

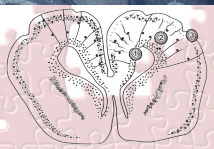


Szentágothai & Arbib, *Neurosci Res Program Bull*, 1974

A *Locus Minoris Resistentiae*



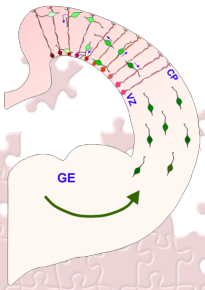




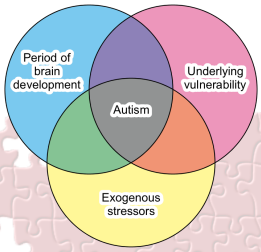
Rakic, *Cereb Cortex*, 2003

Casanova, Handbook of Autism, 2012
Sarnat, 2006

Pyramidal Cells and Interneurons



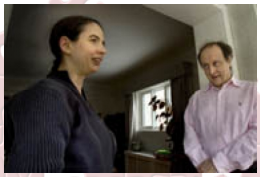
Triple-hit Hypothesis



Yokota et al., *PLoS One*, 2007

Casanova, *Brain Pathol*, 2007

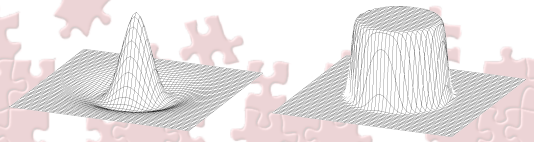
Atypical Lateral Connectivity: a Neural Basis for Altered Visuo-Spatial Processing in Autism



- Luc Keita, Laurent Mottron, Michelle Dawson, and Armando Bertone
- Used a lateral masking paradigm to assess the functional integrity of lateral interactions mediating visuo-spatial processing within early visual areas in autism.
- There is altered lateral connectivity differentially affecting perception at the earliest levels of feature extraction.

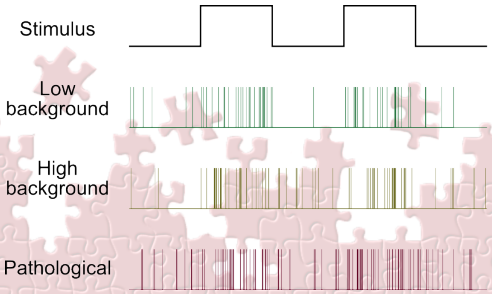
Keita, Biol Psy, 2011

Inhibitory Deficit in Autism

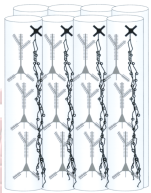


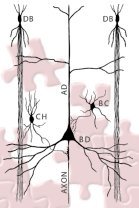
Casanova, *Neuroscientist*, 2006

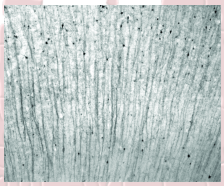
Information (Neuronal Activity) and Background



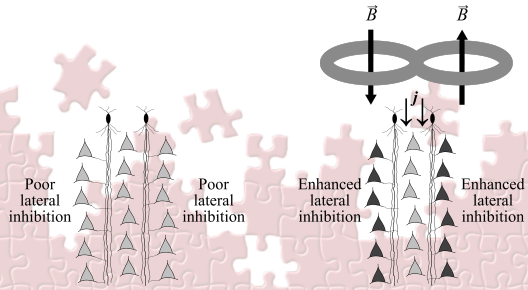
Inhibitory Surround of Minicolumns



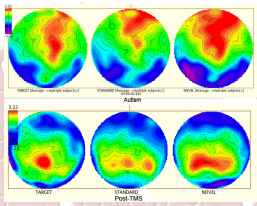




"Vertical Stream of Inhibition" Provided by the Axon Bundles of Double-bouquet Cells

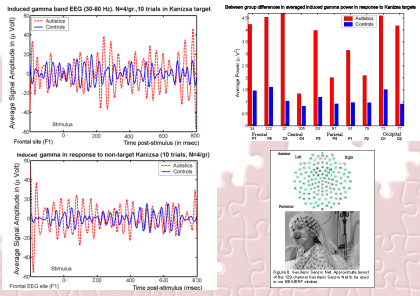


Changes after rTMS



Before rTMS participants with ASD showed large responses over the frontal cortices to all three stimuli with evidence of a lack of stimulus differentiation.

Induced Gamma Frequency Oscillations

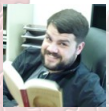


Acknowledgements

Brynn Dombroski

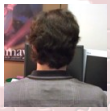
Ayman El-Baz

Shweta Kamat



Ryan Kiser

Tato Sokhadze



Andy Switala

The End