

# **AUTISM**

**AANP 2014**  
**June 12, 2014**

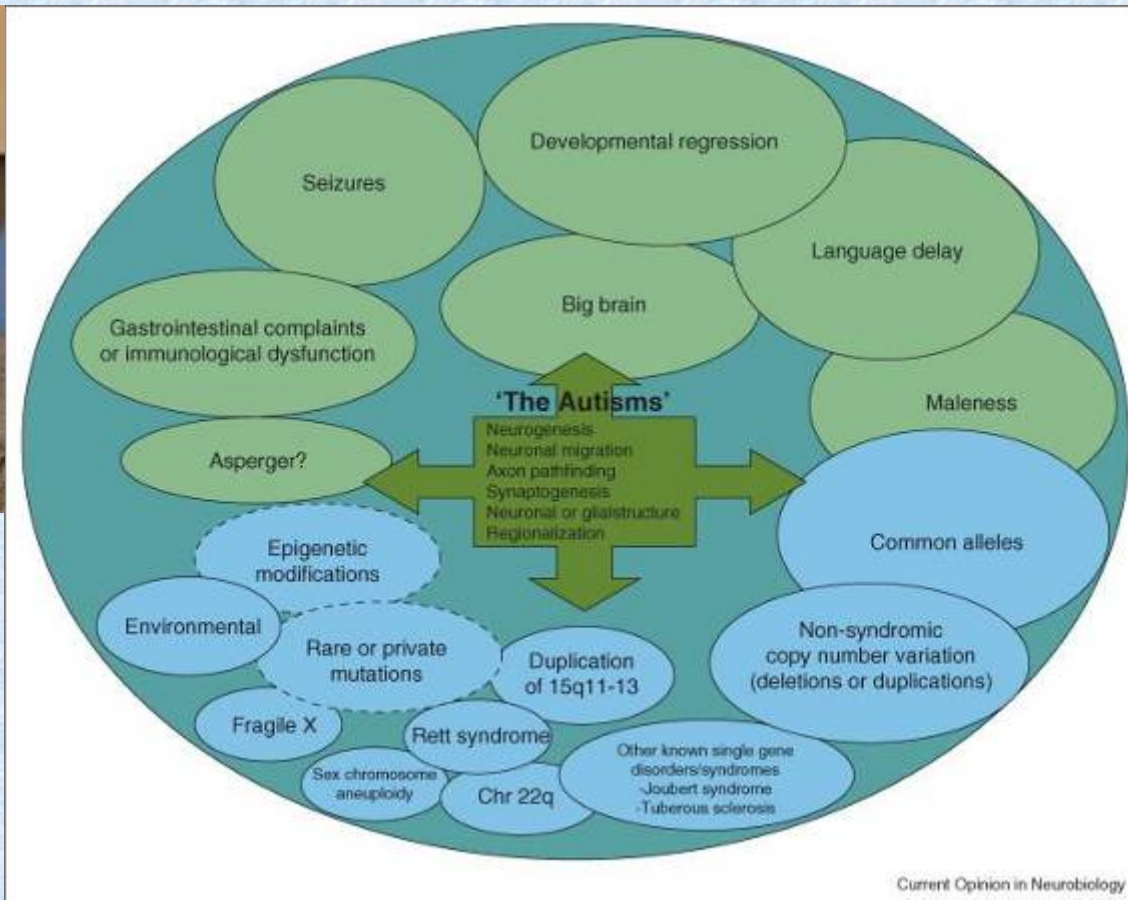
Manuel F. Casanova, MD

Gottfried and Gisela Kolb Endowed Chair in Psychiatry  
University of Louisville

How many are there?



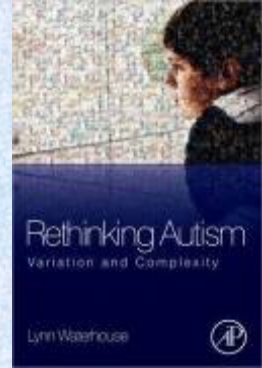
# The Autisms



Robert Schultz has said “If you’ve seen one child with autism, you’ve seen one child with autism. Autism’s like a snowflake”



# Rethinking Autism



- Autism should not be considered a set of discrete disorders, but rather, a continuous range of individually rare conditions. Holt and Monaco, 2011
- The concept of autism as a unitary disorder resulting from a common cause is close to being abandoned. Boucher, 2011

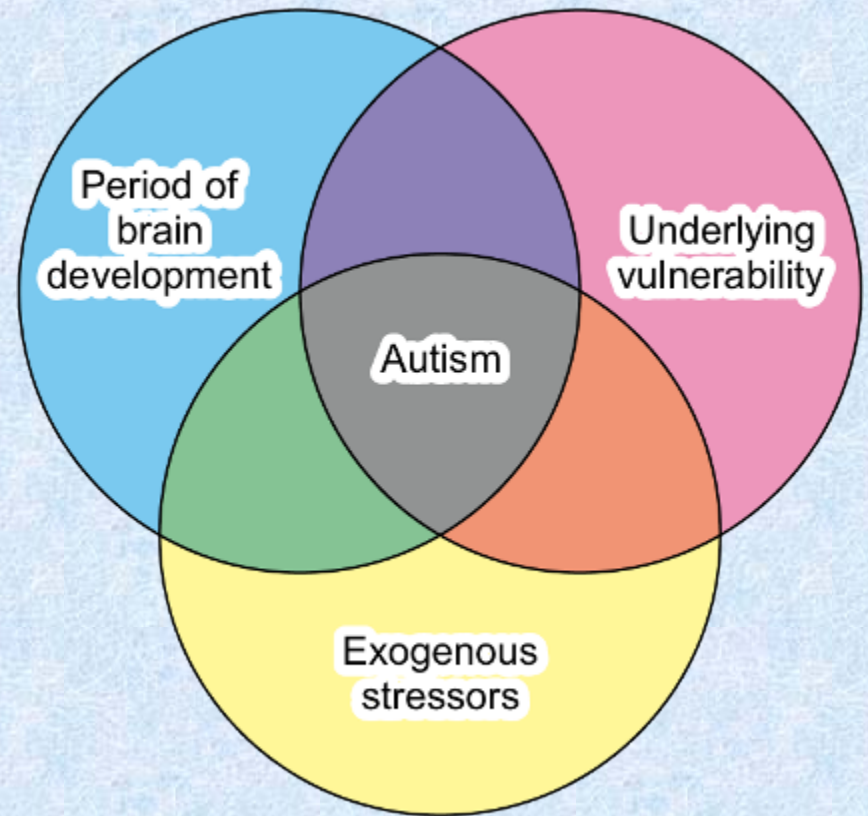
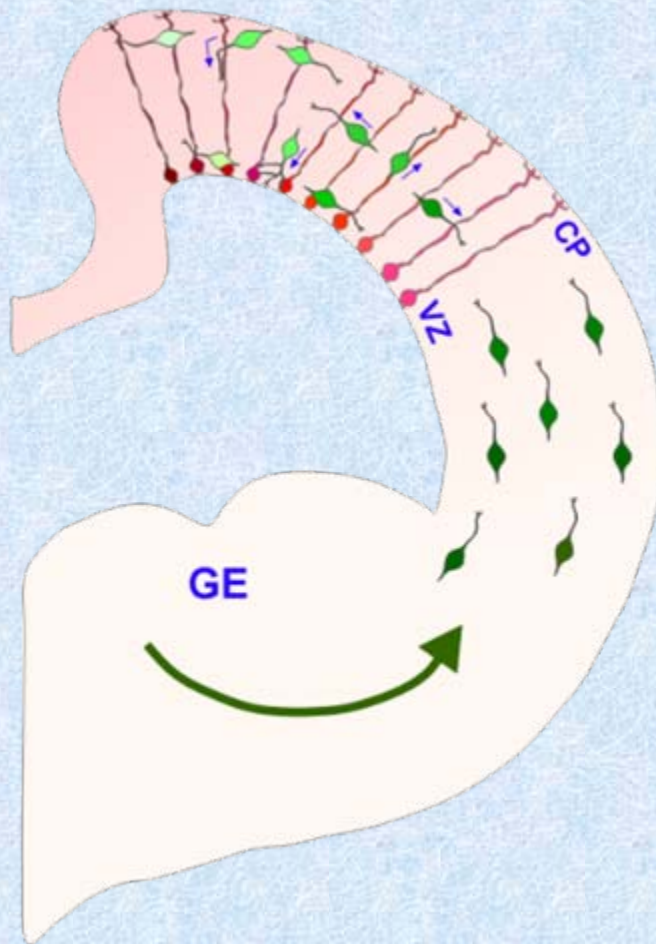
Researchers “should be hunting for what is similar, for the unifying characteristic [of autism]” Margaret Bauman



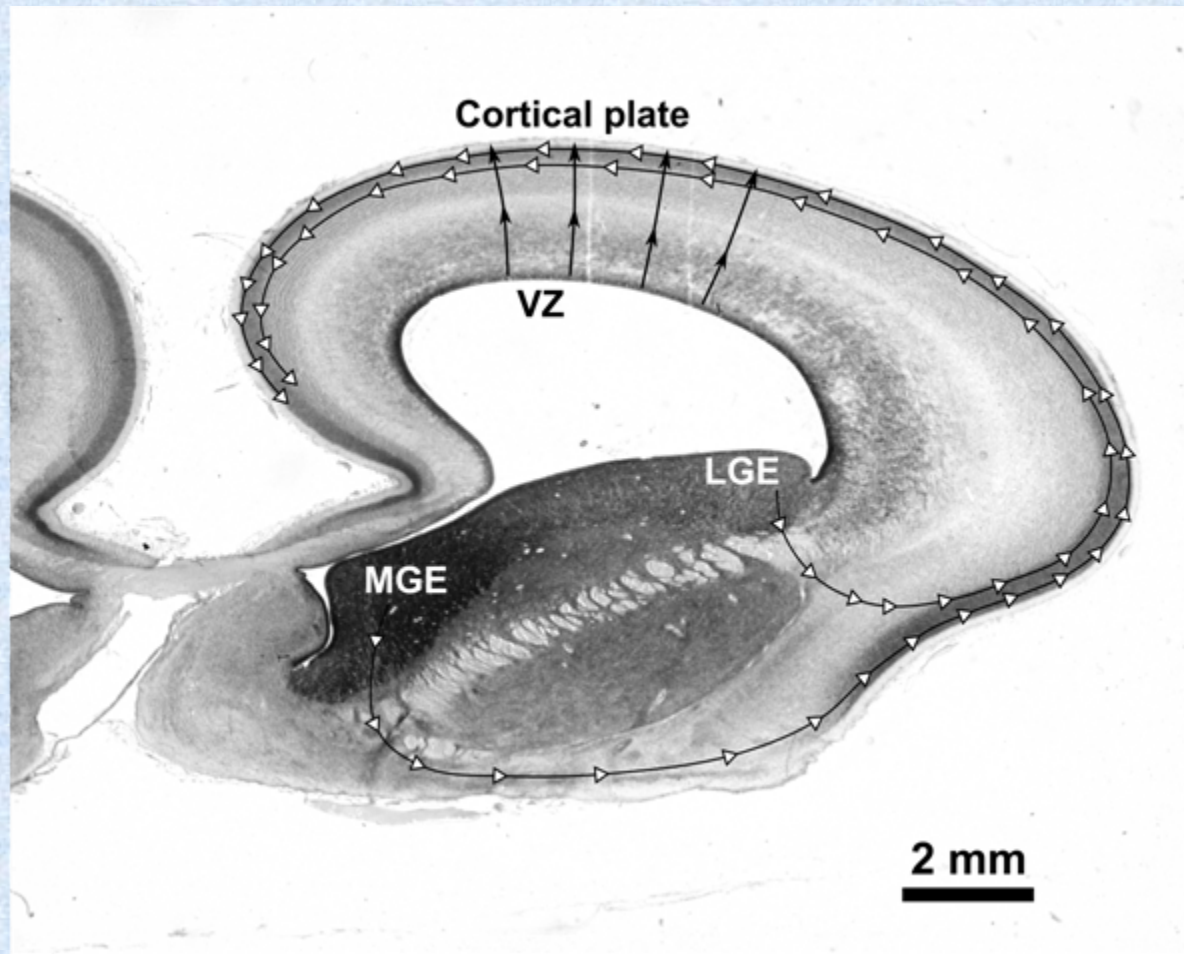
Darby (1976) concluded that the variability he observed in clinical presentation suggested that autism was the expression of a number of disorders. Many years after the fact he published a letter to the editor of the American Journal of Psychiatry entitled: “Autism Syndrome as a Final Common Pathway of Behavioral Expression for Many Organic Disorders” (Darby and Clark, 1992). The espoused concept reminds us of a similar proposal by Bellak (1958) who claimed a “final common pathway” to the nature of schizophrenia wherein a variety of insults were somehow funneled to provide a similar set of manifestations.

## Pyramidal Cells and Interneurons

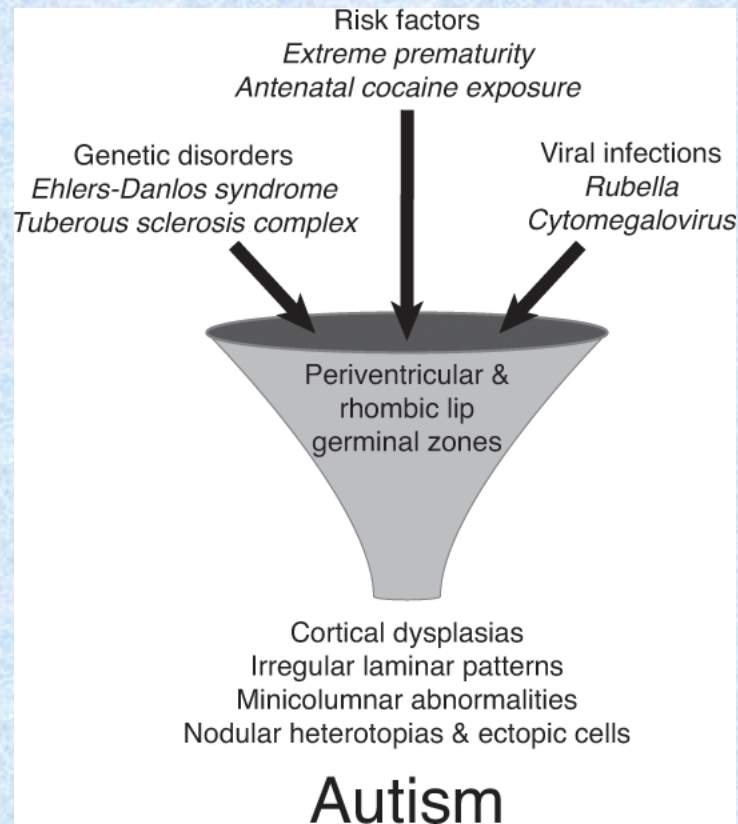
## Triple-hit Hypothesis



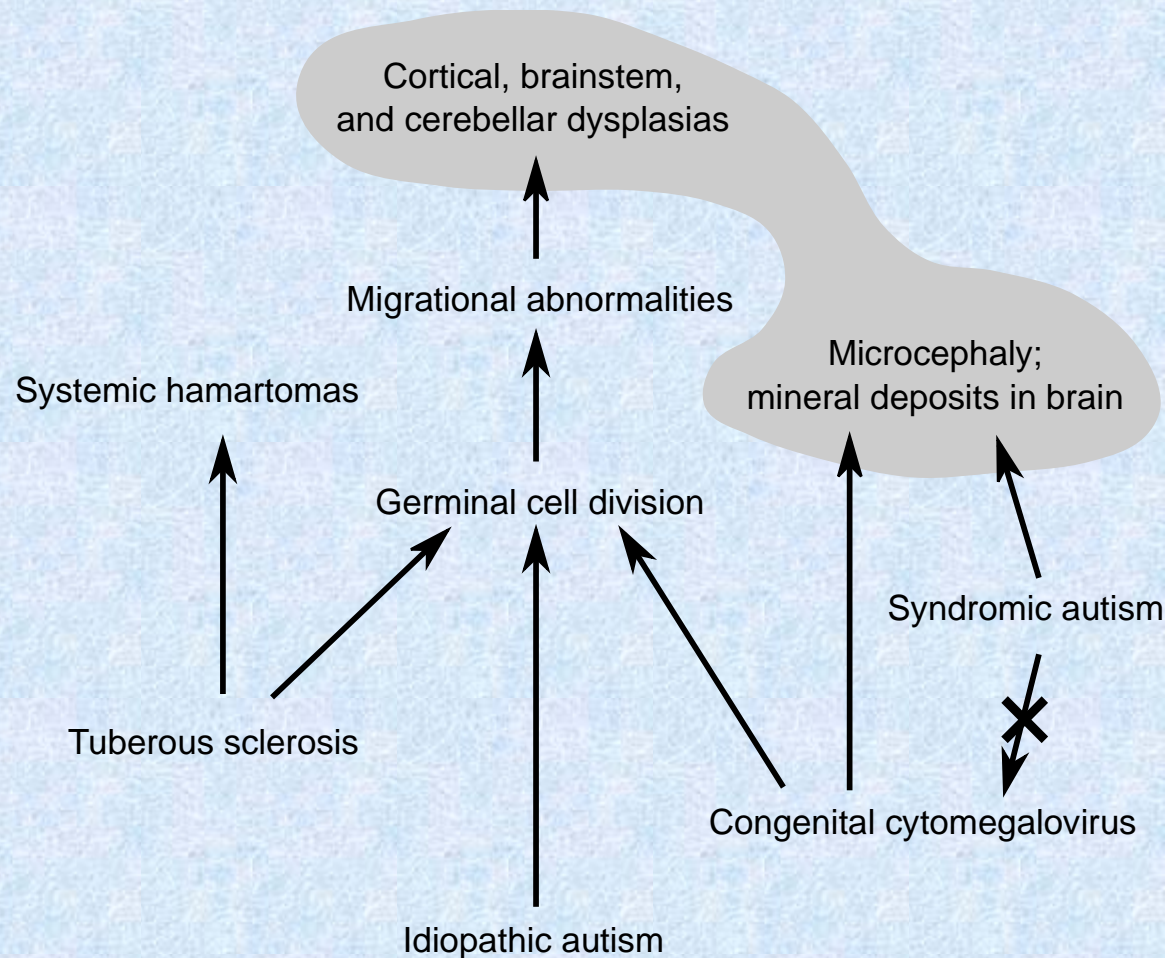
# Radial and tangential migration to the cortical plate



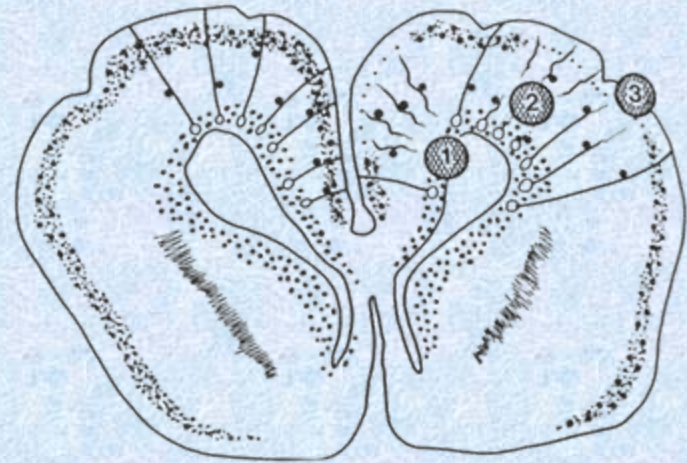
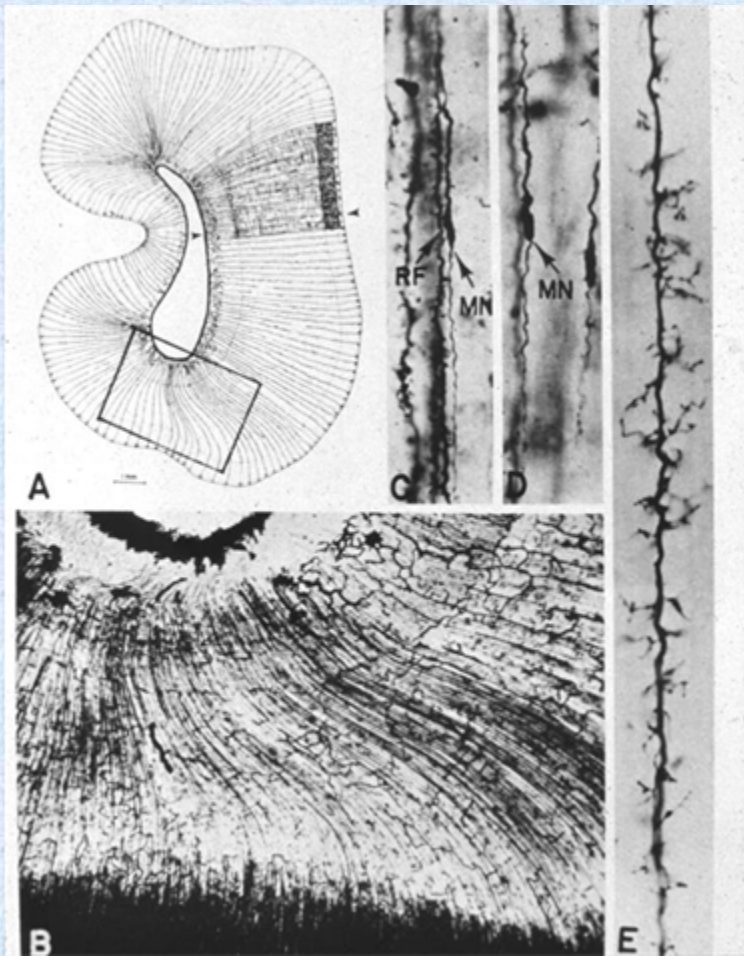
# Locus Minoris Resistentiae



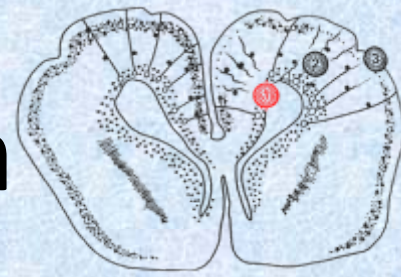
# Autism as a Sequence not a Syndrome



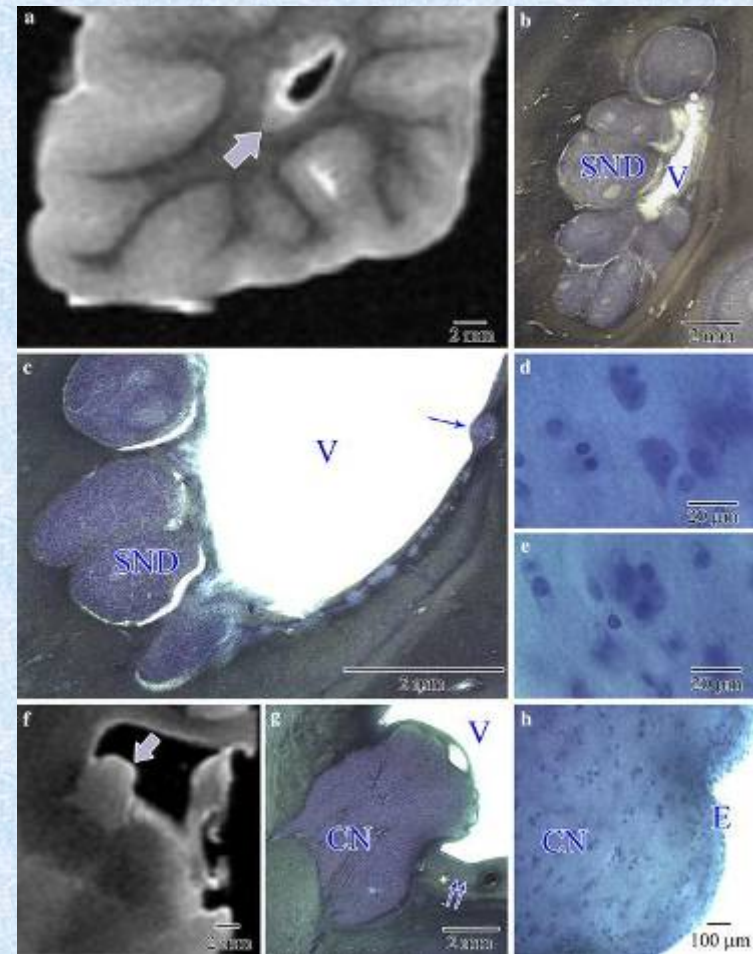
# *A Locus Minoris Resistentiae*

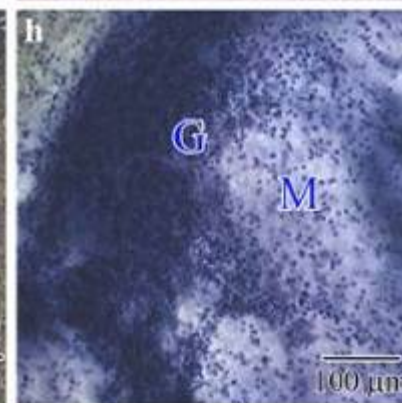
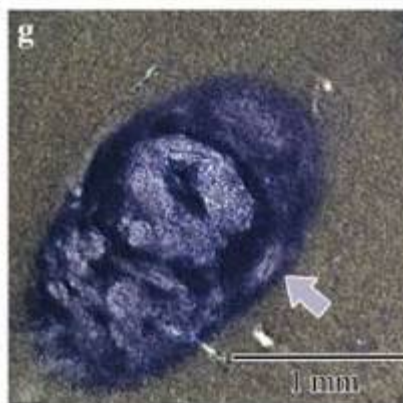
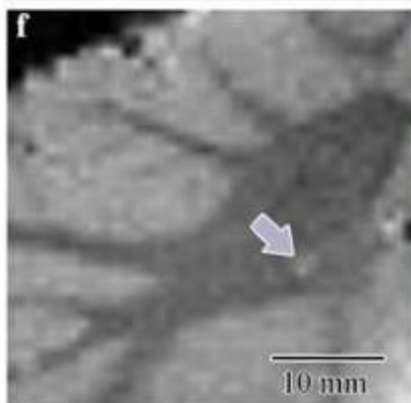
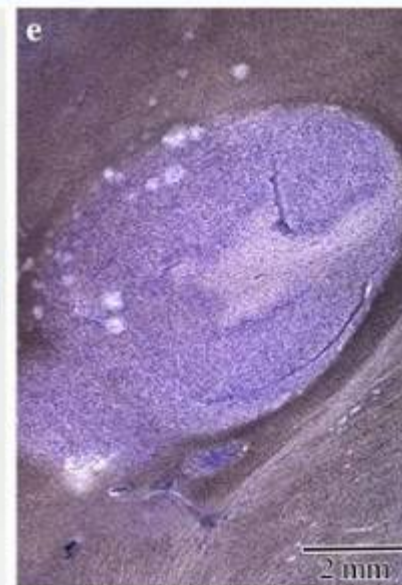
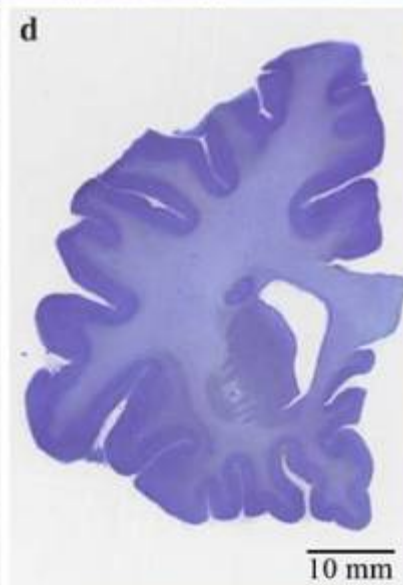
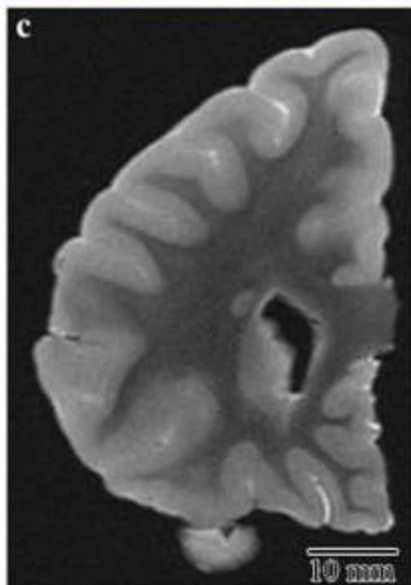
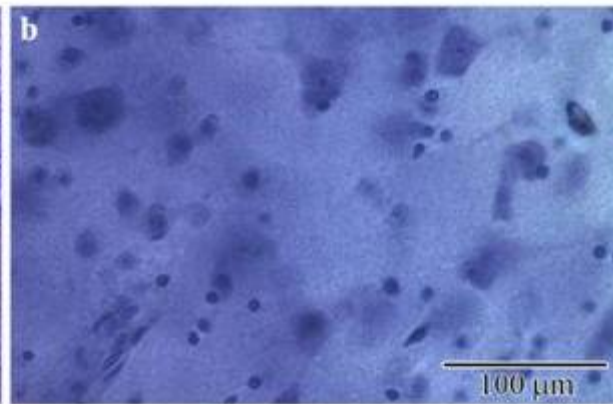
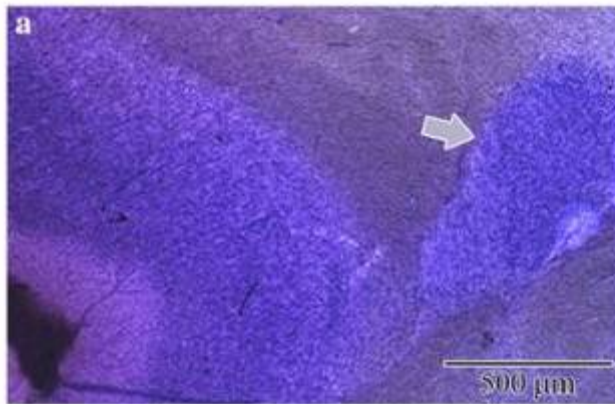


# Heterotopias in Autism

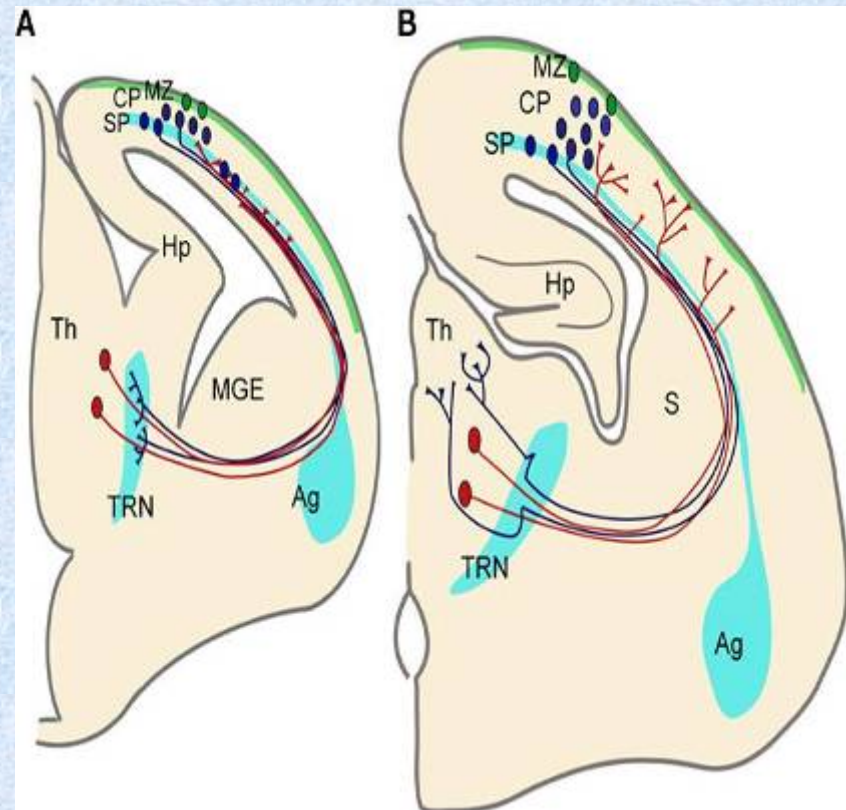
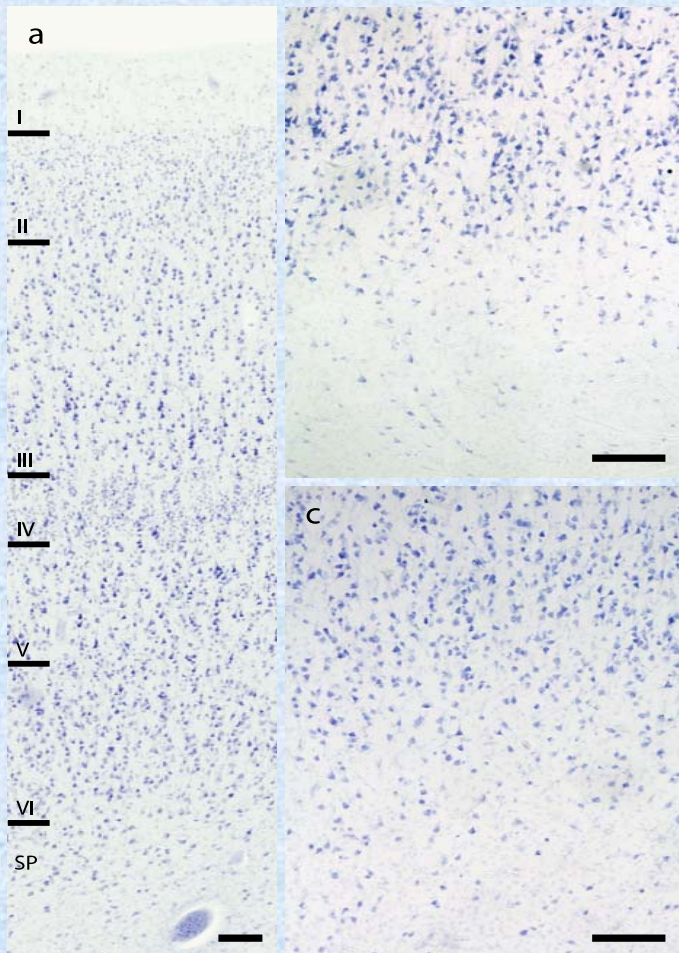


- “Heterotopias” are malformative lesions comprised of “normal” cells in the wrong location.
- Studies in autism suggest a defect in radial migration involving: 1) its onset out of their precursor field, and, 2) ongoing migration through the white matter (intermediate zone).





# The subplate in autism



## Quantification of the Gray/White Matter Boundary in Autism Spectrum Disorders

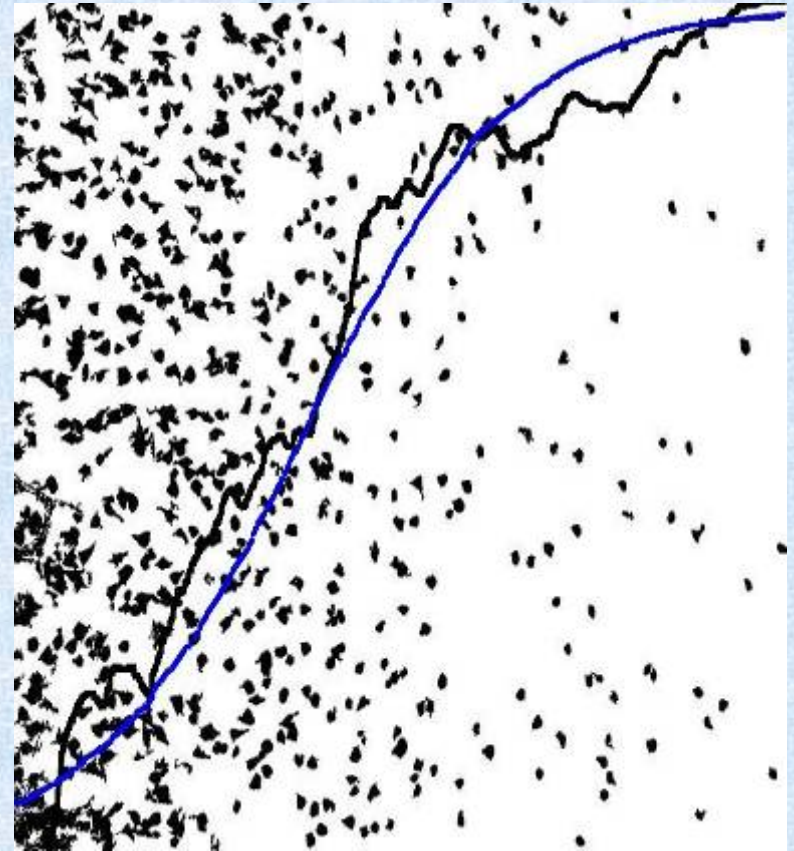
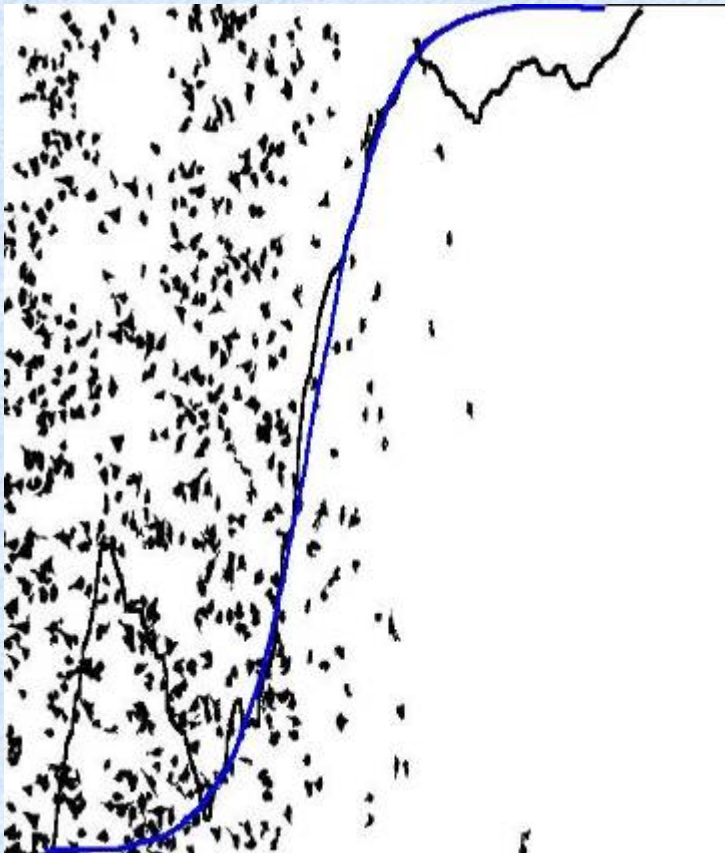
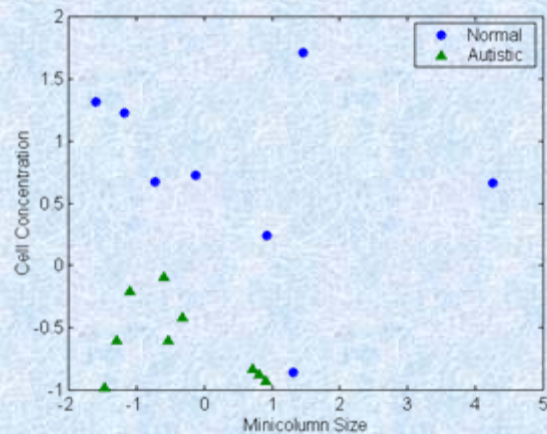
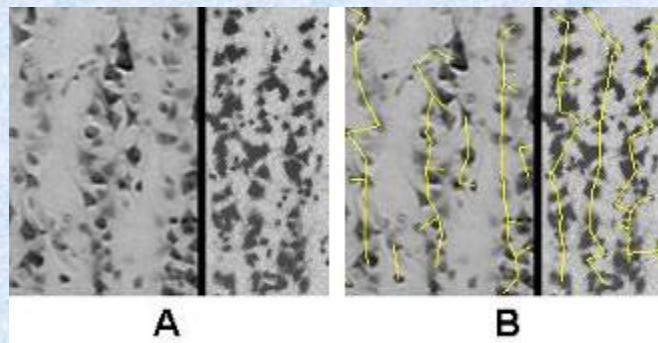


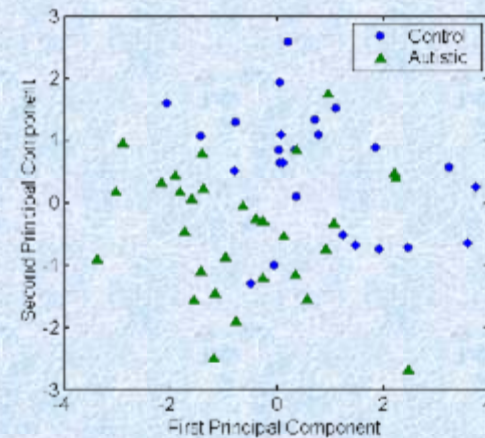
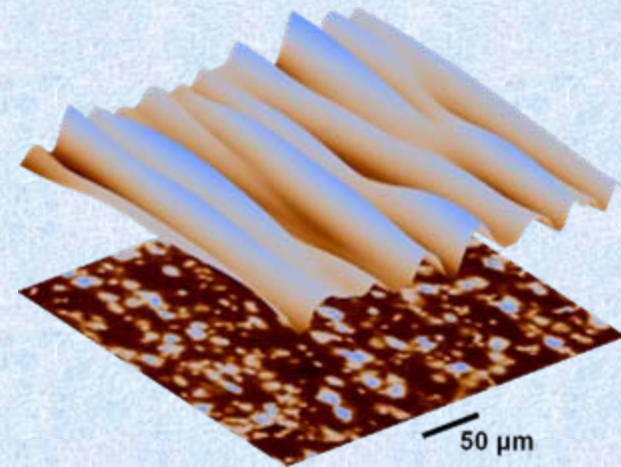
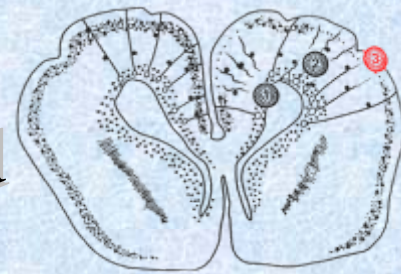
Image at left from control brain and on right from an autistic individual. Study of Thomas Avino and Jeffrey Hutsler.

# Minicolumn Method



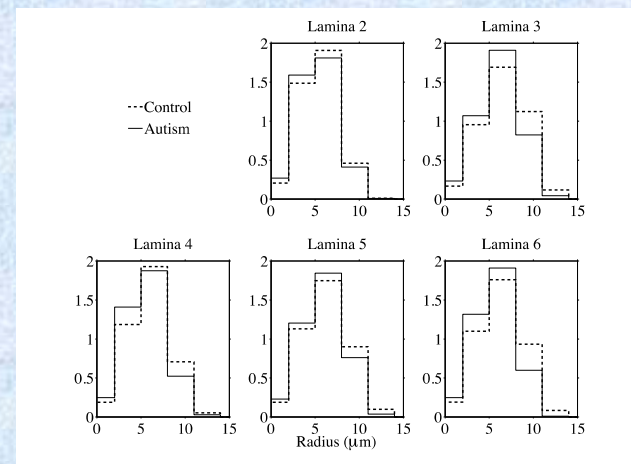
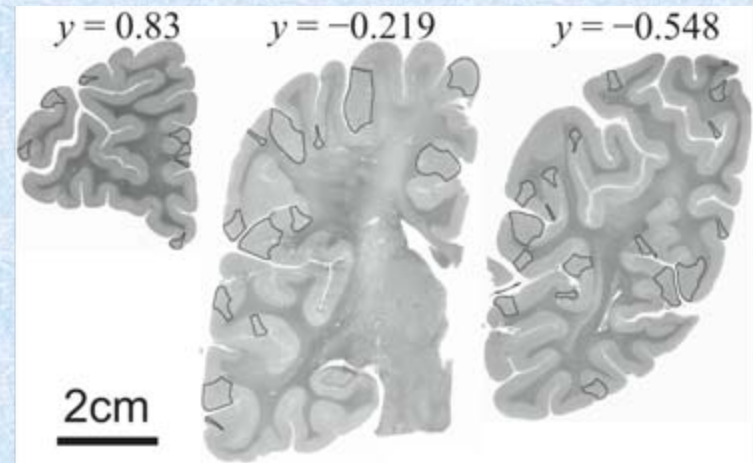
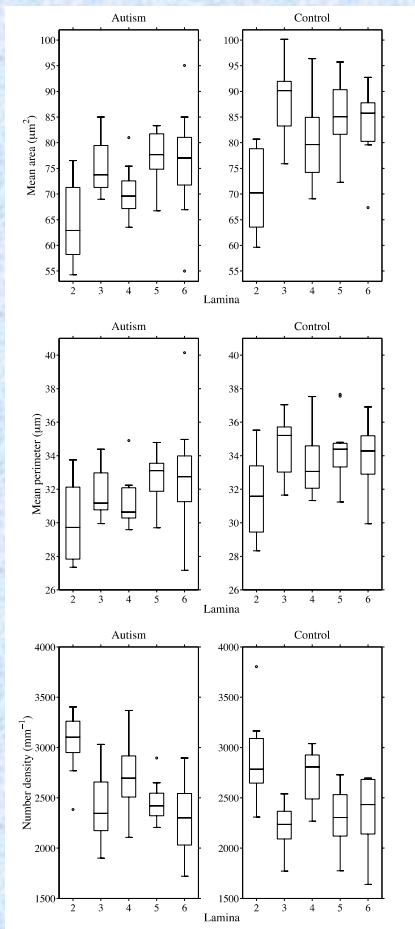
Casanova et al., Neurology, 2002

# GLI Method



Casanova et al., J Child Neurol, 2002

# Focal cortical dysplasias in ASD



# Macroscopic Correlates of a Putative Minicolumnopathy

## Clinical and Macroscopic Correlates of Minicolumnar Pathology in Autism

### ABSTRACT

All subcortical arrangements are primarily nuclear in type. The cortex has been the first part of the brain to evolve a radial and laminar arrangement of cells. The resultant modular arrangement is based on the cell minicolumn: a self-contained ecosystem of connectivity linking afferent, efferent, and interneuronal connections. Recently, the cell minicolumn has been found to be abnormal in patients with autism. This article relates different aspects of the cell minicolumn and larger-scale neuronal assemblies to potential research techniques and their application to clinical practice. (*J Child Neurol* 2002;17:692-695).

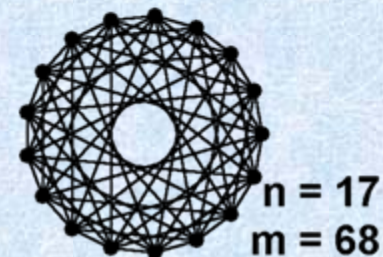
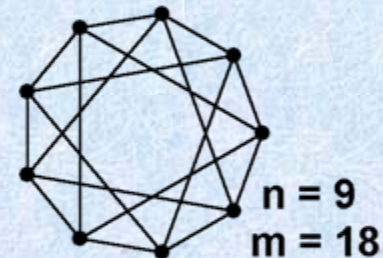
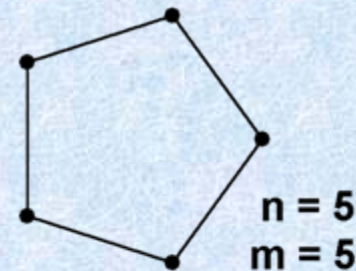
Within the neurosciences, researchers link anatomy to function (eg, an infarct of the corticospinal tract and contralateral hemiparesis/hemiplegia). However, considerations of cognition and behavior dilute the significance of this approach. Because pinpoint neuroanatomic localization for these domains is difficult, research usually emphasizes large-scale neuronal networks. It is less well known that smaller and smaller units of circuitry compose these networks themselves, giving rise to a modular organization of the brain.

Because microscopic anatomic evidence of cortical modules in humans is necessarily postmortem or surgical, it cannot give direct information regarding cognitive or behavioral functions. While focusing on autism, we relate aspects of the modular organization of the brain (large-scale networks) to potential research techniques and their application to clinical practice (eg, magnetic resonance imaging [MRI], electroencephalography [EEG], functional MRI, and therapeutic trials).

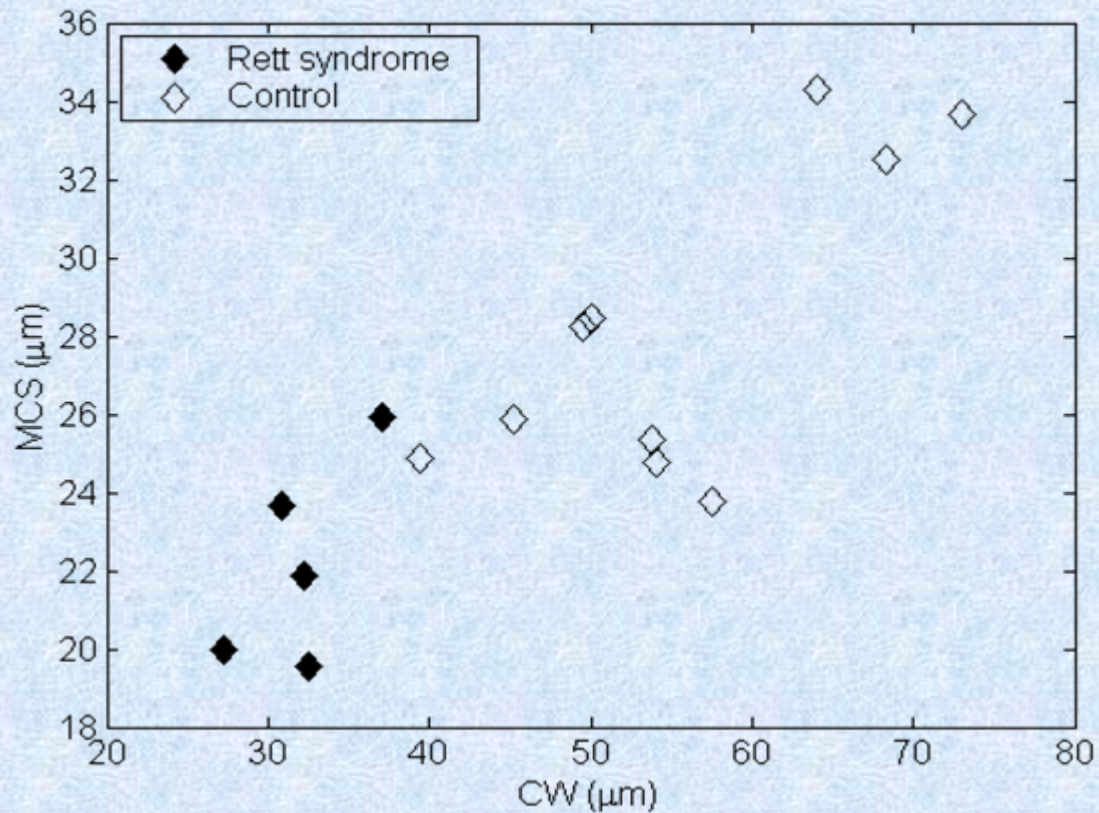
Recently, our group has described abnormalities in the minicolumnar organization of the brains of autistic individuals.<sup>1</sup> We found significant differences in the horizontal space that separates cell columns and in their internal structure, that is, in the relative dispersion of cells. We reproduced the results while employing a different technique, the Gray Level Index method, and applied it equally to all of the Brodmann's areas examined (9, 21, 22) in both hemispheres.<sup>2</sup>

Abnormalities in the modular organization of the brain are not unique to autism but appear in other pervasive developmental disorders of childhood, primarily Asperger's syndrome.<sup>3</sup> These findings distance themselves from classic neuropathology by emphasizing abnormalities in cell assemblies rather than single-cell pathology (eg, cell loss, homogenization of cytoplasm, etc).

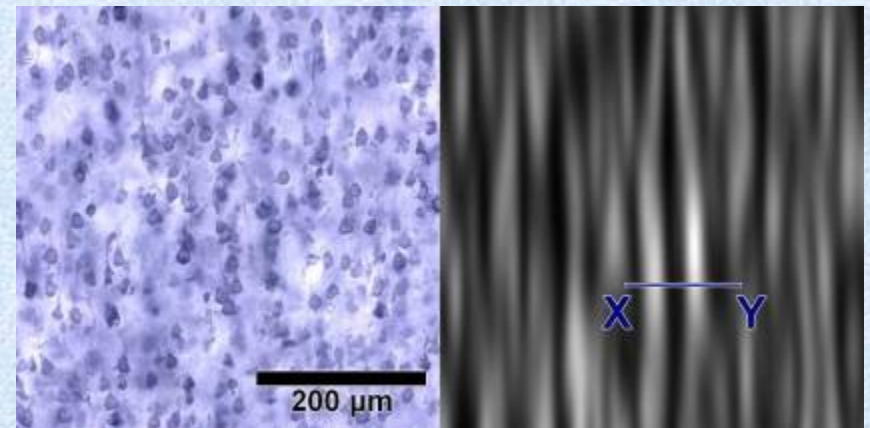
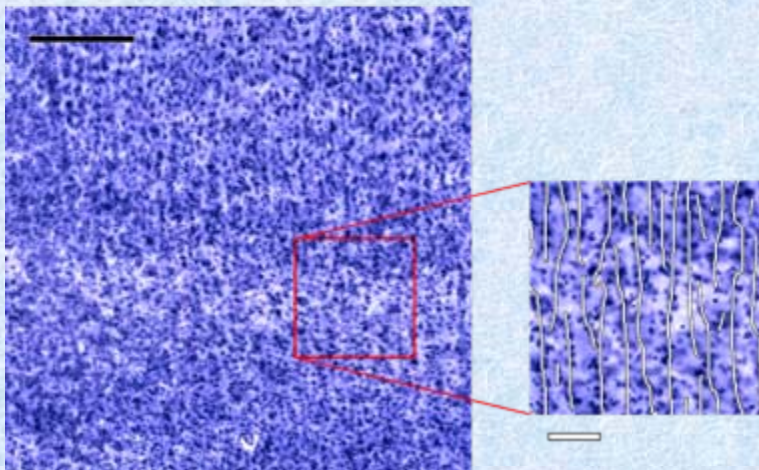
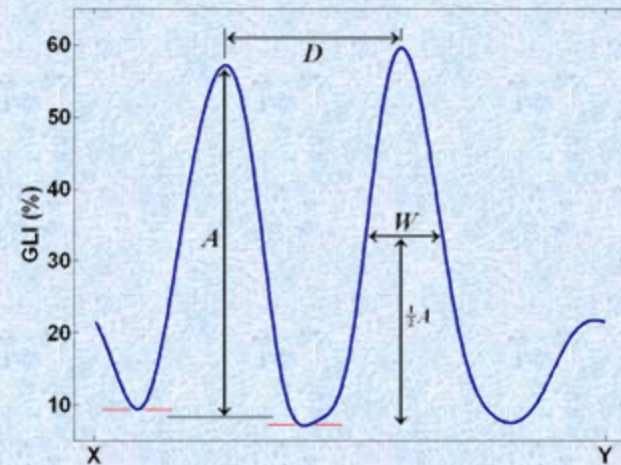
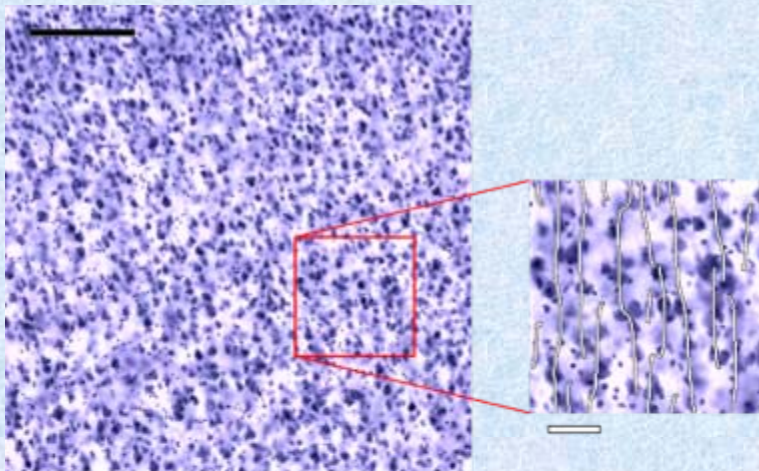
Minicolumns are composites of 80 to 100 neurons arranged radially like pearls on a string. Forty to 80 minicolumns make up a segregate or macrocolumn. Both the number of minicolumns and its constituent cells appear to be defined during gestation.<sup>4</sup> Minicolumns provide the basic unit of circuitry within the brain by tying together interacting afferent, interneuronal, and efferent connections. Not surprisingly, abnormalities of this cell assembly specify



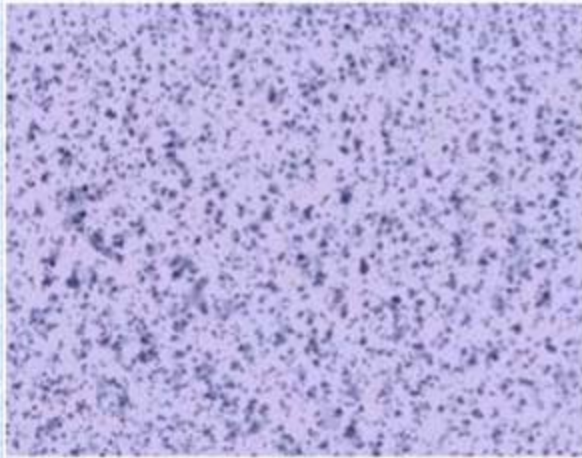
# Rett Syndrome



# Increased Number of Minicolumns in Autism

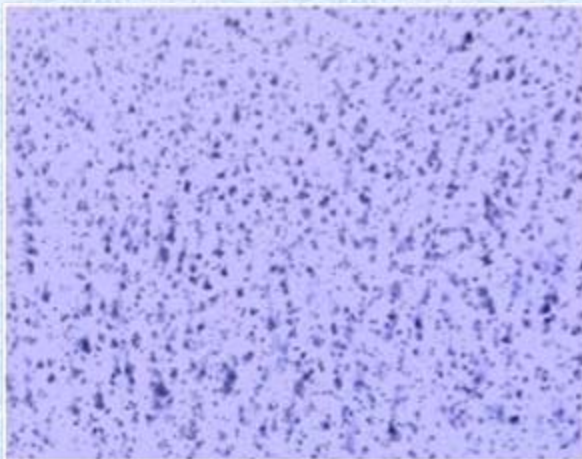


# Spatial Statistics: Neuronal Density



24 year old, autistic  
male

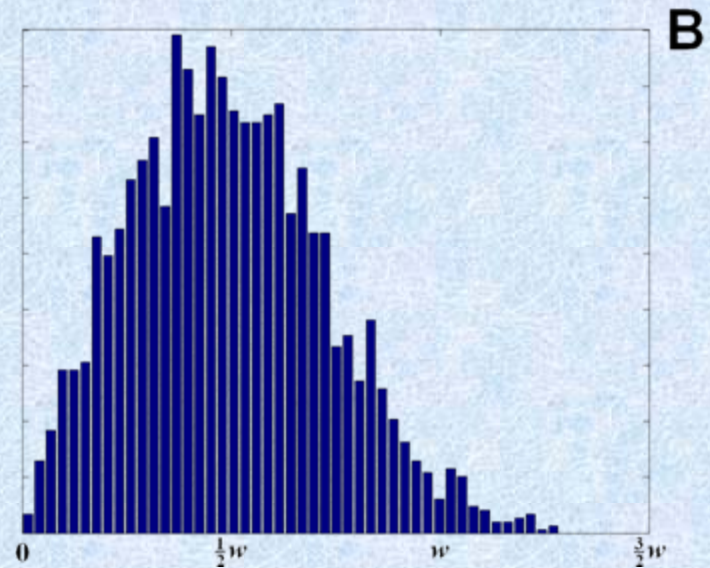
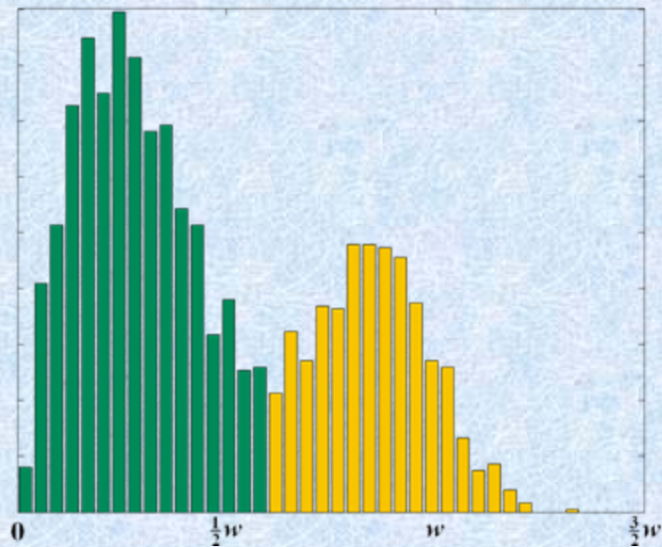
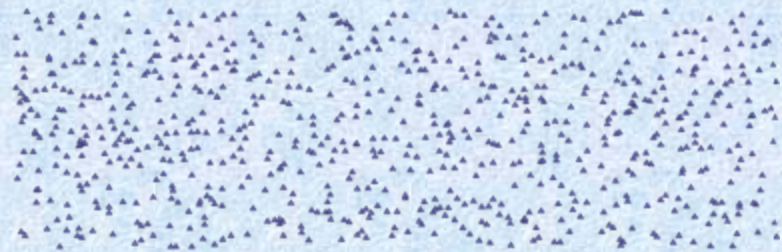
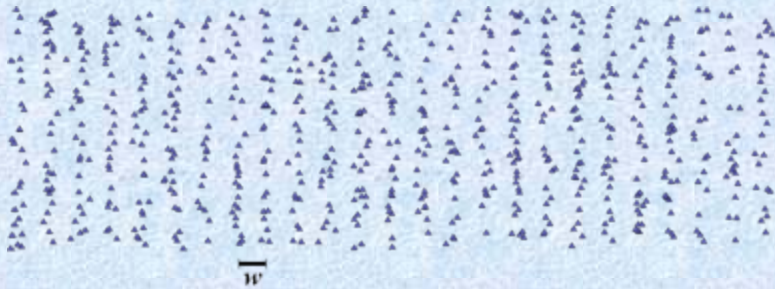
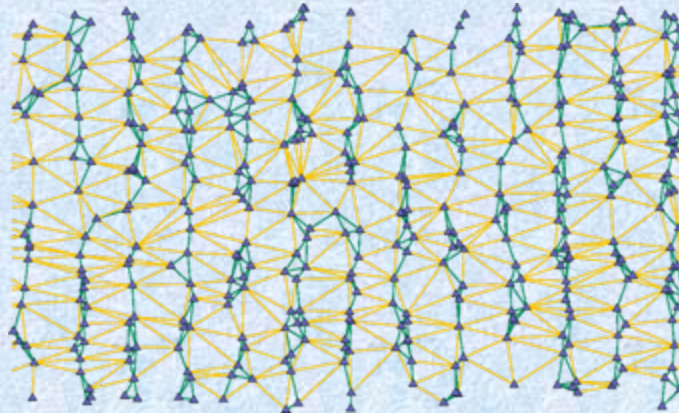
$$\lambda = 6900 \text{ mm}^{-2}$$



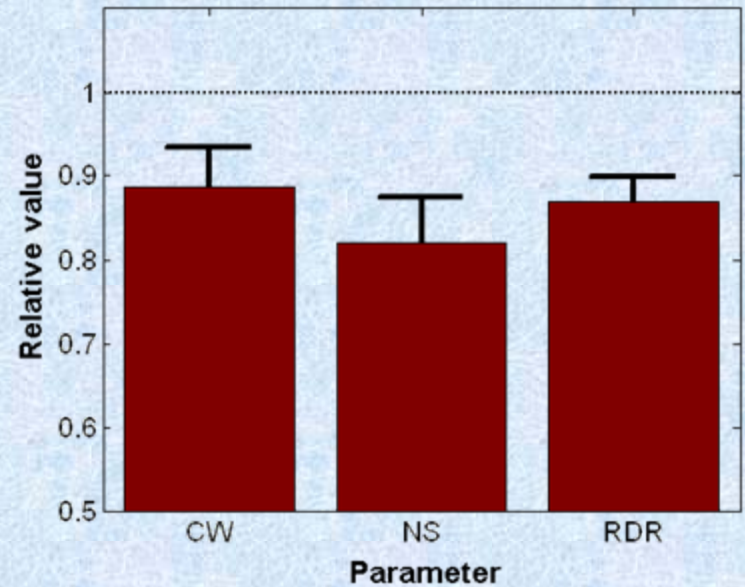
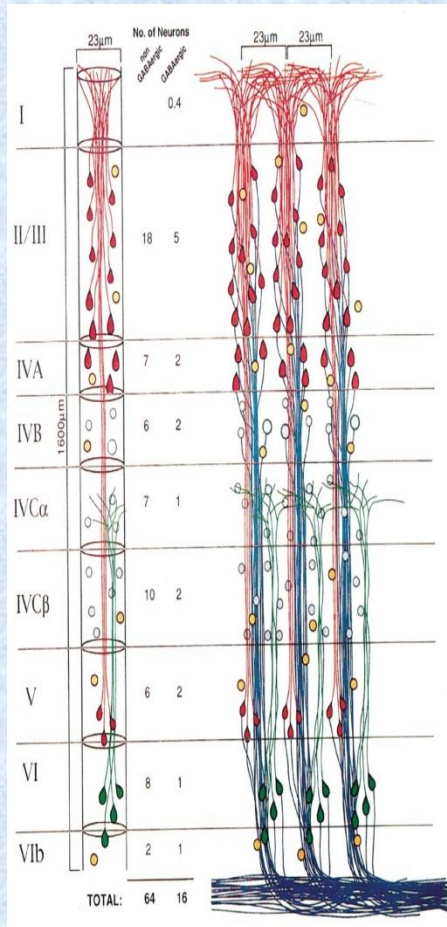
25 year old, non-  
autistic male

$$\lambda = 5200 \text{ mm}^{-2}$$

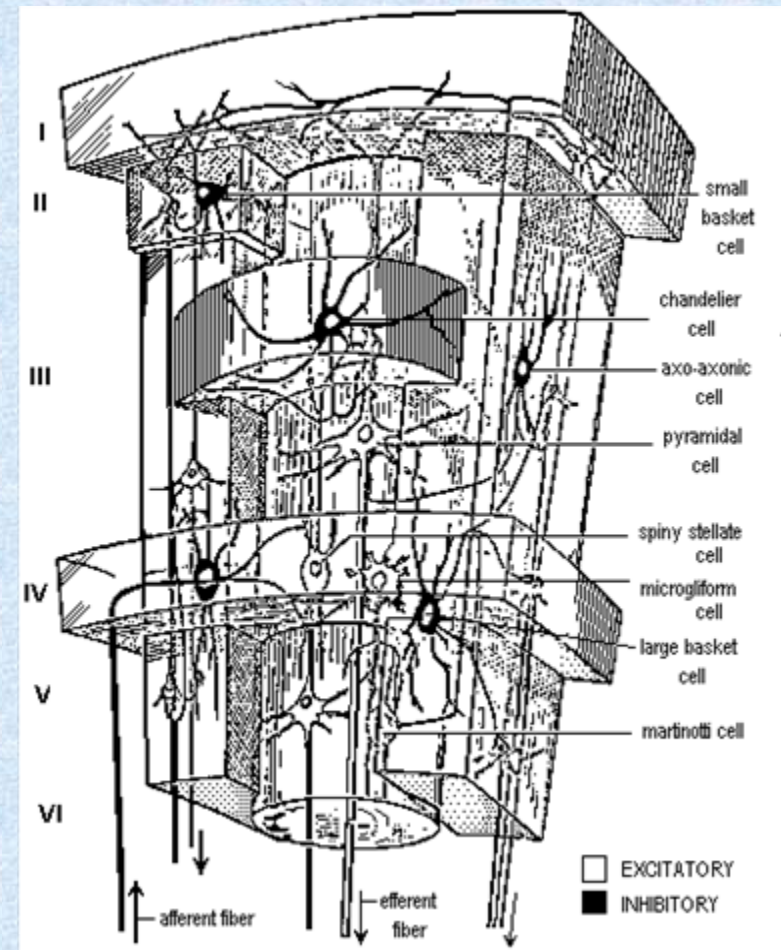
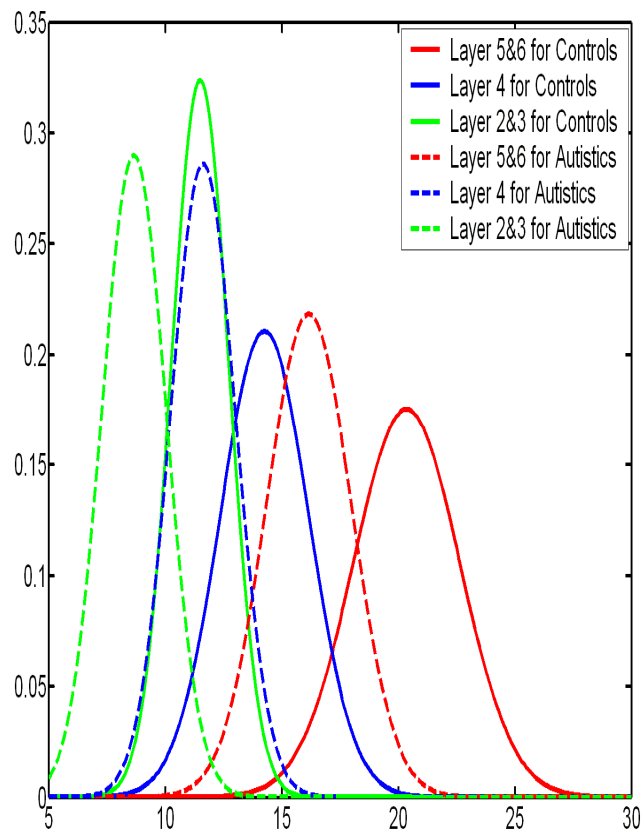
# Delaunay Triangulation: Edge Distances



# Minicolumns in Autism

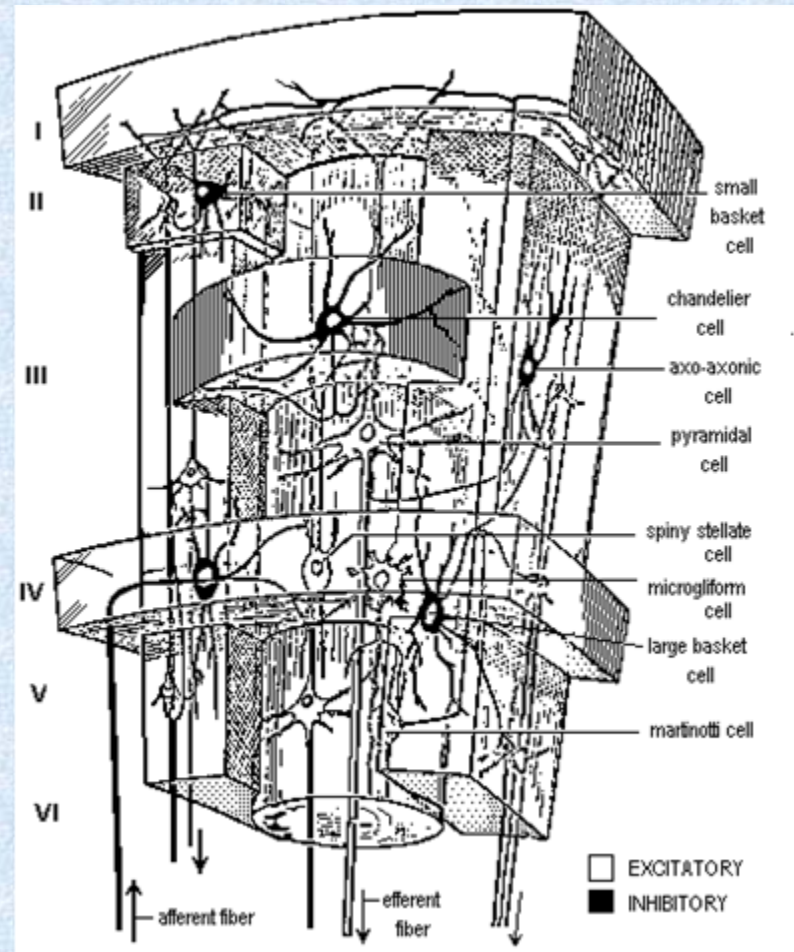


# Minicolumnar Width by Lamina in Autism and Controls

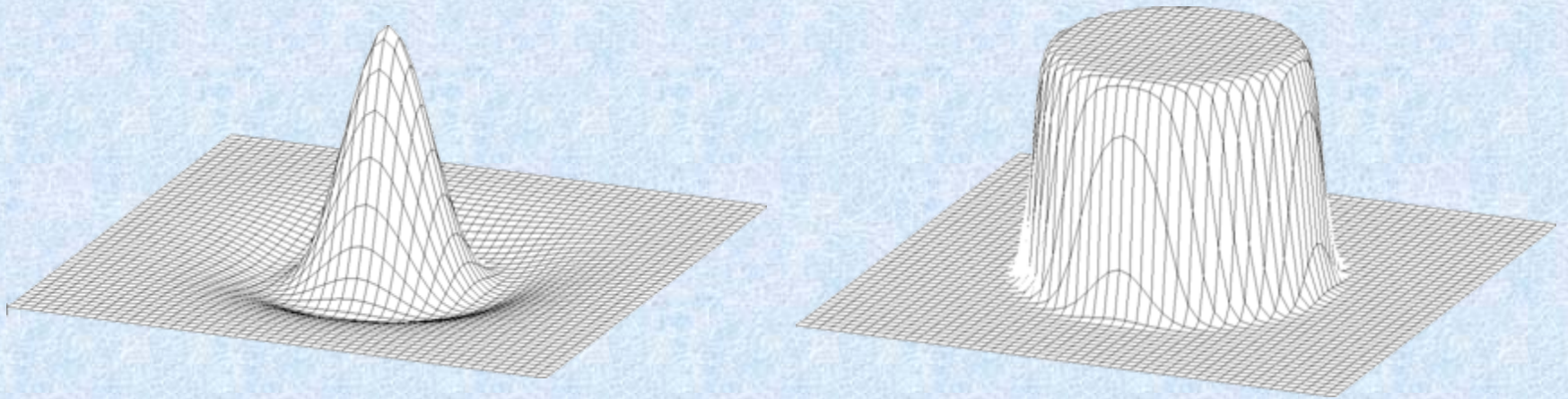


Casanova, Brain Pathology 2008

# Shower Curtain of Inhibition

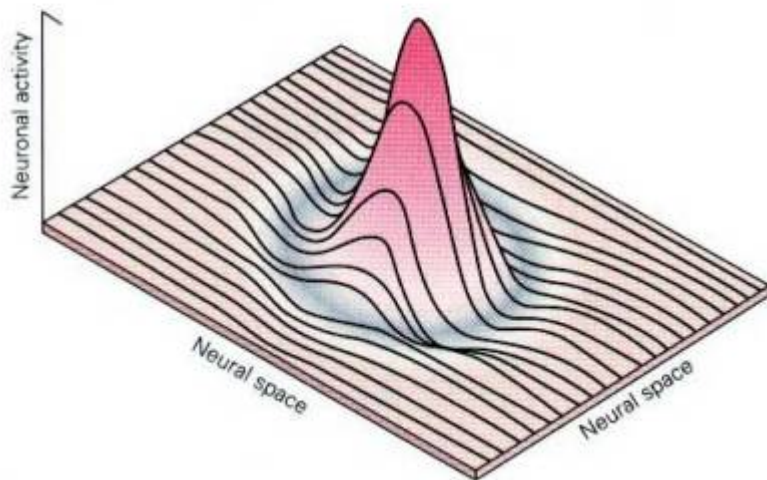


# Inhibitory Deficit in Autism

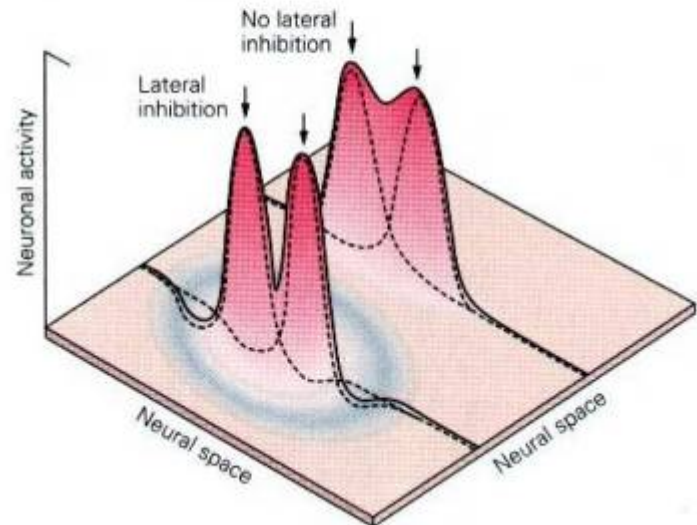


## Inhibition helps to sharpen stimulus selectivity

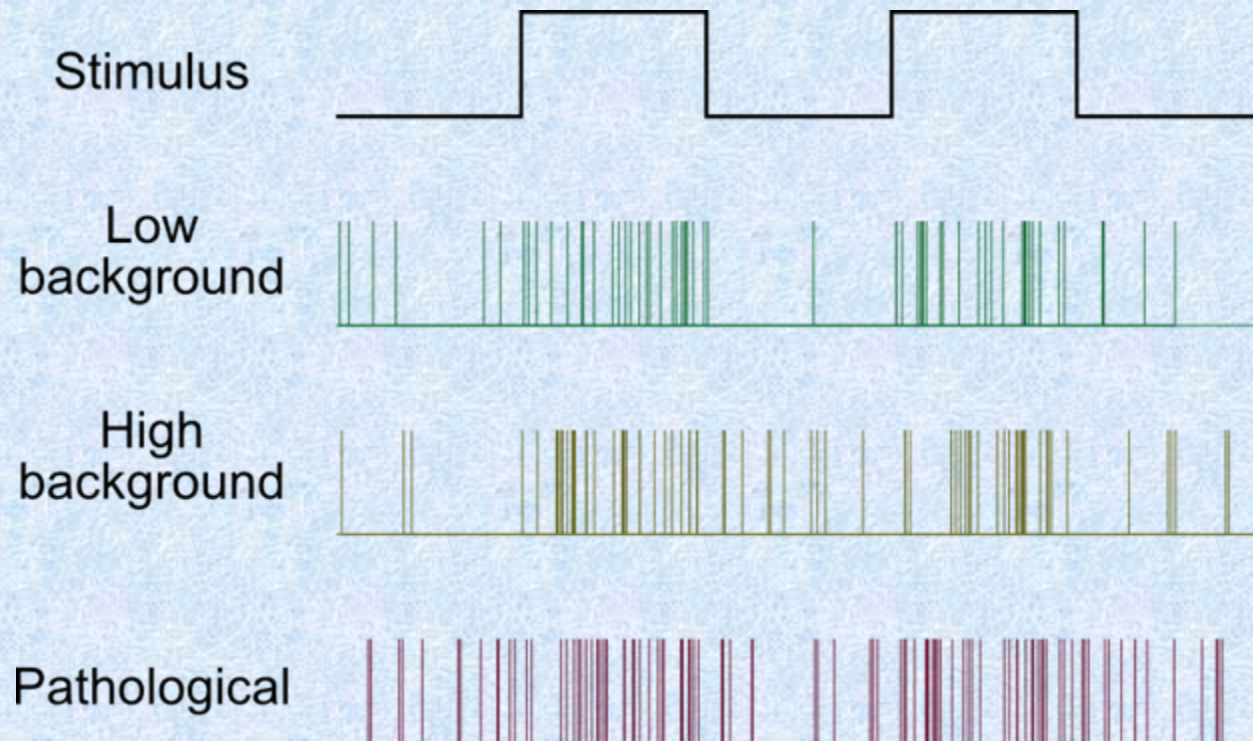
**A** One-point stimulus



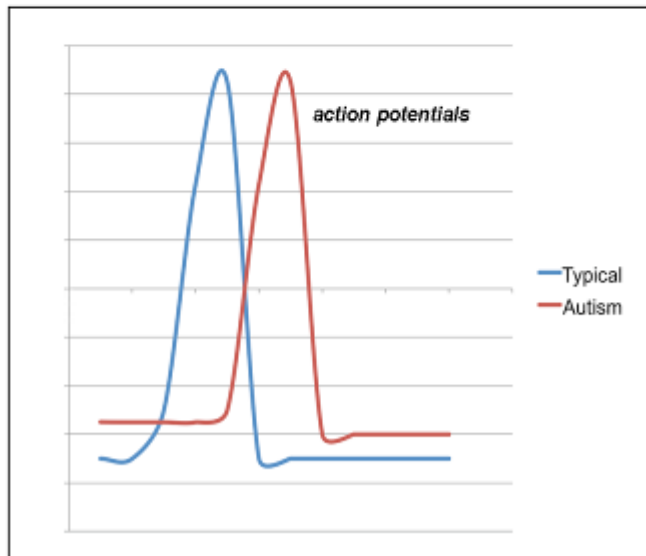
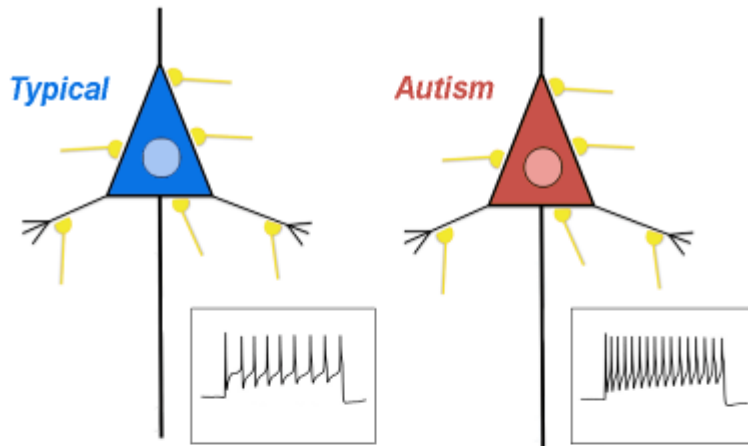
**B** Two-point stimulus



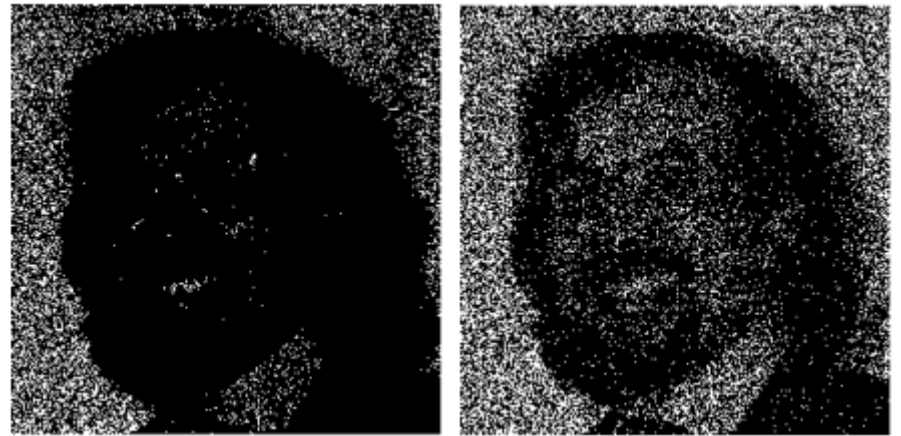
# Information (Neuronal Activity) and Background



# Stochastic Resonance



*“... adding noise to a signal raises the maximum possible combined signal level. Counterintuitively, this means that adding the right amount of noise to a weak signal can raise it above the threshold for detection and make it easier to detect and not less so.”*



*Simonotto et al. (1997)*

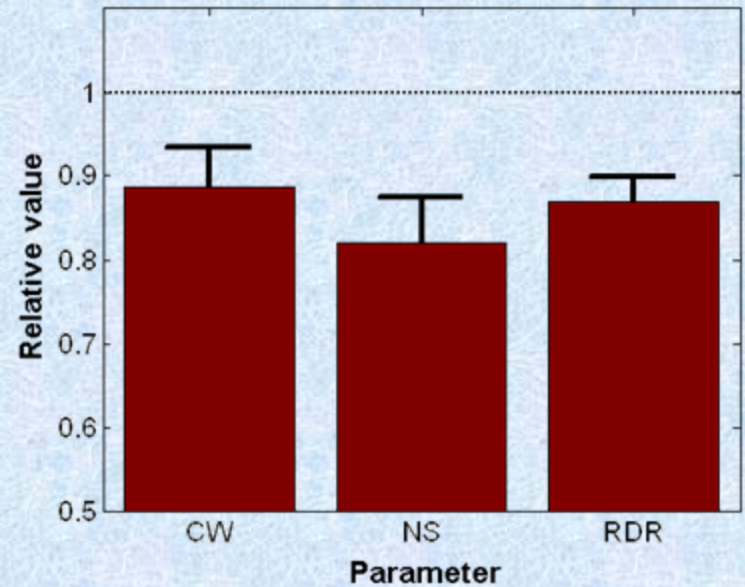
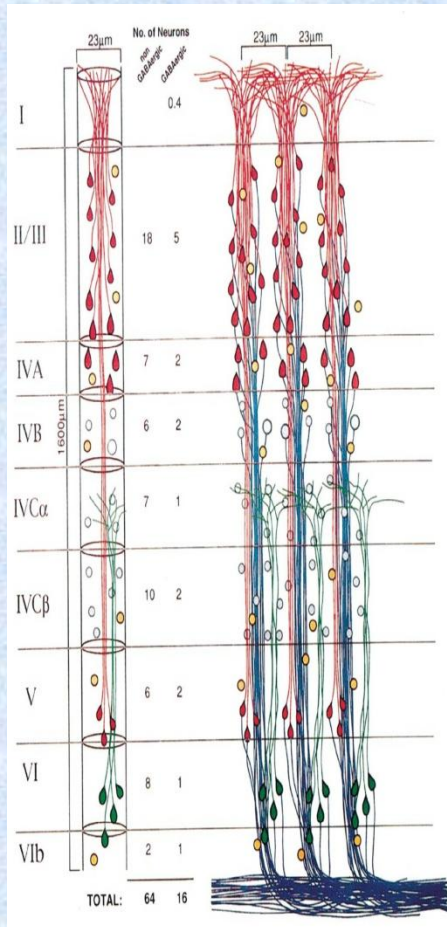
# The Noisy Brain: Part 1

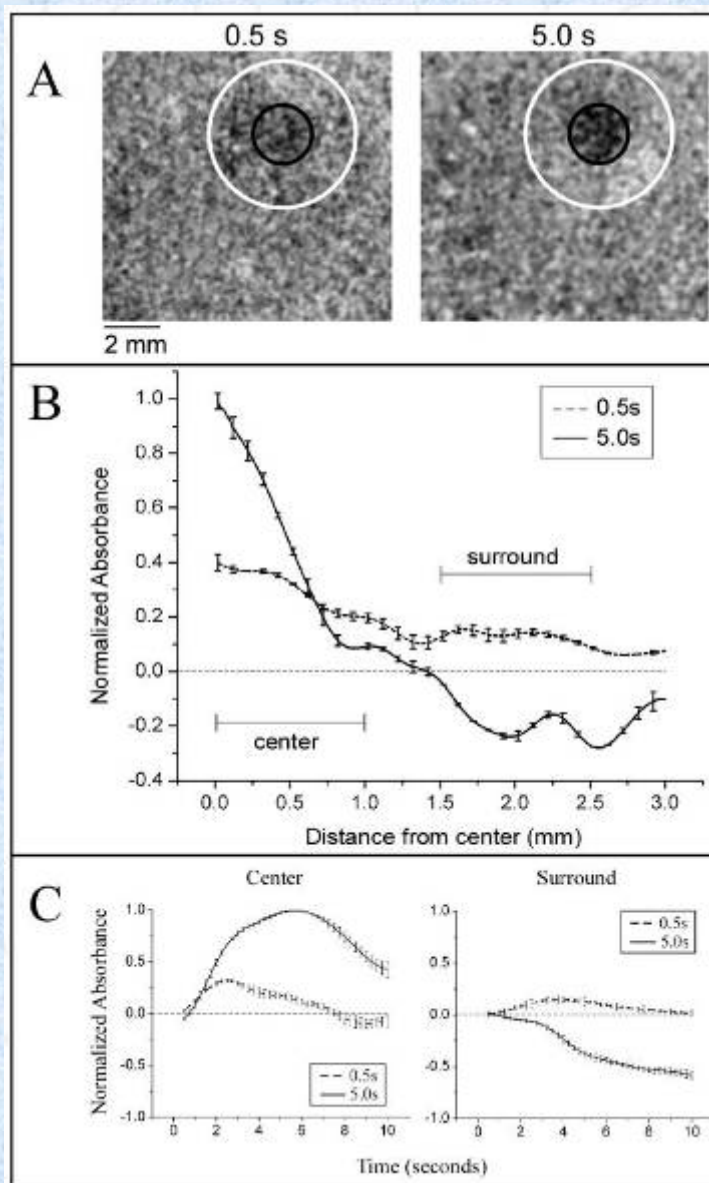
- 1) “What researchers found was that in fact stimulus overload is devastating to the brain’s- to the self’s- capacity to maintain itself. Entirely normal people who are severely overloaded, especially by unpredictable and uncontrollable stimuli, can show impaired functioning, raised physiological stress, internal chaos. Impulsive actions, and a “lower level of adaptation: to life’s challenges.”
- 2) “Because research shows that prolonged states of sensory overload (or noise) are actually traumatizing, we can conclude that patients suffering from severe mental disorders are actually being traumatized by their own brains.”

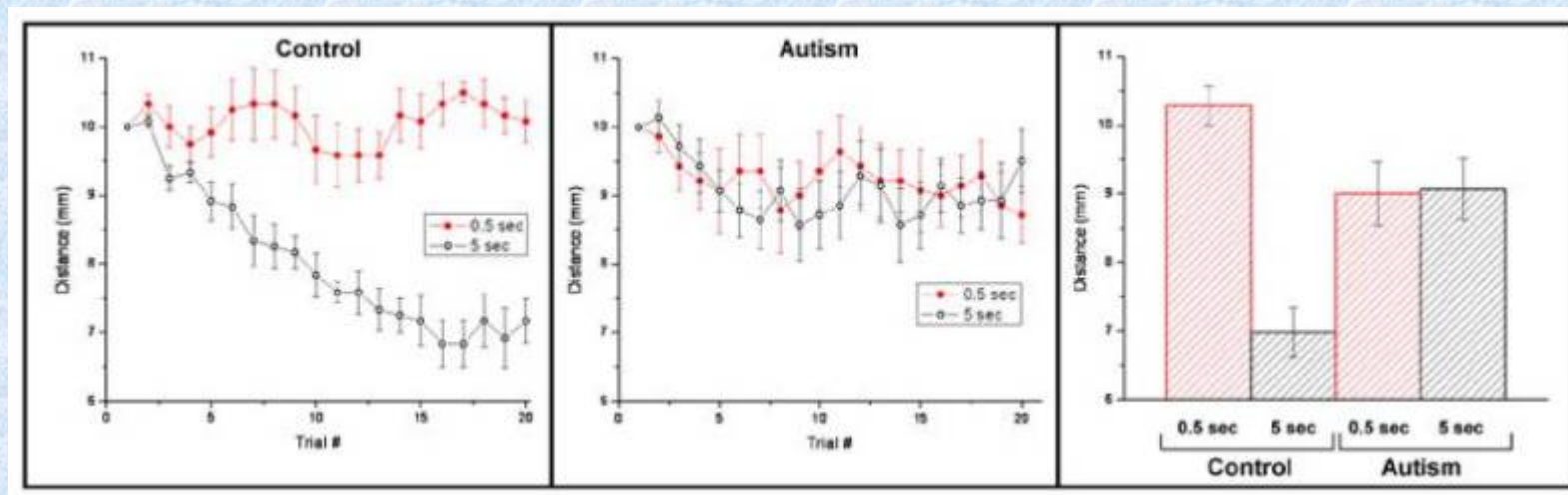
# The Noisy Brain: Part 2

- 1) “Noise affects this top level, causing a person afflicted to fall back to a more primitive, “lower” level of brain functioning that corresponds to the social strategies of the adolescent or child. (Or lower still...where we respond reflexively instead of thoughtfully.”
- 2) “Finally, beyond both of these difficulties, intense physiological arousal also impairs reasoning ability, a phenomenon psychiatrists describe as becoming *concrete*. Once we have become concrete, we take things at face value; we are no longer responding to the subtle clues and subtext of social interactions...But what happens when people become concrete is that they have no way of gauging the depth, the possible subtexts, of any particular exchange.”

# Minicolumns in Autism

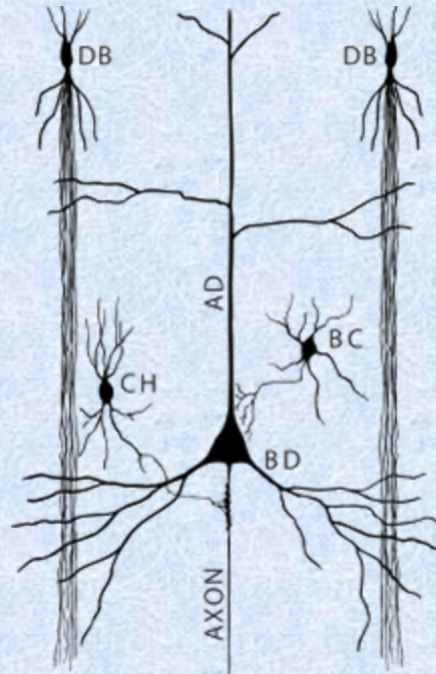
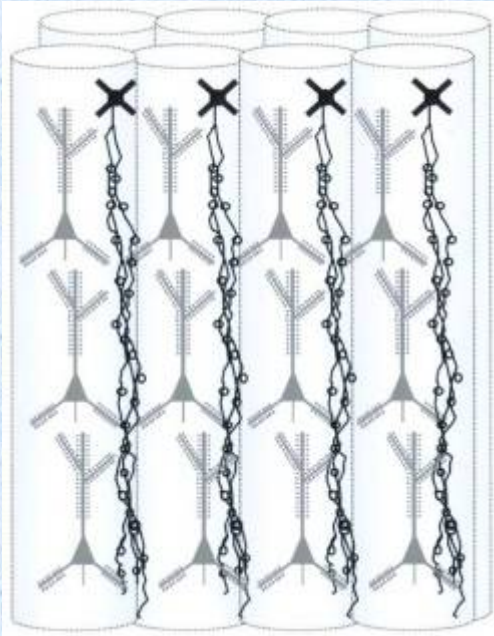




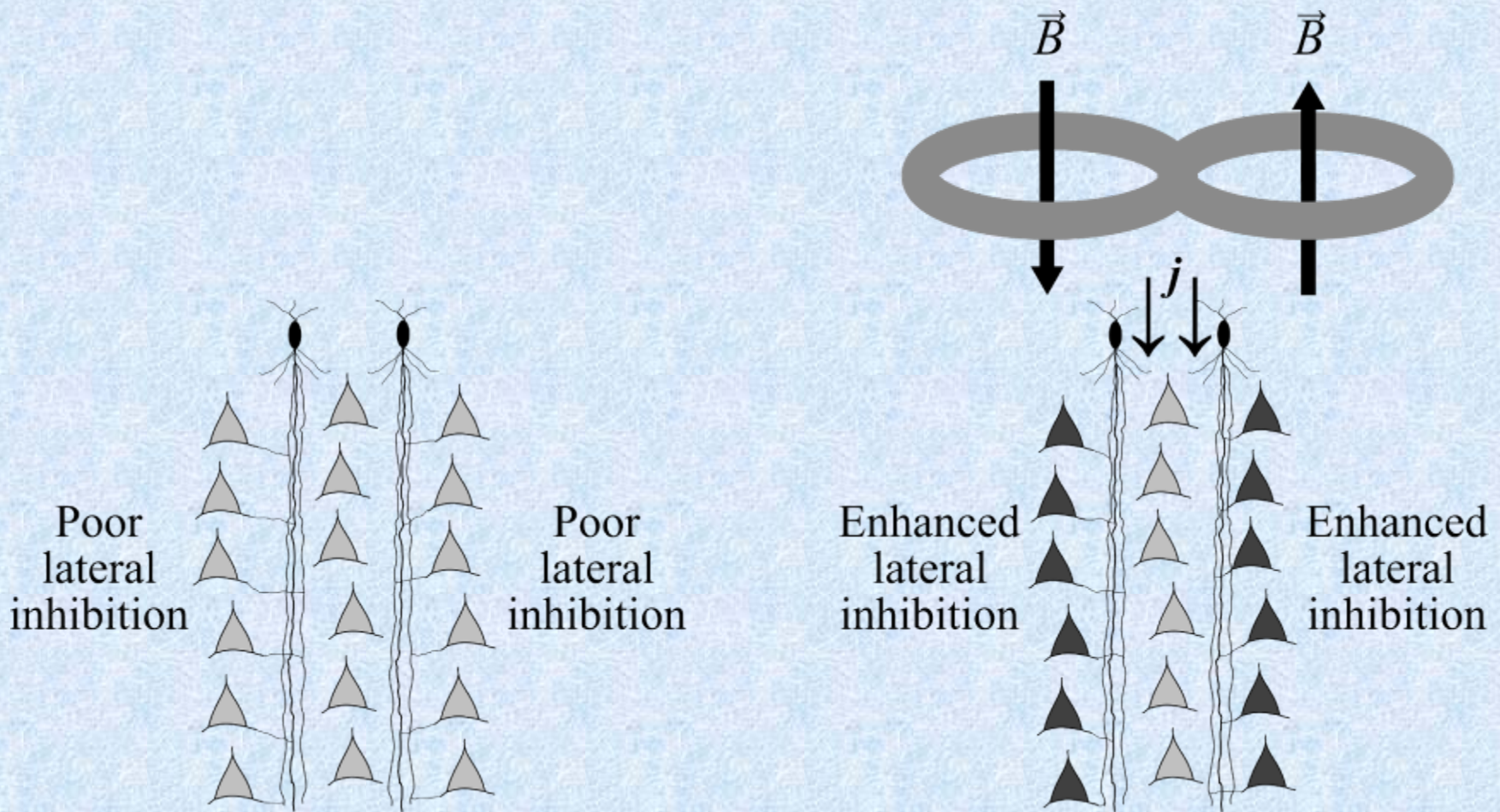


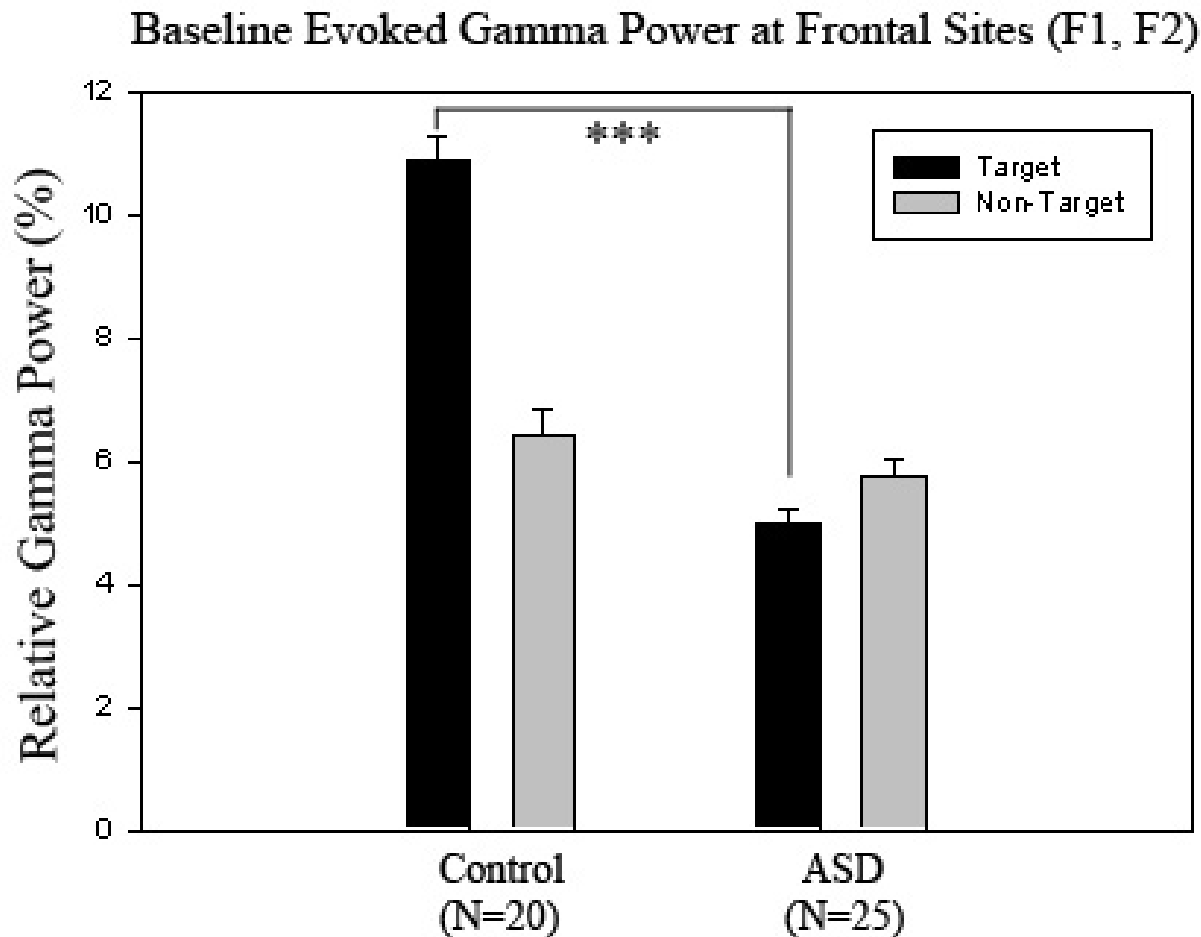
Spatial localization under 2 conditions of adapting stimulus duration for adults with and without autism (Tommerdahl et al., 2007).

# Inhibitory Surround of Minicolumns



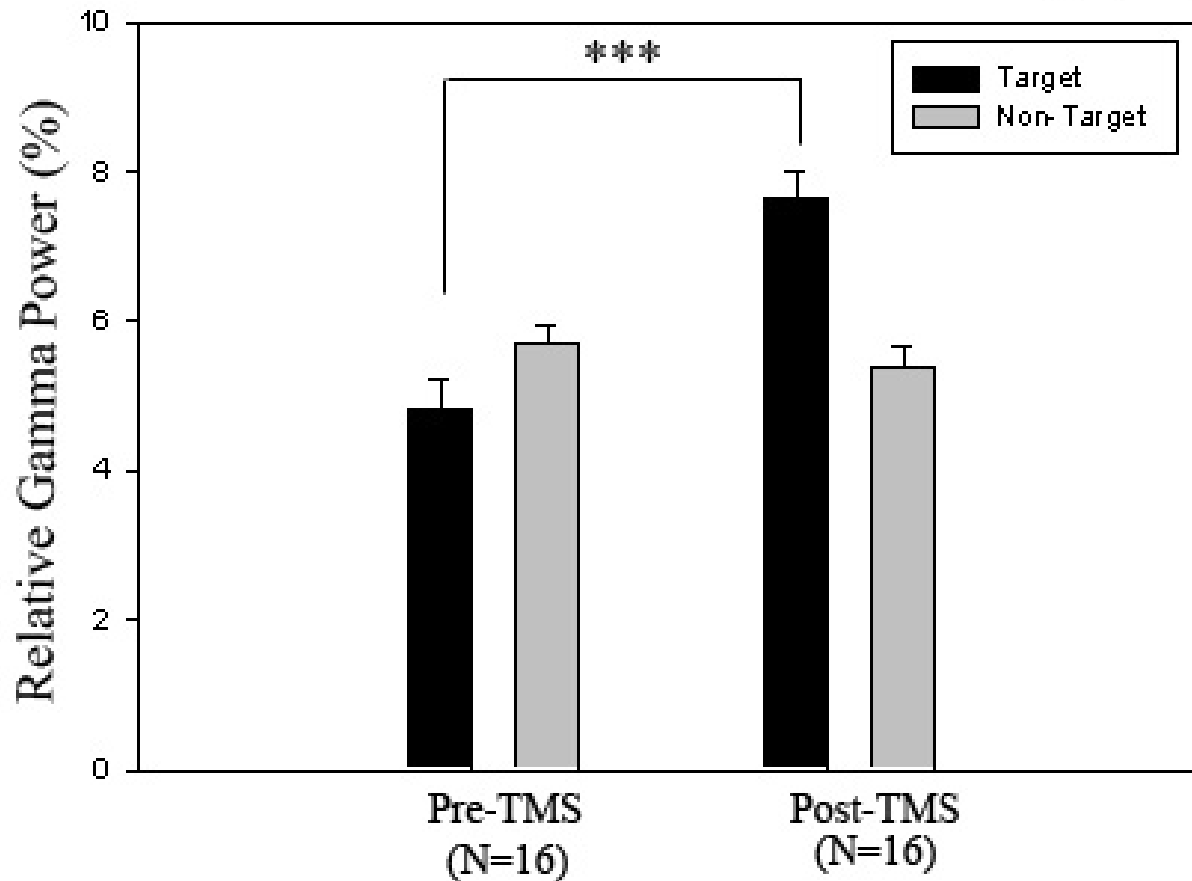
# “Vertical Stream of Inhibition” Provided by the Axon Bundles of Double-bouquet Cells





Participants with ASD also showed evidence of a lack of stimulus discrimination compared to controls evidenced by gamma EEG power.

## TMS Affects Evoked Gamma Power at Frontal Sites (F1, F2)



After rTMS individuals with ASD showed significant improvement in cortical discrimination of stimuli as evidenced by gamma EEG power.

