Cortical Architecture and Connection Patterns

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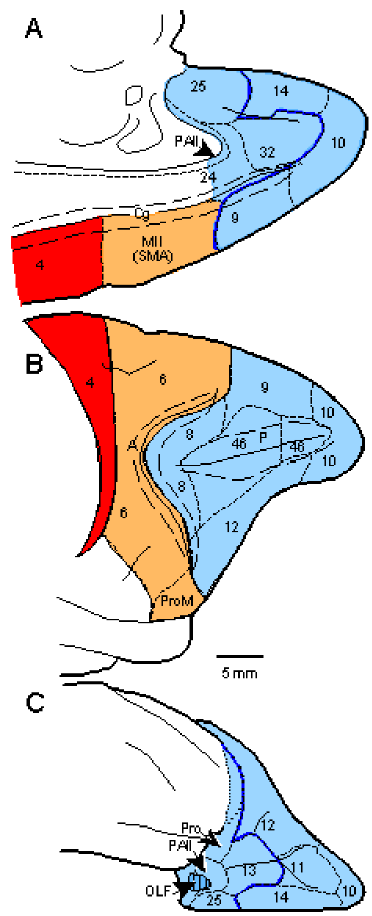
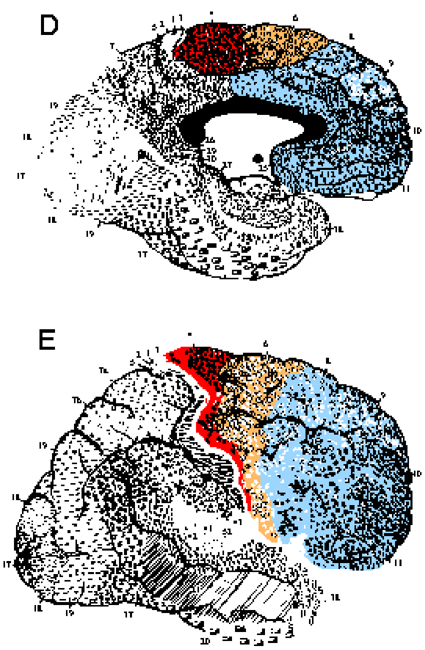
Rhesus monkey | Human



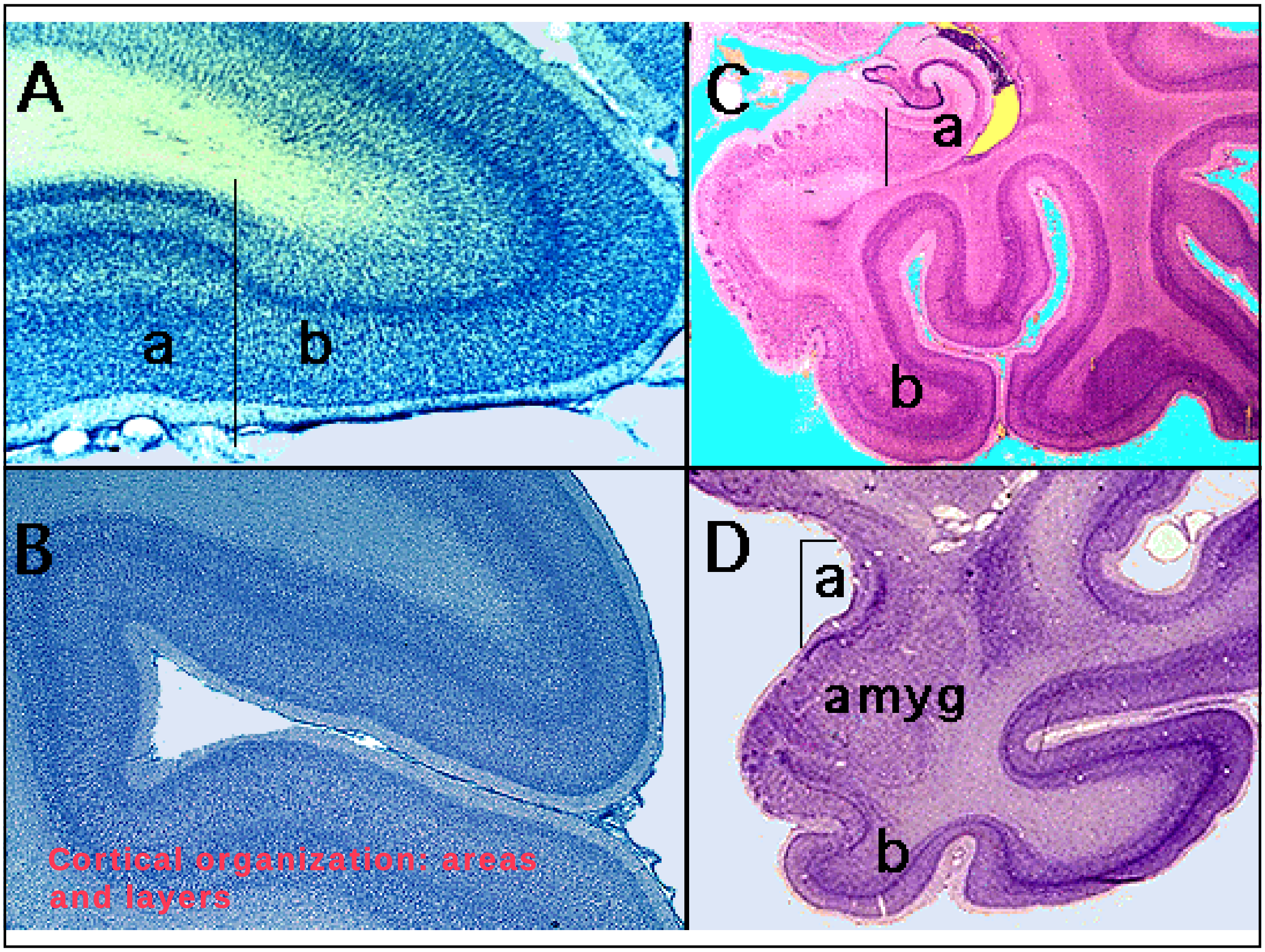


Prefrontal cortex
Premotor cortex
Motor cortex

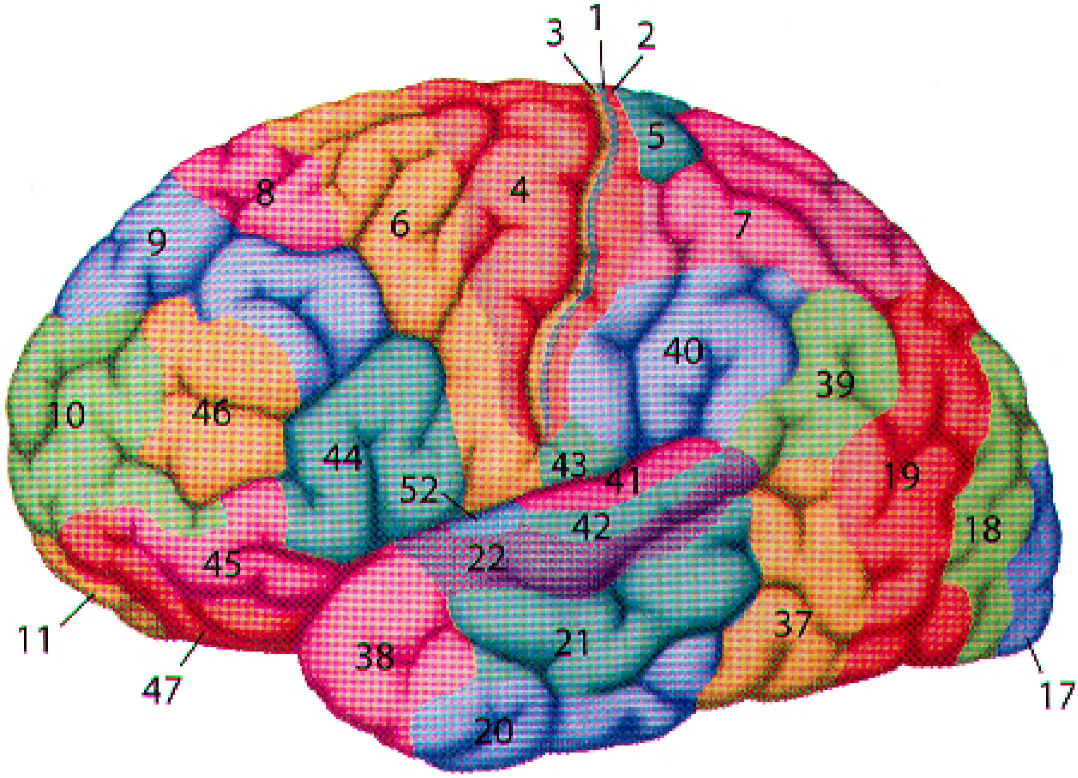
Adapted from: Barbas et al., 2002

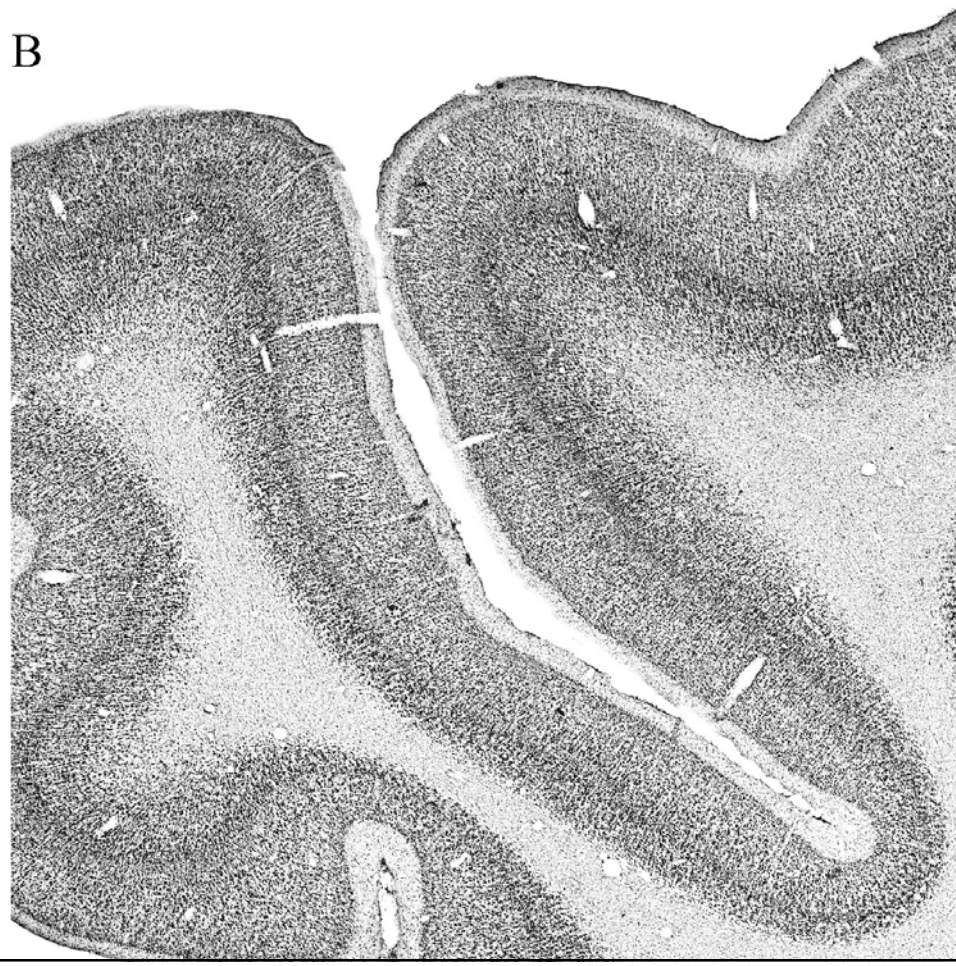
Cortical architecture:
why it matters

The non-uniformity of the cortex

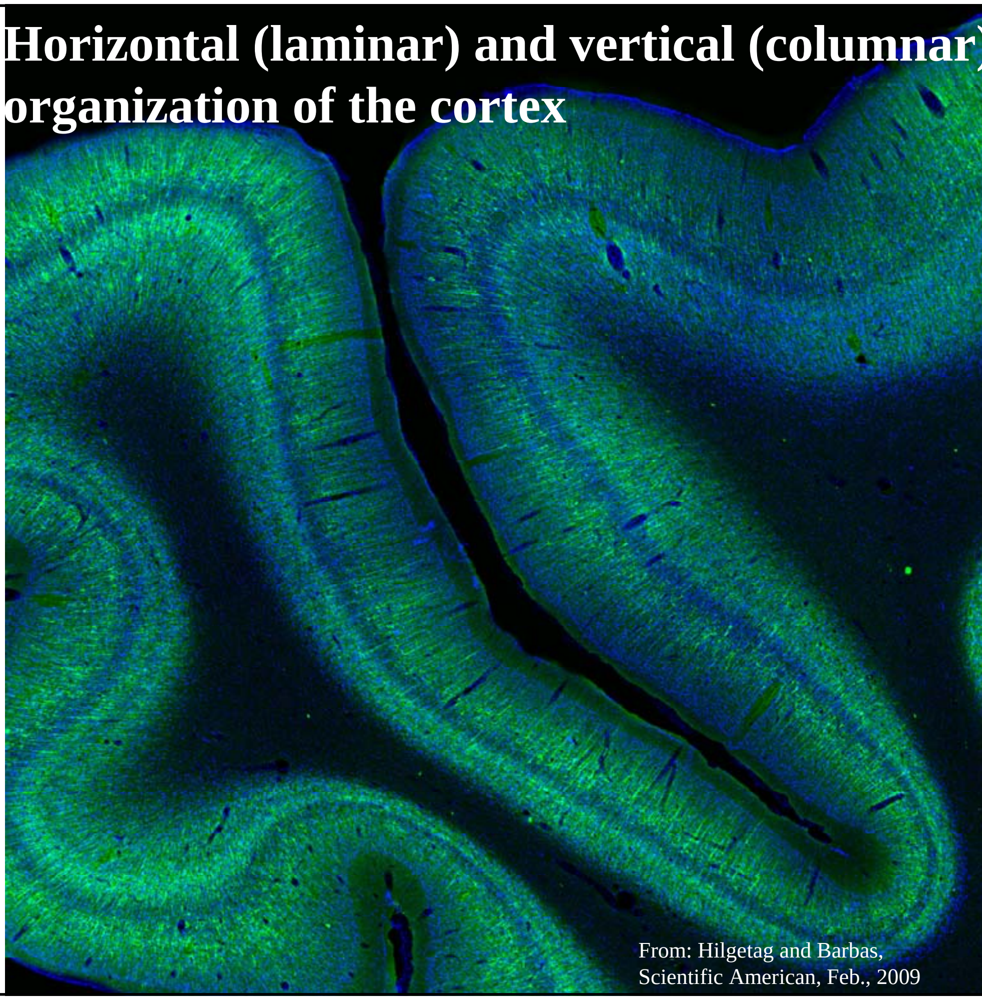

A
a
b
C
a
b
B
Cortical organization: areas and layers
D
a
amyg
b

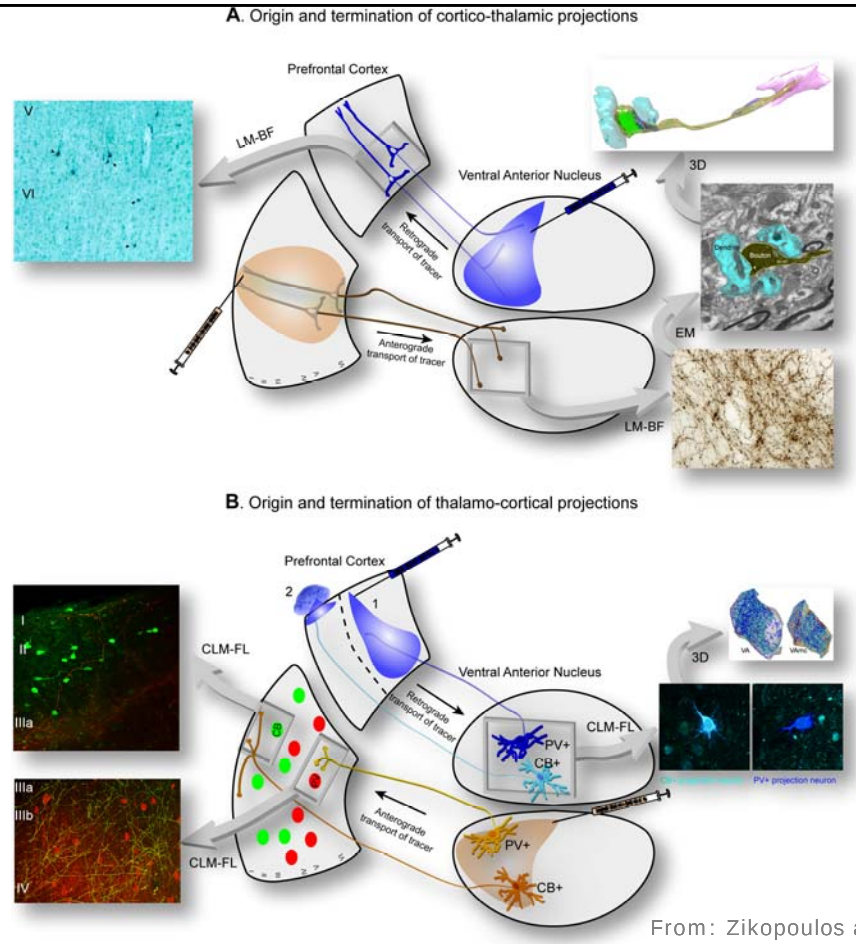
Cerebral Cortex: Brodmann map





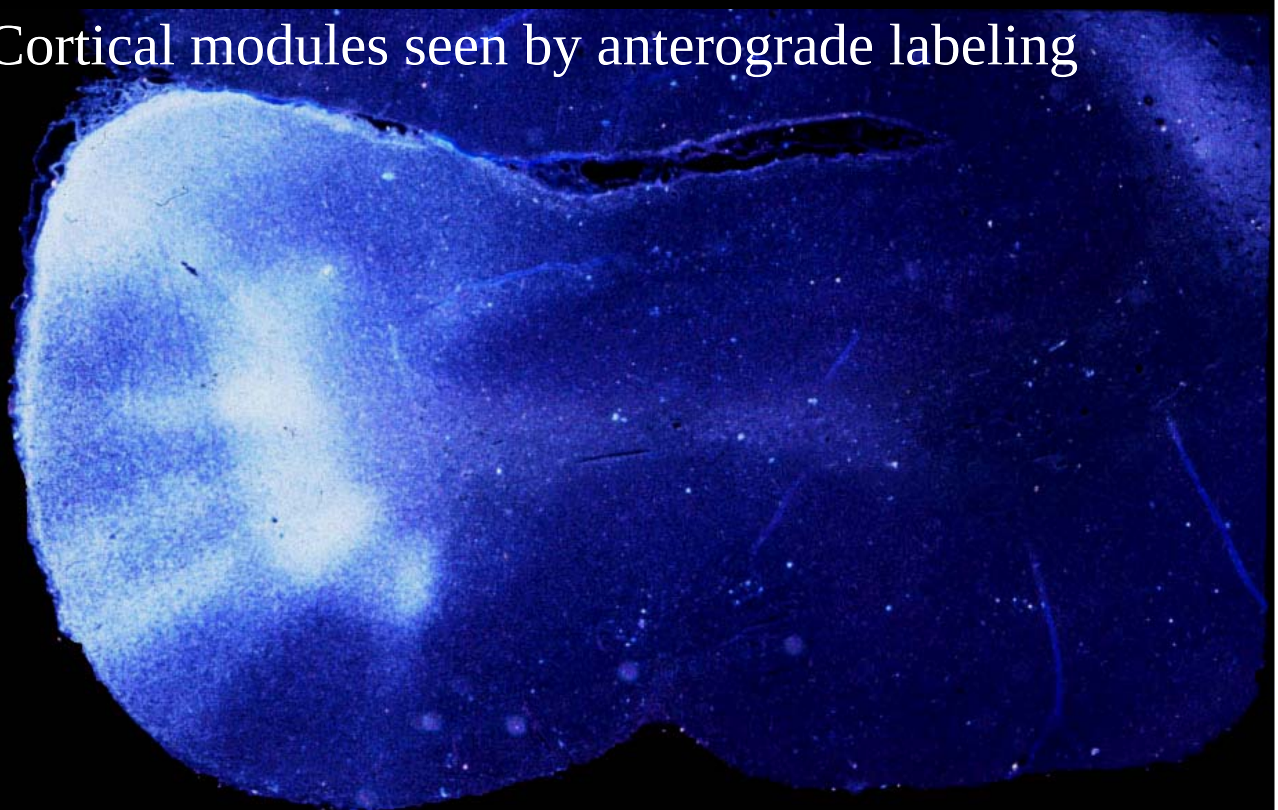
Adapted from:
Barbas, 2011


Horizontal (laminar) and vertical (columnar) organization of the cortex
From: Hilgetag and Barbas, Scientific American, Feb., 2009

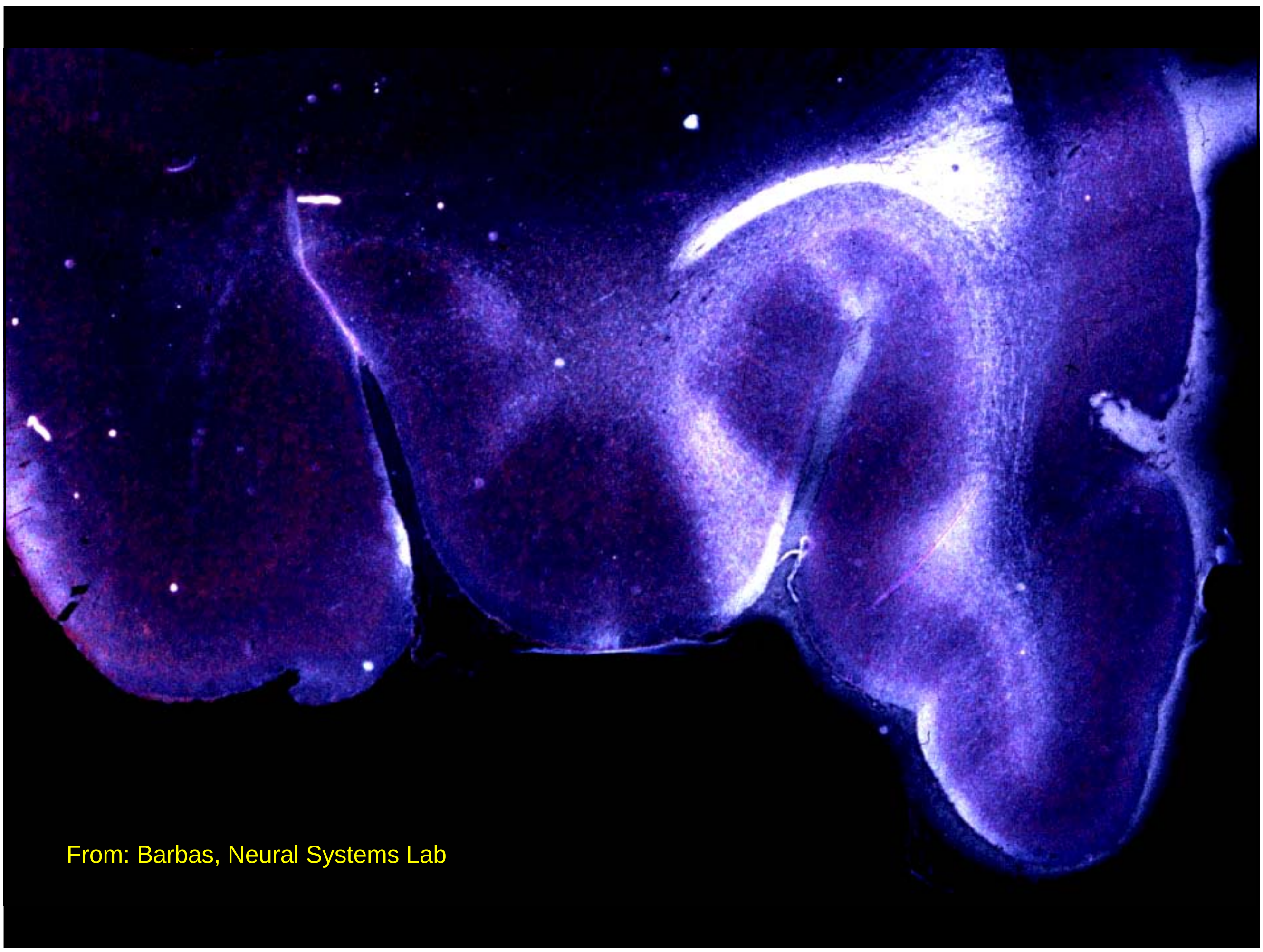


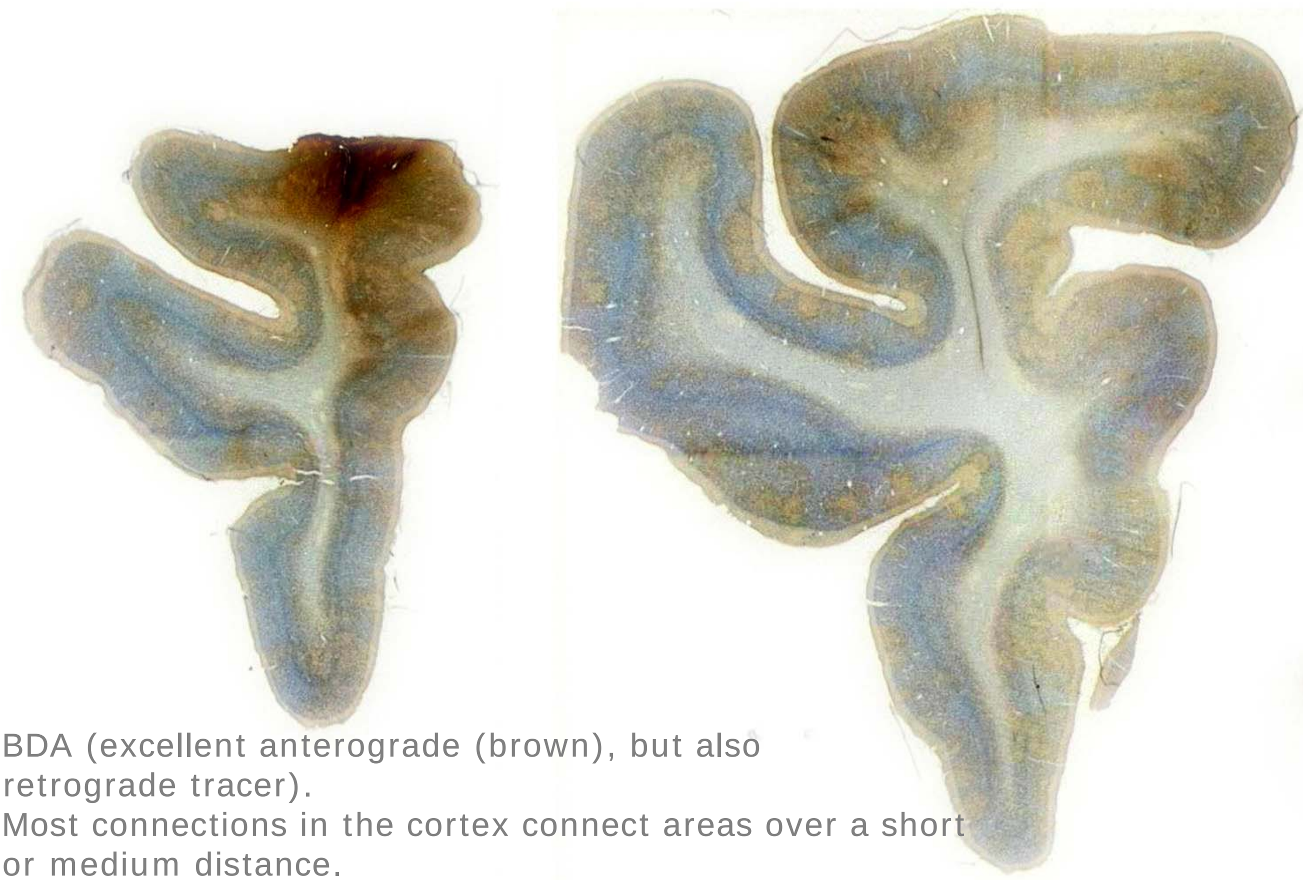
From: Zikopoulos and Barbas, 2007.

Cortical modules seen by anterograde labeling

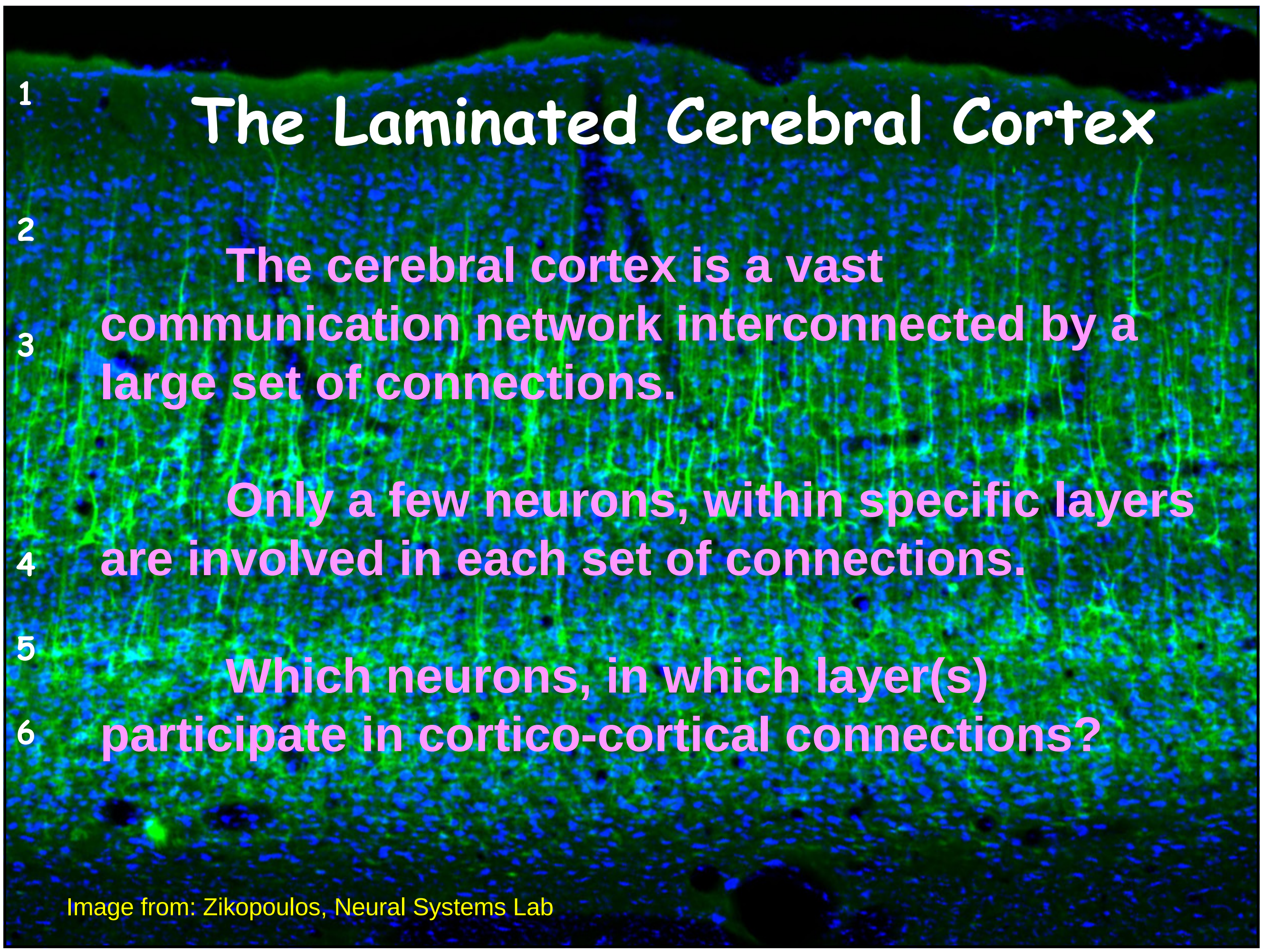


Adapted from: Barbas and Pandya, 1989


From: Barbas, Neural Systems Lab

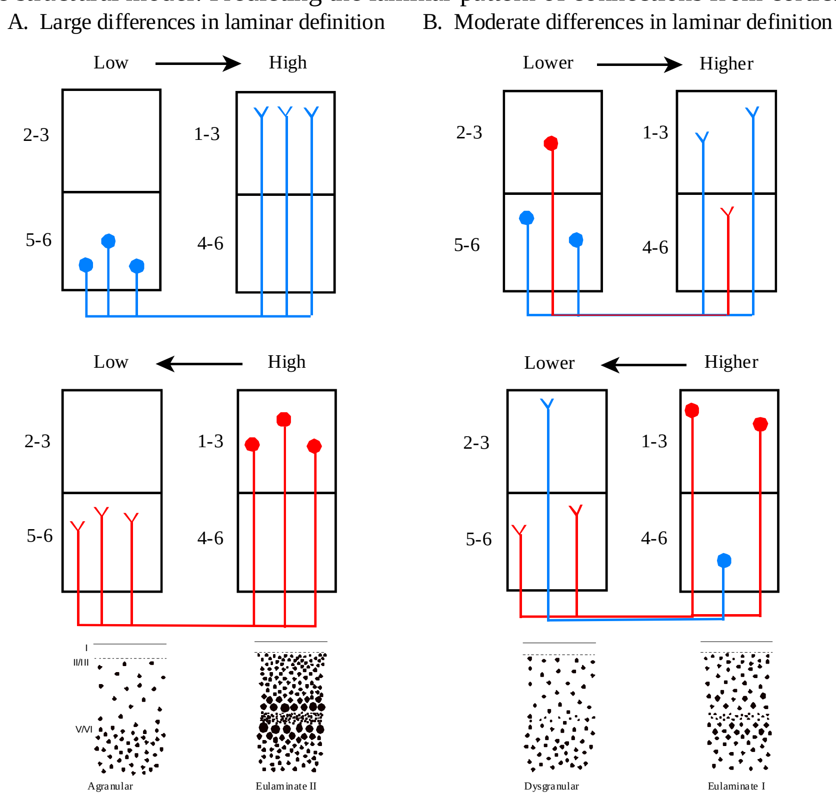


BDA (excellent anterograde (brown), but also retrograde tracer).
Most connections in the cortex connect areas over a short or medium distance.


1
The Laminated Cerebral Cortex
2
The cerebral cortex is a vast communication network interconnected by a large set of connections.
3
Only a few neurons, within specific layers are involved in each set of connections.
4
5
Which neurons, in which layer(s) participate in cortico-cortical connections?
6
Image from: Zikopoulos, Neural Systems Lab

Linking cortical architecture to corticocortical connections

The structural model: Predicting the laminar pattern of connections from cortical structure

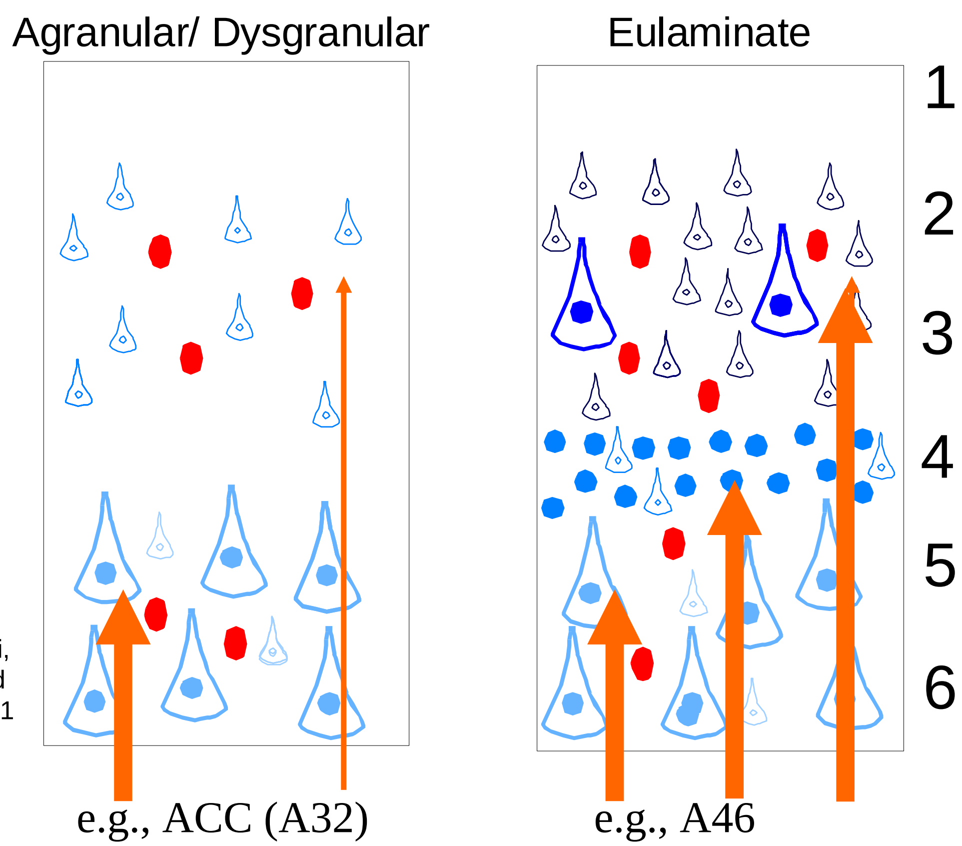


Adapted from: Barbas and Rempel-Clower, 1997

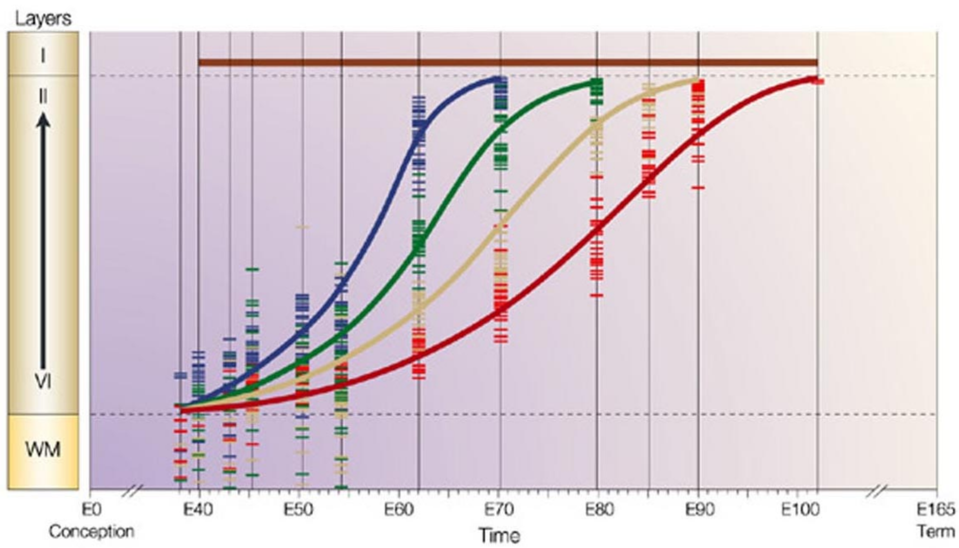
How do graded cortical connections come about?

If architecture is central to the pattern of connections, how does graded cortical architecture come about?

Hypothesis for Development



Based on: Dombrowski, Hilgetag and Barbas, 2001

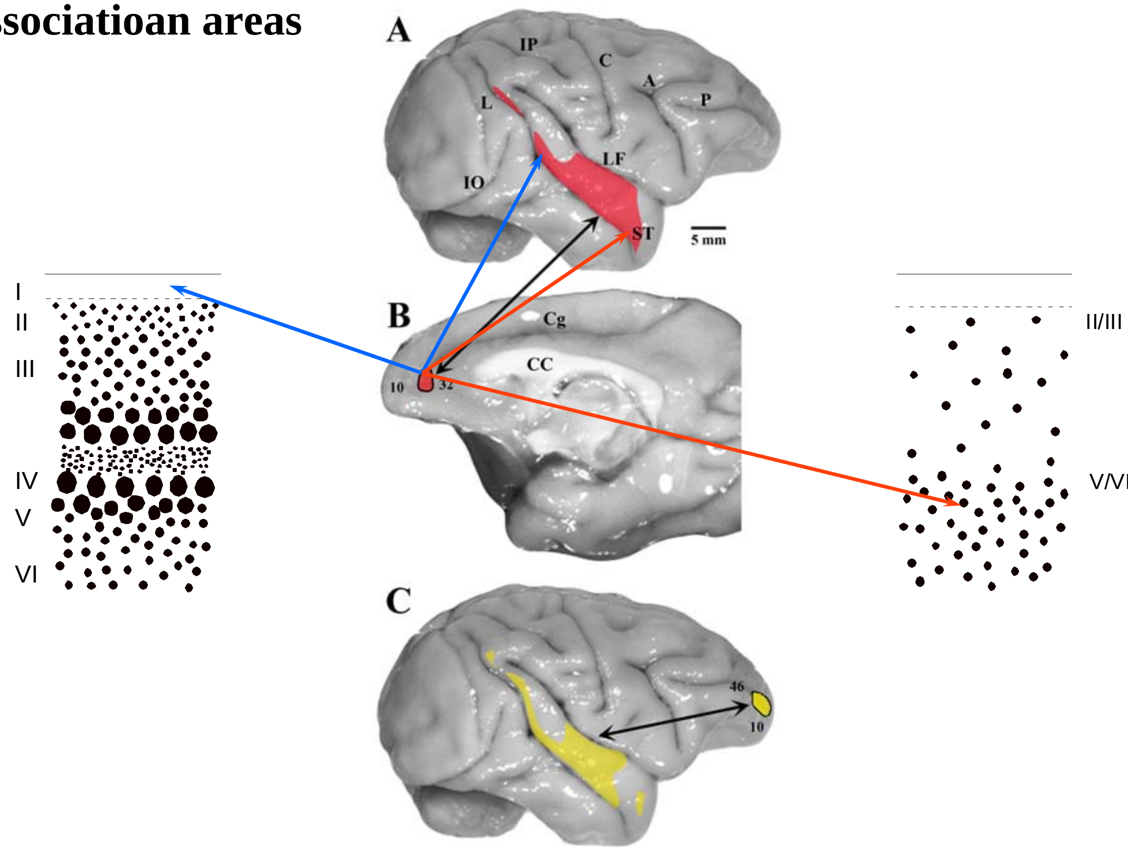


From Rakic, P. 2002 **Nature Reviews | Neuroscience**

Figure 2 | Relationship between the time of origin and the final position of cortical neurons in the macaque monkey. Representation of the positions of heavily labelled neurons in the four representative cytoarchitectonic cortical areas. Each monkey was injected with 10 mCi kg-1 of 3H-thymidine (3H-dT) on a selected embryonic day (E) and killed postnatally. A representation of the approximate position of layers I–VI and the white matter (WM) is on the left. Embryonic days are represented on the horizontal axis, starting with the beginning of the second fetal month (E34) and ending at term (E165). Positions of the vertical lines indicate the embryonic day on which an animal received a pulse of 3H-dT. On each vertical line, short horizontal markers indicate positions of the heavily labelled neurons encountered in a 2.5-mm-long strip of cortex. Blue, Brodmann area (BA) 24; green, BA 11; yellow, BA 46; red, BA 17. Layer I neurons in the primates are generated throughout the entire period of neurogenesis in each area (brown).

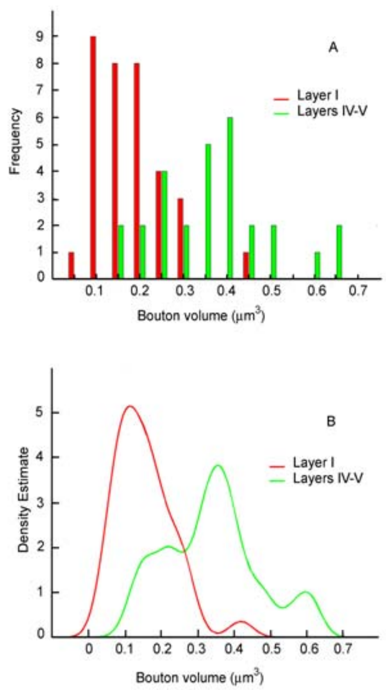
Does the laminar origin and termination of connections matter for neural processing?

Bidirectional connections of medial prefrontal cortex with auditory associatioan areas

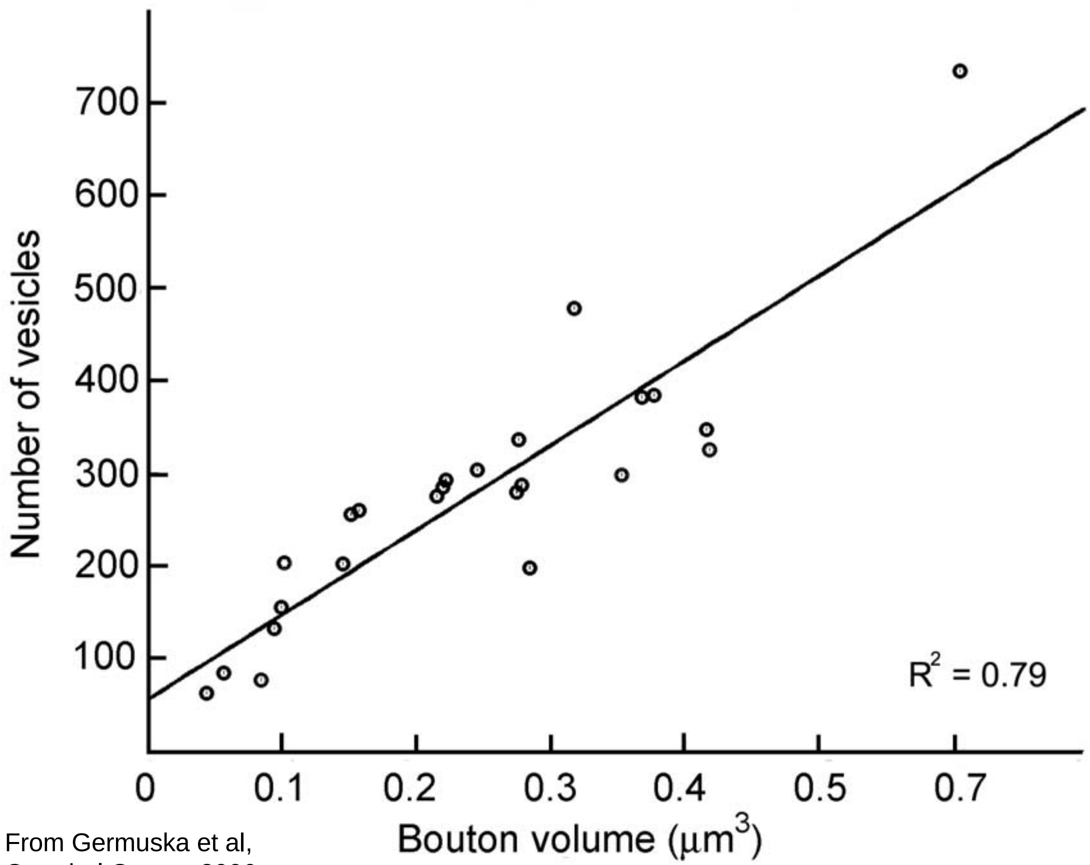


Adapted from: Barbas et al, 1999

Prefrontal pathways at the synaptic level: axonal boutons terminating in the middle layers are larger than boutons terminating in layer I of superior temporal auditory association cortex



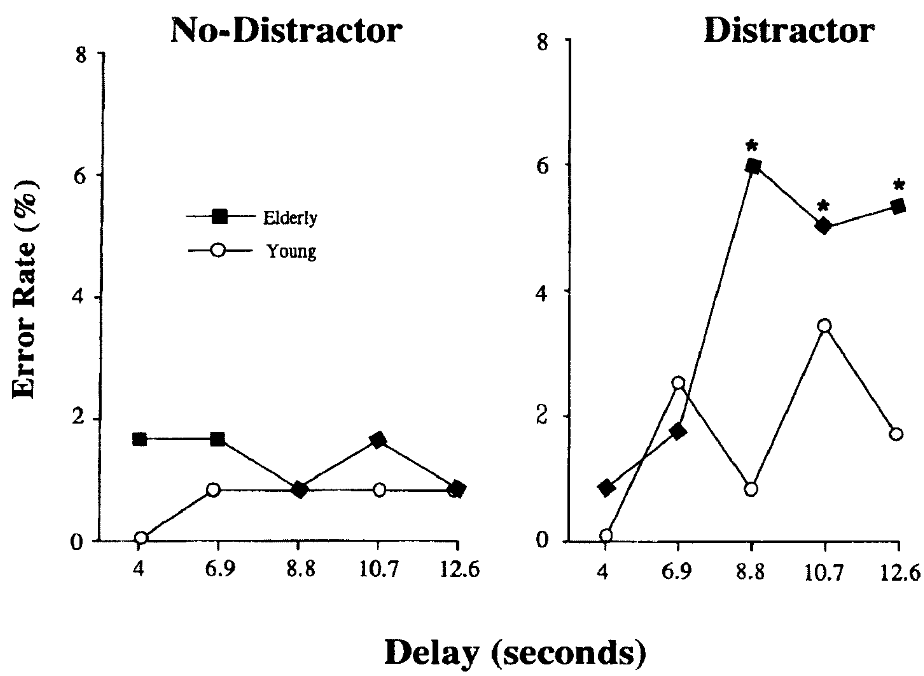
From Germuska et al,
Cererbal Cortex, 2006



From Germuska et al,
Cererbal Cortex, 2006

Do other features of the laminar origin and termination of connections matter?

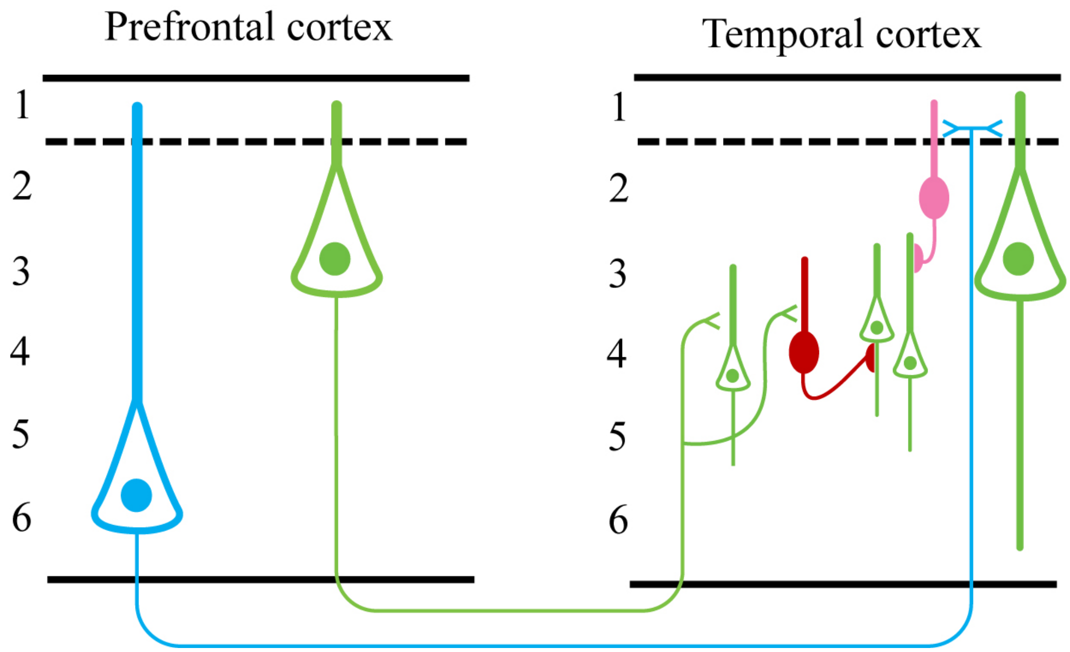
A closer look at the microenvironment of laminar connections



From Chao and Knight, 1997

Corticocortical connections
in primates are excitatory;
but the prefrontal cortex has a
major role in inhibitory control

Interaction of prefrontal pathways with excitatory and inhibitory systems: corticocortical connections

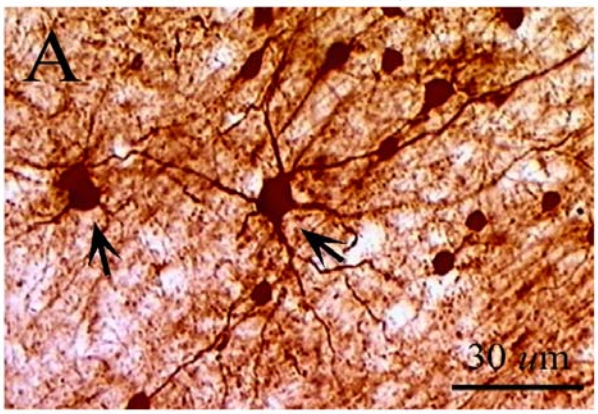


The microenvironment of the origin and termination of laminar-specific connections varies.

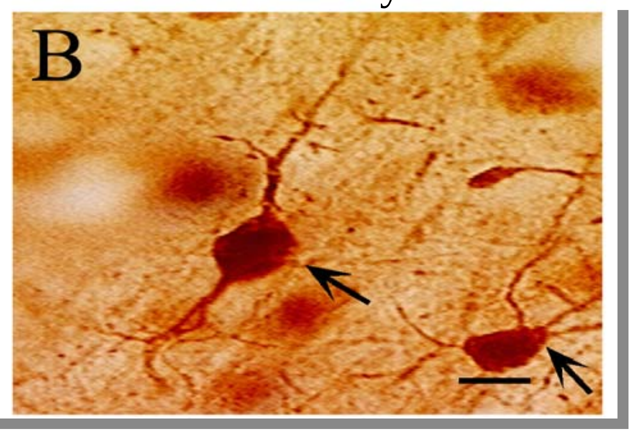
From Barbas, 2006

Differences in neurochemical classes of inhibitory neurons

Parvalbumin inhibitory neurons



Calbindin inhibitory neurons

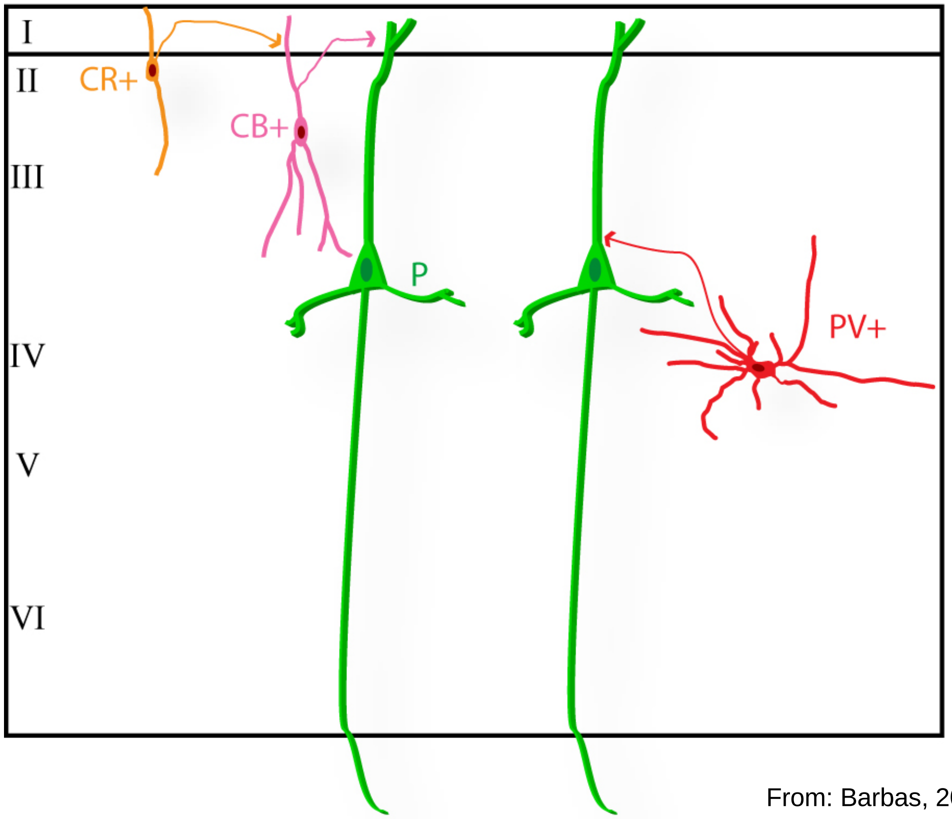


Parvalbumin positive neurons predominate in the middle cortical layers; they are basket or chandelier type inhibitory neurons, targeting the proximal dendrite or axon initial segment of other neurons.

Calbindin positive neurons predominate in the superficial cortical layers; they are double bouquet type inhibitory neurons, targeting the distal dendrite of other neurons.

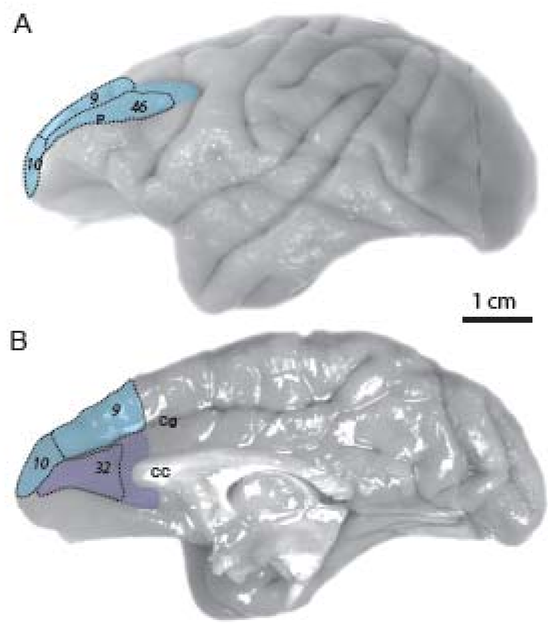
Images from: Barbas, Neural Systems Lab

Calretinin neurons inhibit
other inhibitory neurons
in the upper cortical layers



From: Barbas, 2011

Dorsolateral prefrontal areas: cognitive processes and working memory

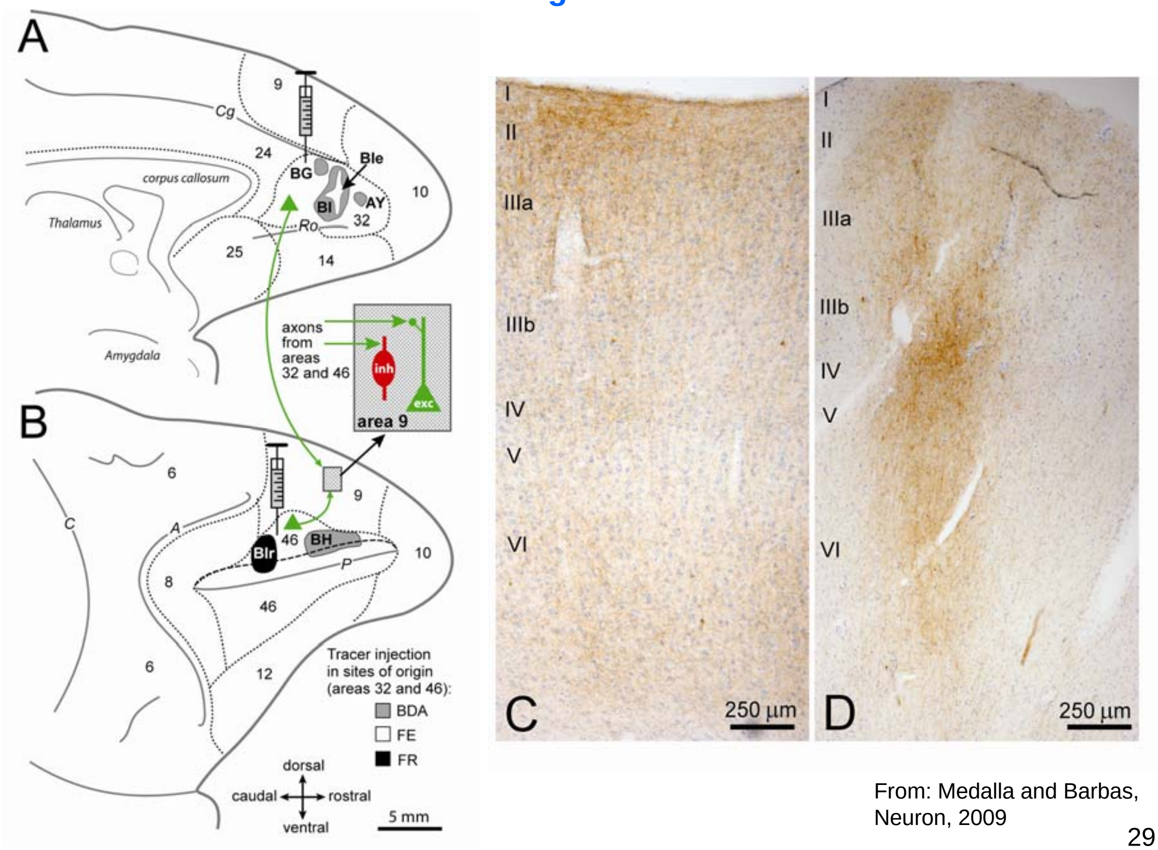


Adapted from: Medalla and Barbas, Neural Systems Lab

Anterior cingulate cortex (ACC): long term memory, emotions, and attentional regulation

ACC has the strongest connections within the prefrontal cortex

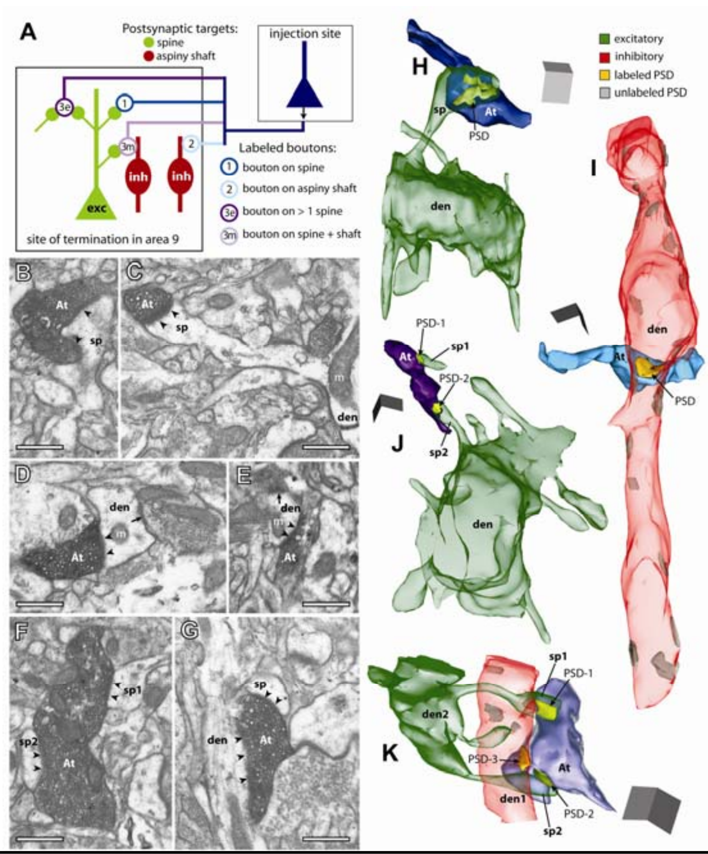
Synaptic interactions of auditory-related prefrontal areas associated with attention and cognitive control



From: Medalla and Barbas, Neuron, 2009

29

Interaction of prefrontal pathways at the synaptic level



From: Medalla and Barbas, Neuron, 2009

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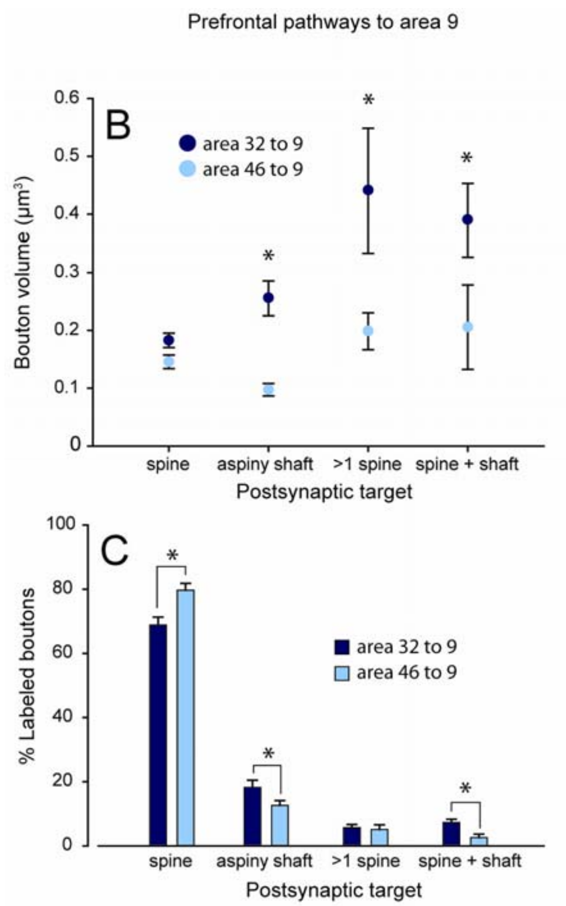
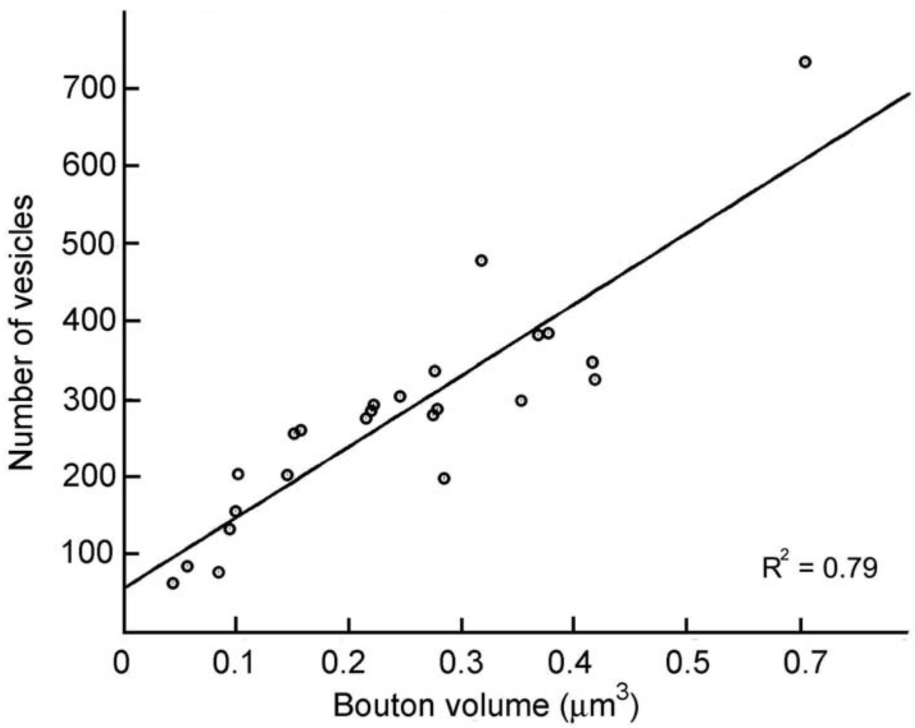


The ACC (area 32) targets more inhibitory sites in DLPFC (area 9), and the synapses are larger than the pathway linking two related areas (area 46 to 9).

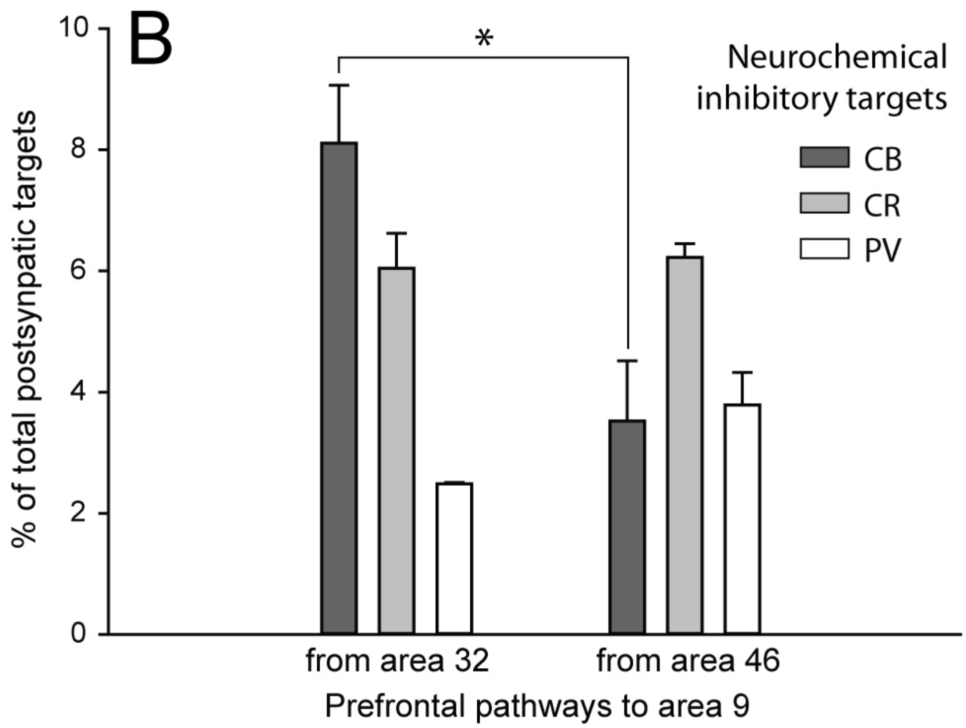
From: Medalla and Barbas, Neuron, 2009

Large boutons have more synaptic vesicles



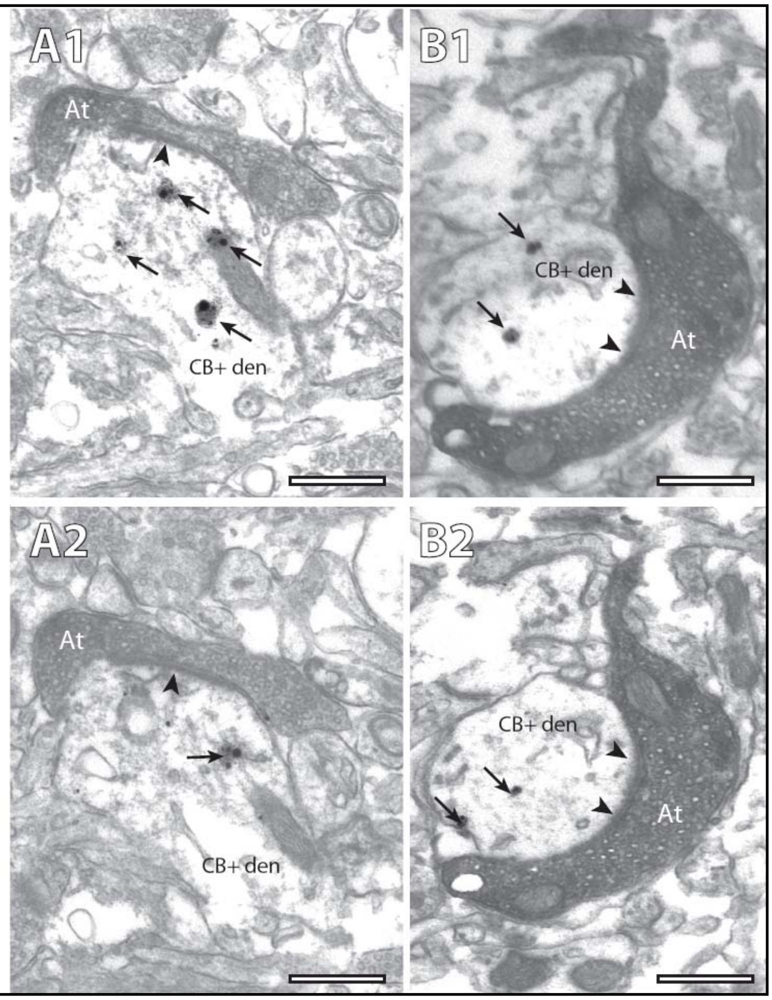
From: Germuska et al., 2006

The ACC targets preferentially CB inhibitory neurons, which are synaptically suited to reduce noise.



From: Medalla and Barbas, Neuron, 2009

- Large ACC boutons on inhibitory neurons in DLPFC
- Mainly target CB+ and CR+ inhibitory neurons



Adapted from: Medalla and Barbas, 2010

Use of principles from architecture and connections to model what may occur in disease:

Schizophrenia

Autism

Perspective on pathology from pathways:

Schizophrenia:
The roots of the disease are in development, affecting the delicate balance of neuronal migration, architecture and ultimately connections

Pathology in schizophrenia

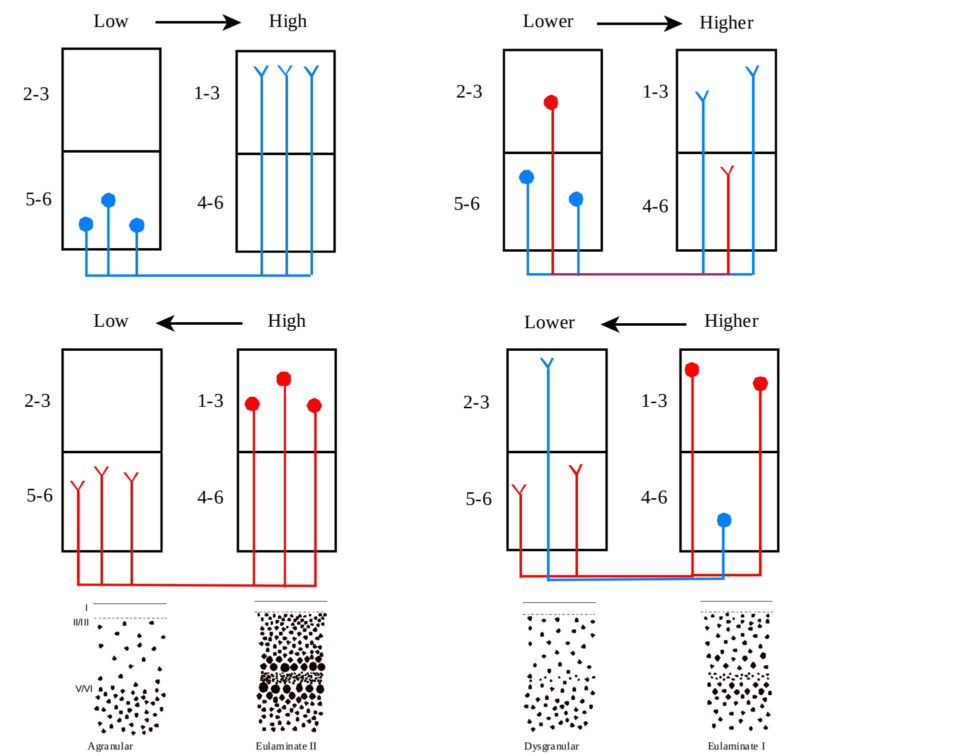
The number of pyramidal (excitatory) neurons is reduced in the deep layers of the anterior cingulate cortex (ACC) in schizophrenia (Benes et al., 2001).

ACC deep layers project to the upper layers of dorsolateral prefrontal cortex (DLPFC).

Linking cortical architecture to corticocortical connections

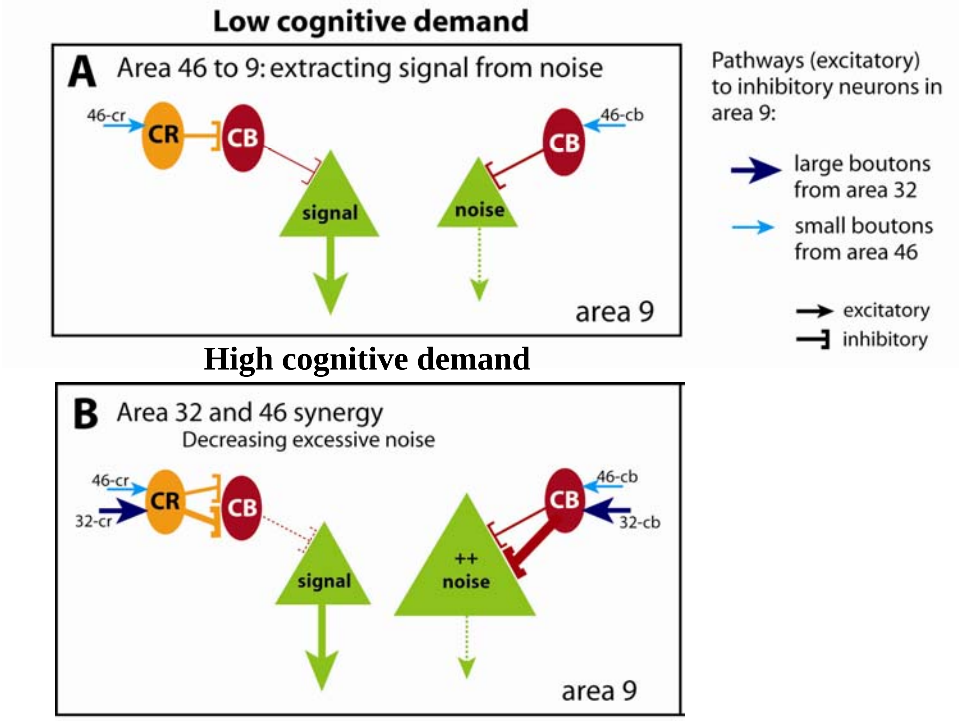
The structural model: Predicting the laminar pattern of connections from cortical structure

A. Large differences in laminar definition B. Moderate differences in laminar definition



Adapted from: Barbas and Rempel-Clower, 1997

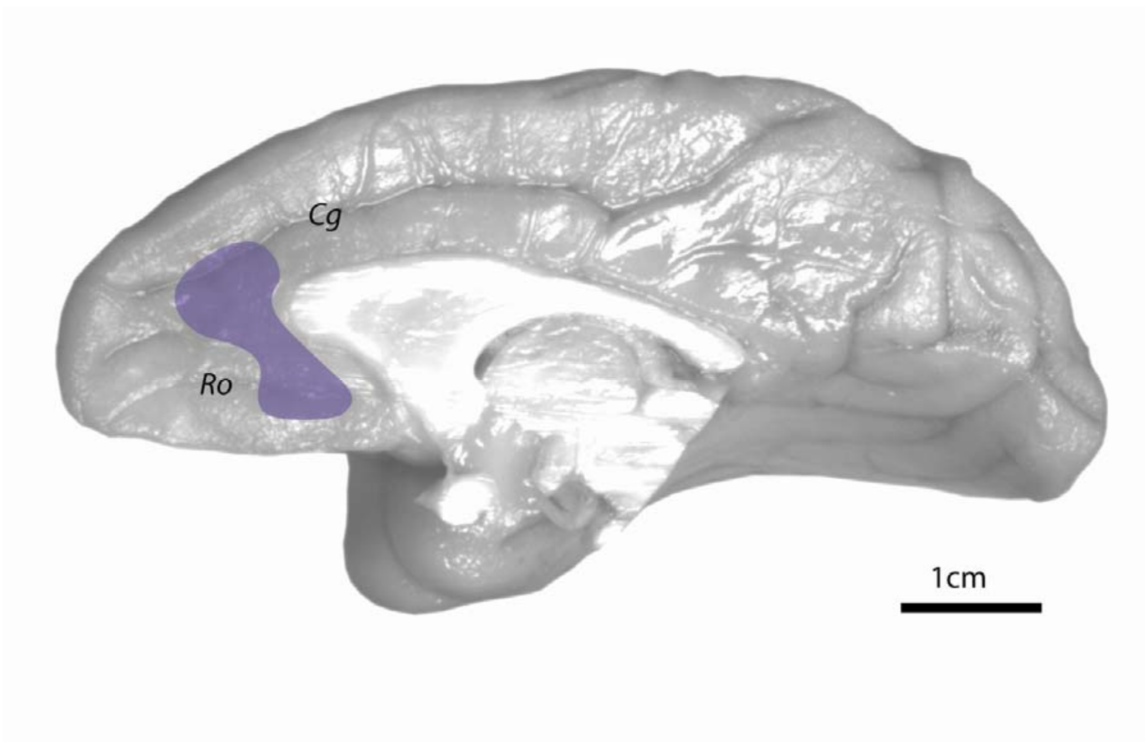
What does the circuitry from ACC (area 32) to DLPFC imply for schizophrenia?



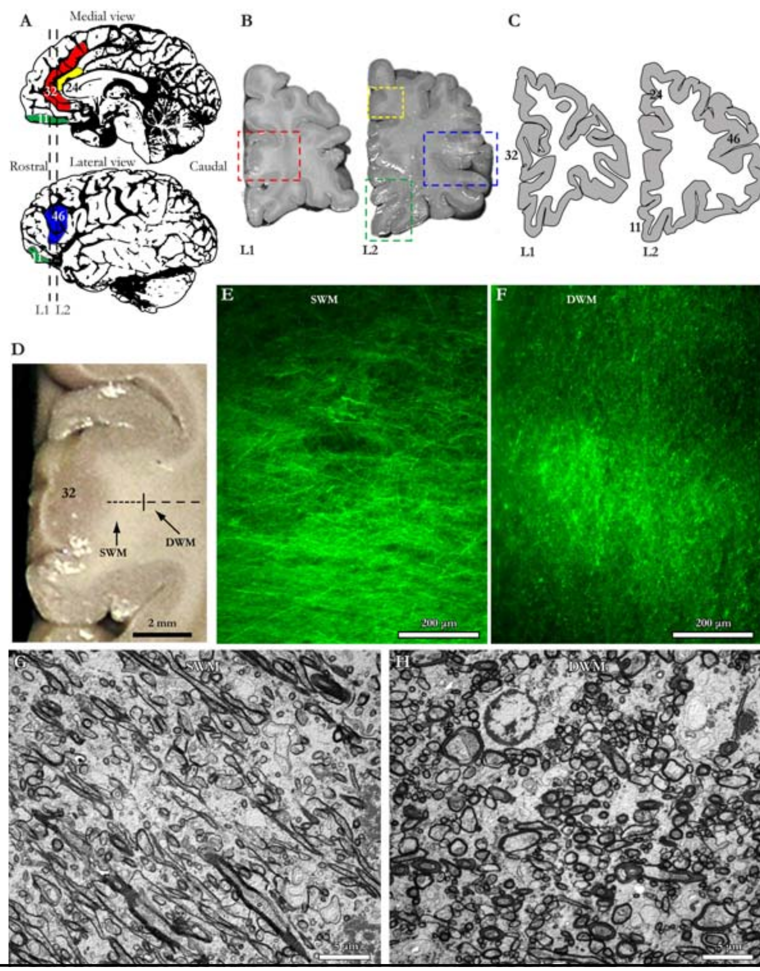
Adapted from: Medalla and Barbas, Neuron, 2009

Circuit Abnormalities in Autism: the White Matter

The white matter below the frontal lobe is enlarged in the brains of children with autism relative to controls.

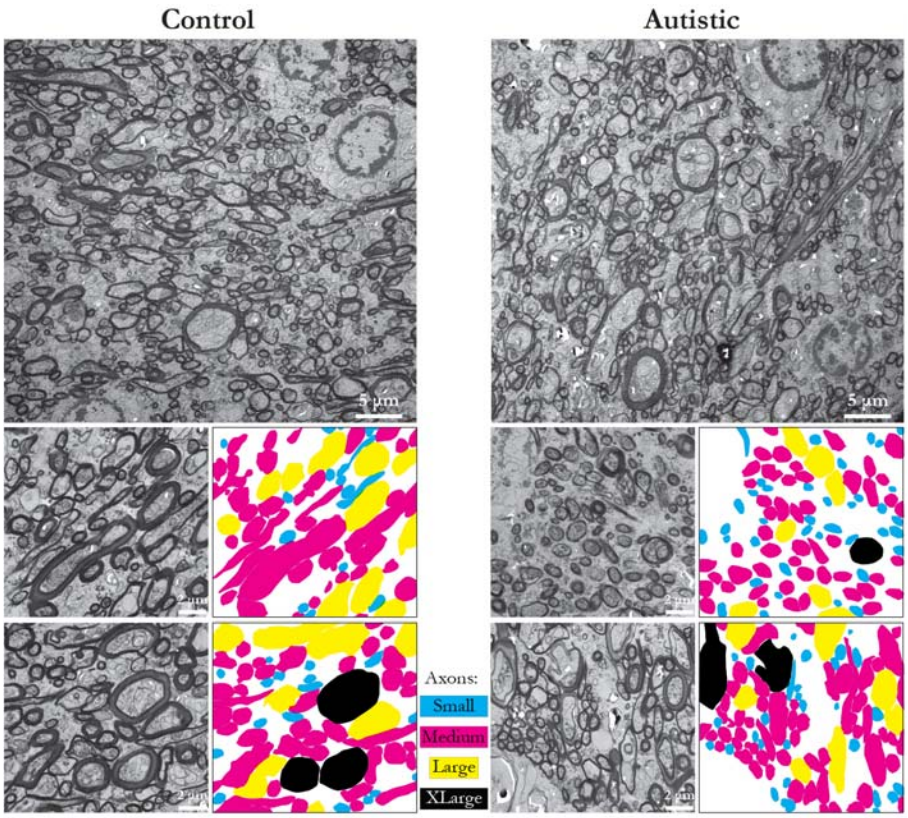


Adapted from: Barbas, 2011

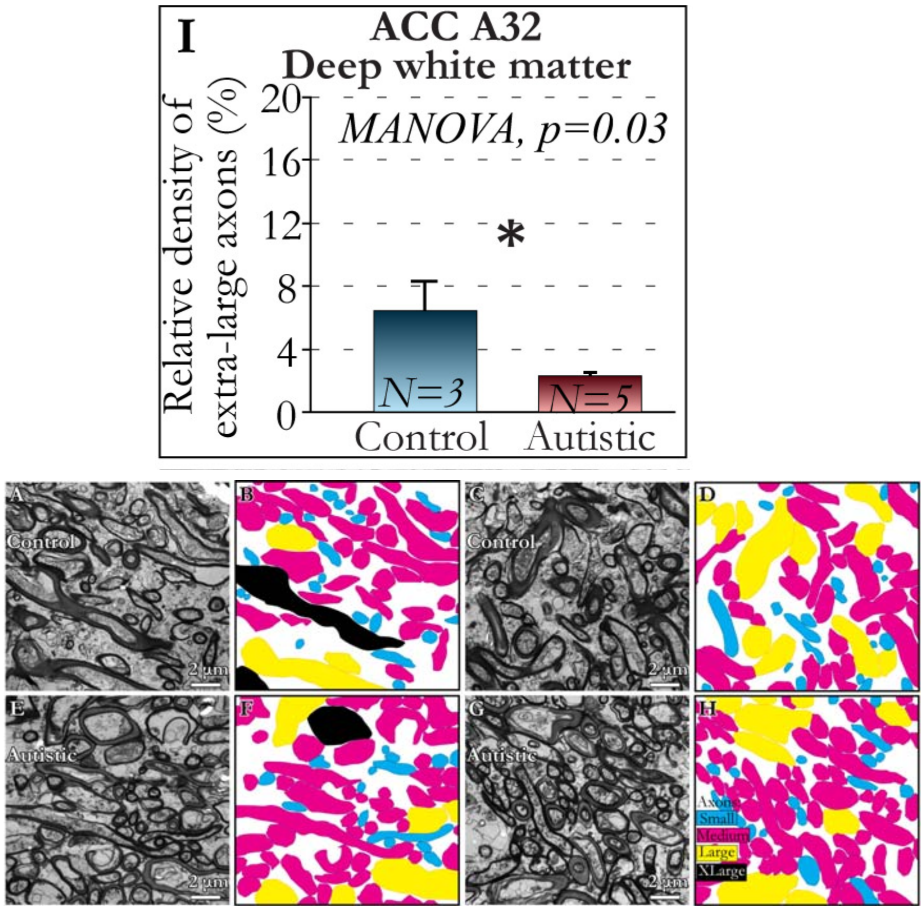


From: Zikopoulos and Barbas, 2010

Unsupervised cluster analysis showed 4 groups of axons

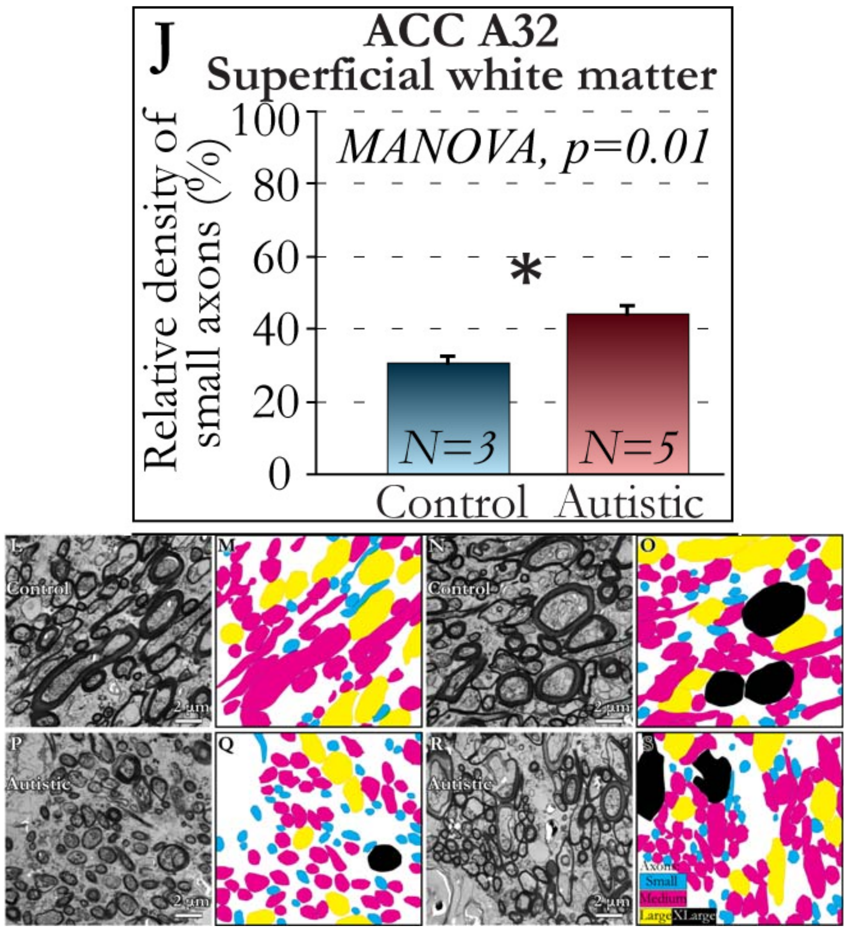


From Zikopoulos and Barbas, J. Neurosci., 2010



From Zikopoulos and Barbas, J. Neurosci., 2010

The autistic cases had fewer extra-large axons than normal controls



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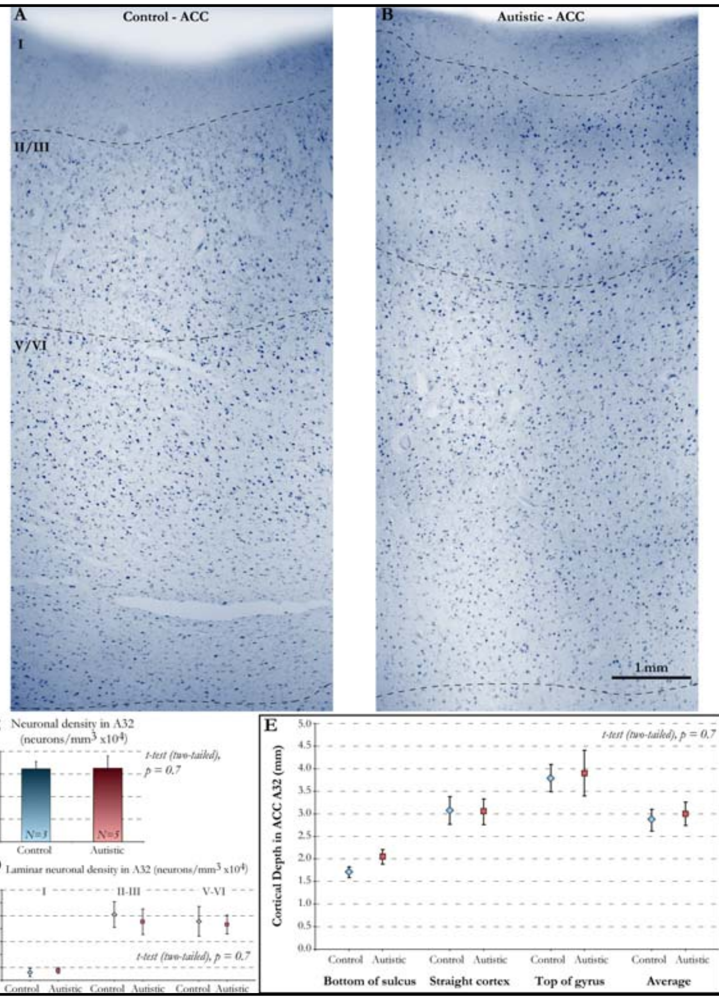

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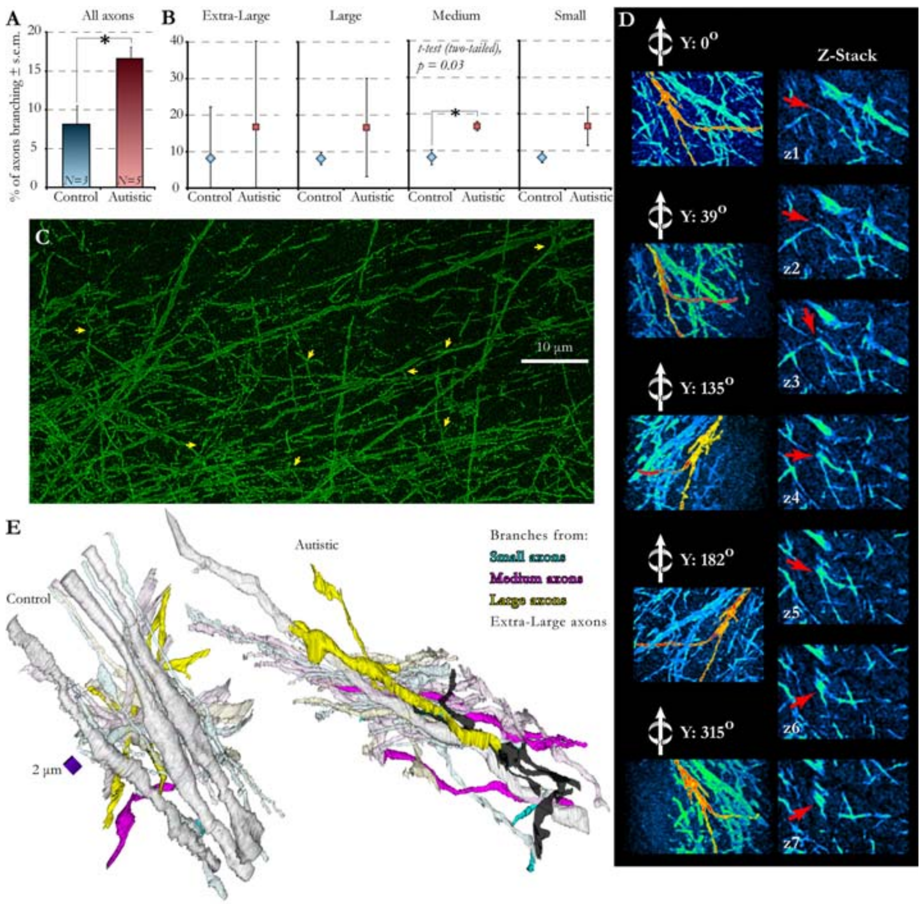

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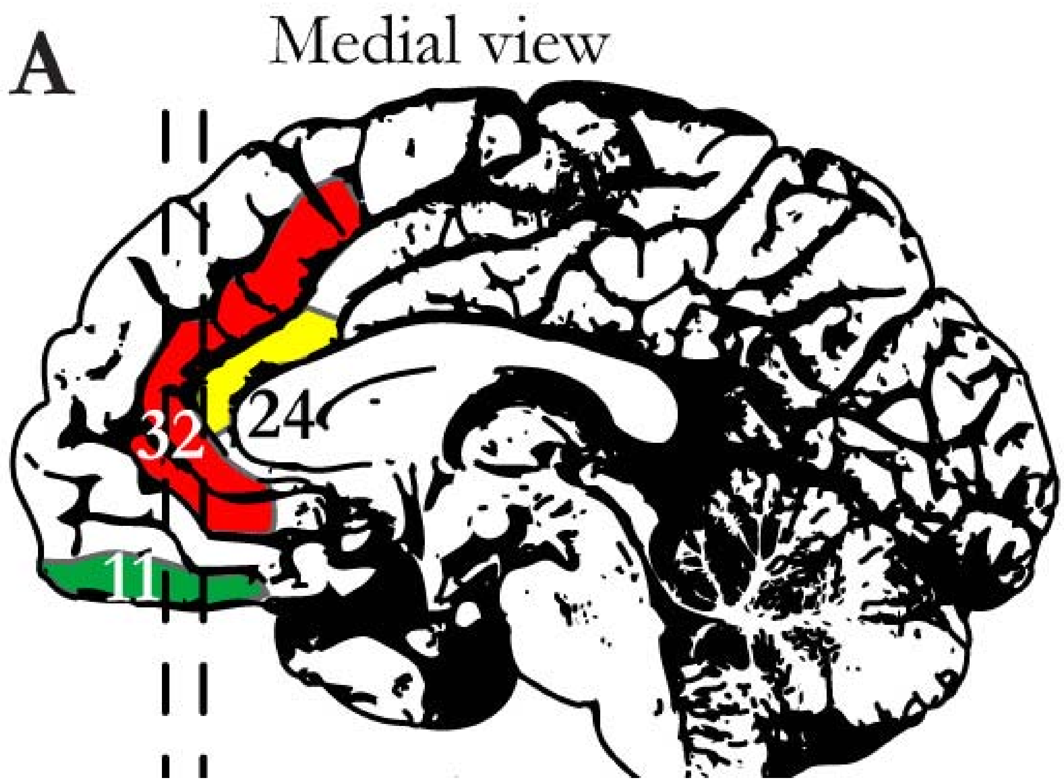
Barbas, J. Neurosci., 2010



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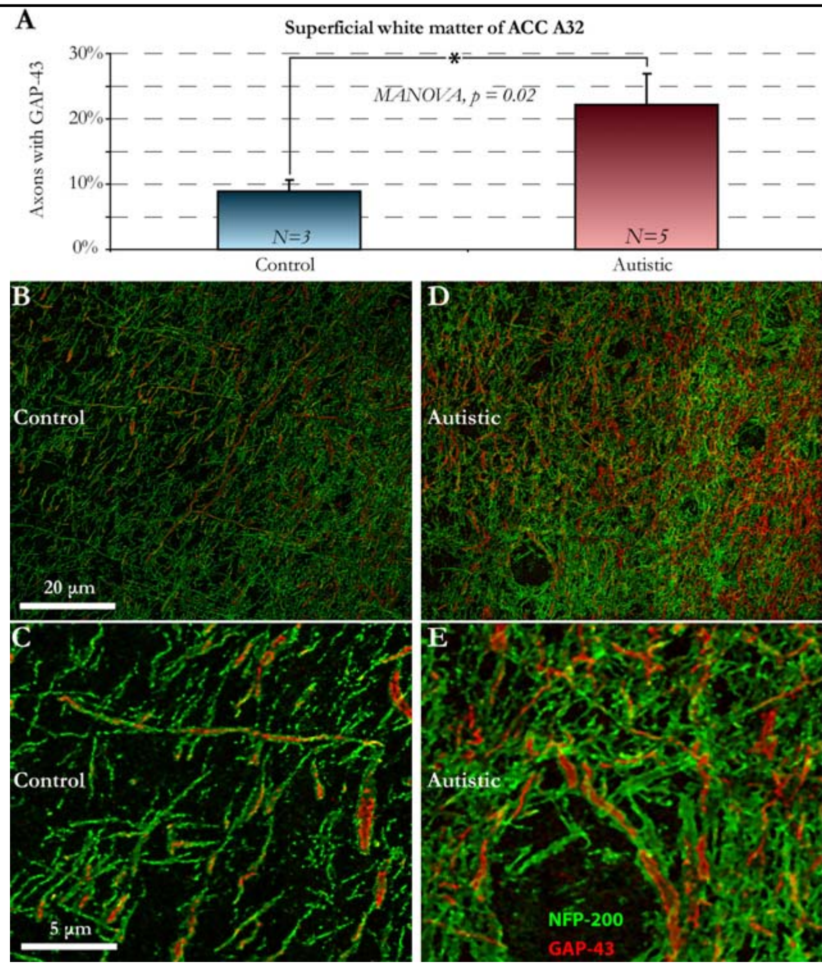

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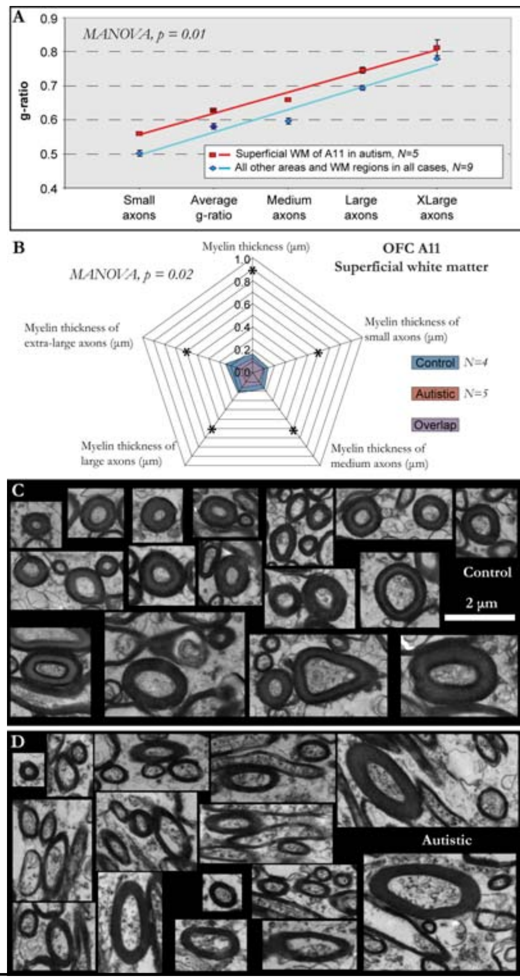

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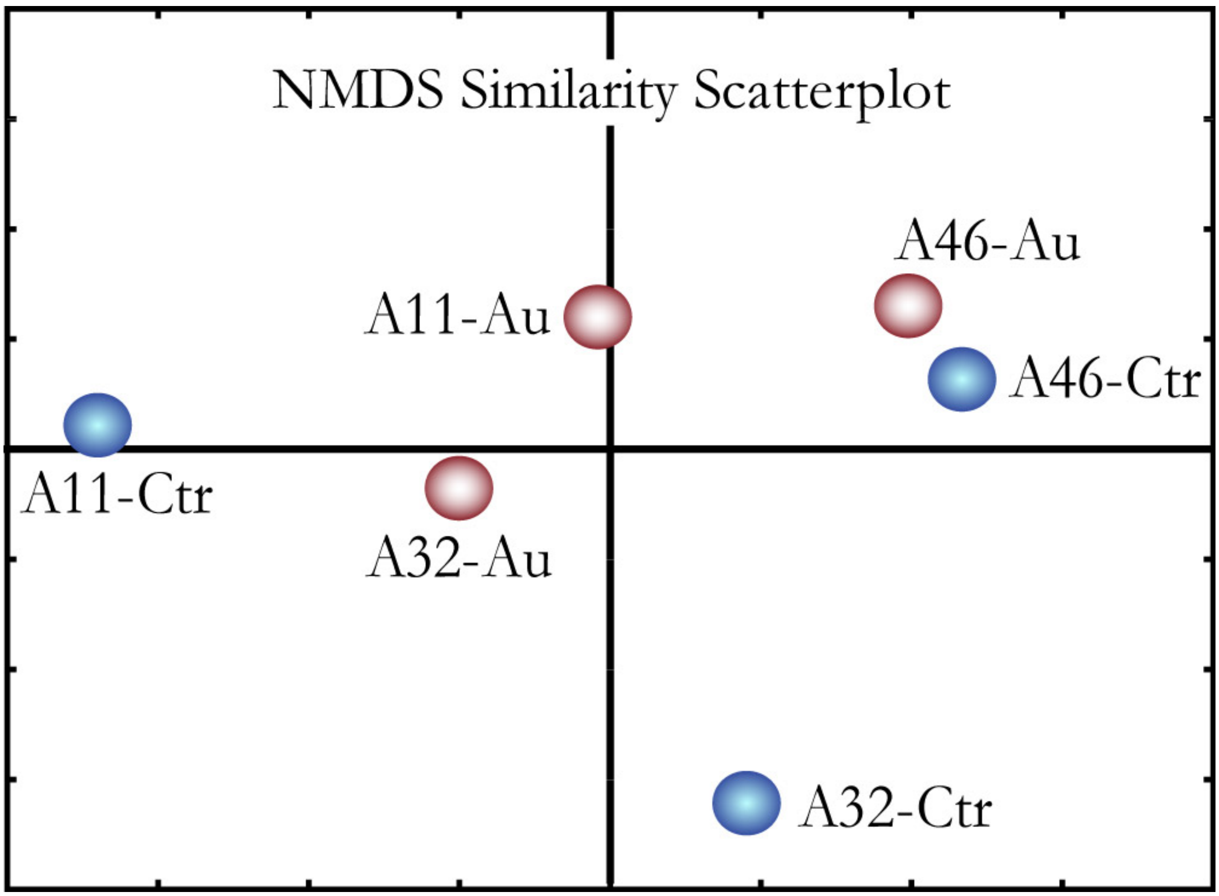
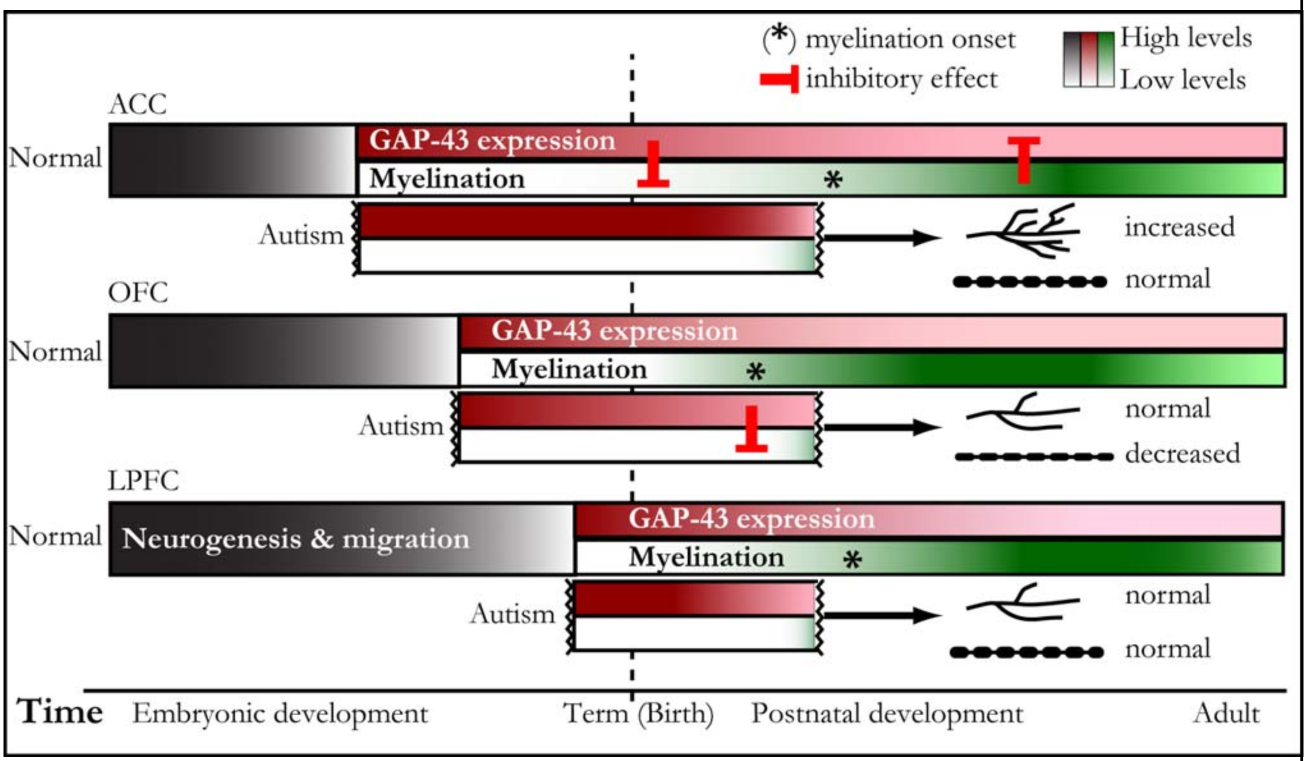


From Zikopoulos and Barbas, 2010

Are the abnormalities in the ACC and orbitofrontal cortex related?



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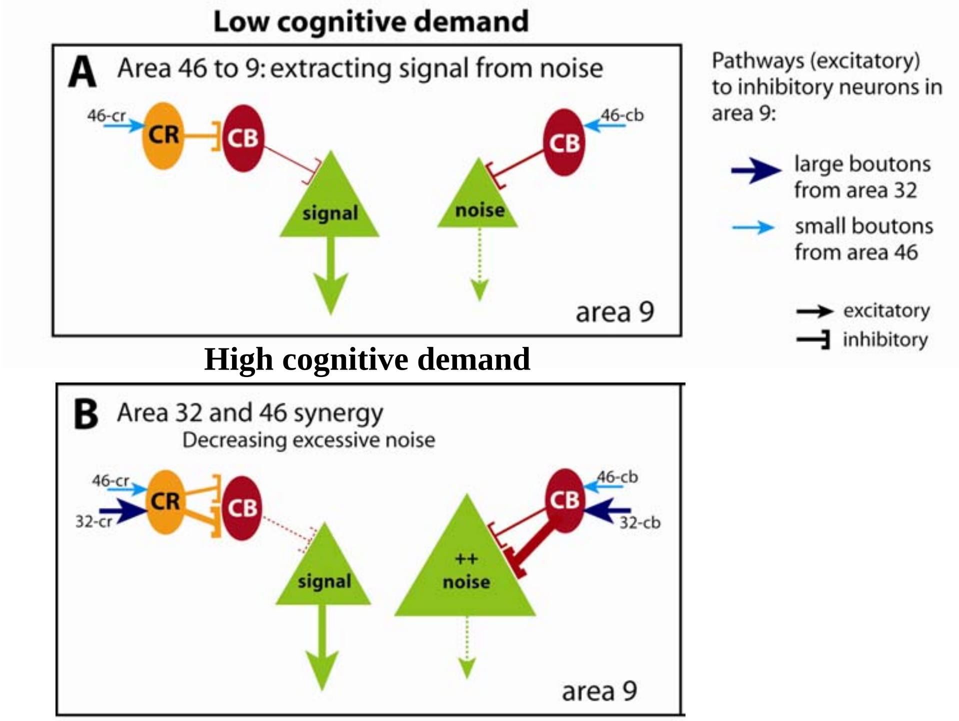
What does the circuitry from ACC (area 32) to DLPFC area 9 imply for autism?



Adapted from: Medalla and Barbas, Neuron, 2009

Superficial white matter: significantly more small axons in autistic cases. Small axons connect nearby areas.

Deep white matter: fewer extra large axons in autistic cases. Large axons connect distant areas.

These findings may help explain physiologic data indicating over-connectivity of nearby areas and long-distance under-connectivity in autism.

Summary:

Cortical structure varies quantitatively in a graded pattern in the mammalian cortex. Prefrontal pathways show specificity in their termination within cortical layers and in their relationship to neurochemically specific classes of inhibitory neurons.

Large terminals from ACC target mostly **inhibitory neurons** in DLPFC, which can suppress ‘noise’. This pathway may be disrupted in schizophrenia and autism.

In the brain of autistic adults, the deep white matter below ACC has fewer large axons that connect distant areas, the upper white matter has excessive number of thin axons that connect nearby areas, and the myelin is thinner below OFC.

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These changes may be explained by a common mechanism affecting axon growth and guidance and the expression of an axon growth protein during development and/or beyond.

Neural Systems Laboratory

http://www.bu.edu/neural/

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