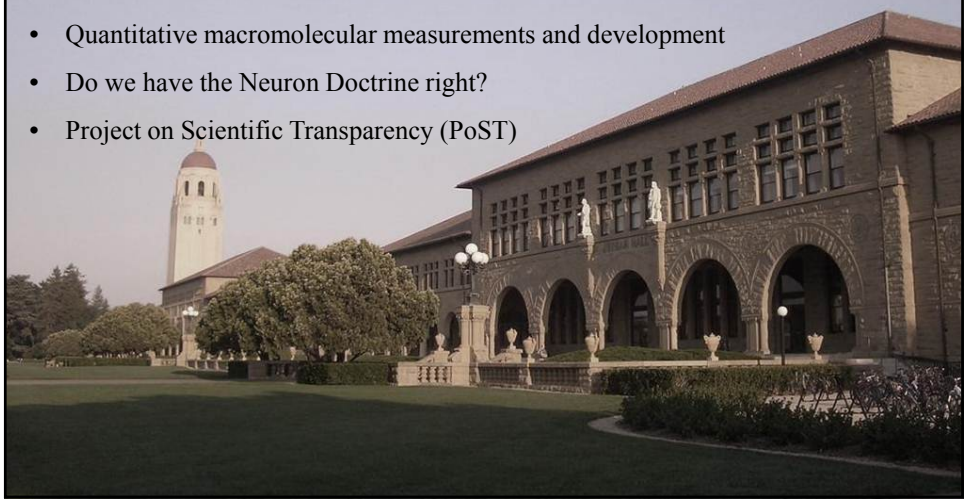
Neuroscience: An overview

- Human and model systems
- Quantitative diffusion measurements and behavior
- Quantitative macromolecular measurements and development
- Do we have the Neuron Doctrine right?
- Project on Scientific Transparency (PoST)



Model neuroscience systems

(from J. Horton)

Potential for molecular and pharmacological interventions

What we want to know

Human

Macaque

Mouse

Challenges to neuroscience model systems

Neurology®

Should clinicians care about preclinical animal research?

Shai D. Silberberg

Neurology 2013;80:1072
DOI 10.1212/WNL.0b013e3182886a51

British Medical Journal 2004

Where is the evidence that animal research benefits humans?

Pandora Pound, Shah Ebrahim, Peter Sandercock, Michael B Bracken, Ian Roberts on behalf of the Reviewing Animal Trials Systematically (RATS) Group

Much animal research into potential treatments for humans is wasted because it is poorly conducted and not evaluated through systematic reviews

Challenges to neuroscience model systems

Cell, Nature, Science, Nature Medicine, ...

Median citation 889, range 639-2233,

(Reprinted) JAMA, October 11, 2006—Vol 296, No. 14 **1731**

RESEARCH LETTER

Translation of Research Evidence From Animals to Humans

To the Editor: Most medical therapies in use today were initially developed and tested in animals,[1] yet animal experiments often fail to replicate when tested in rigorous human trials.[2,3] We conducted a systematic review to determine

Comment. Only about a third of highly cited animal research translated at the level of human randomized trials. This rate of translation is lower than the recently estimated 44% replication rate for highly cited human studies.[4] Limitations of this review include a focus on highly cited animal studies published in leading journals, which by their positive and highly visible nature may have been more likely to translate than less frequently cited research. In addition, this study had limited power to discern individual predictors of translation.

Genomics, too

Genomic responses in mouse models poorly mimic human inflammatory diseases

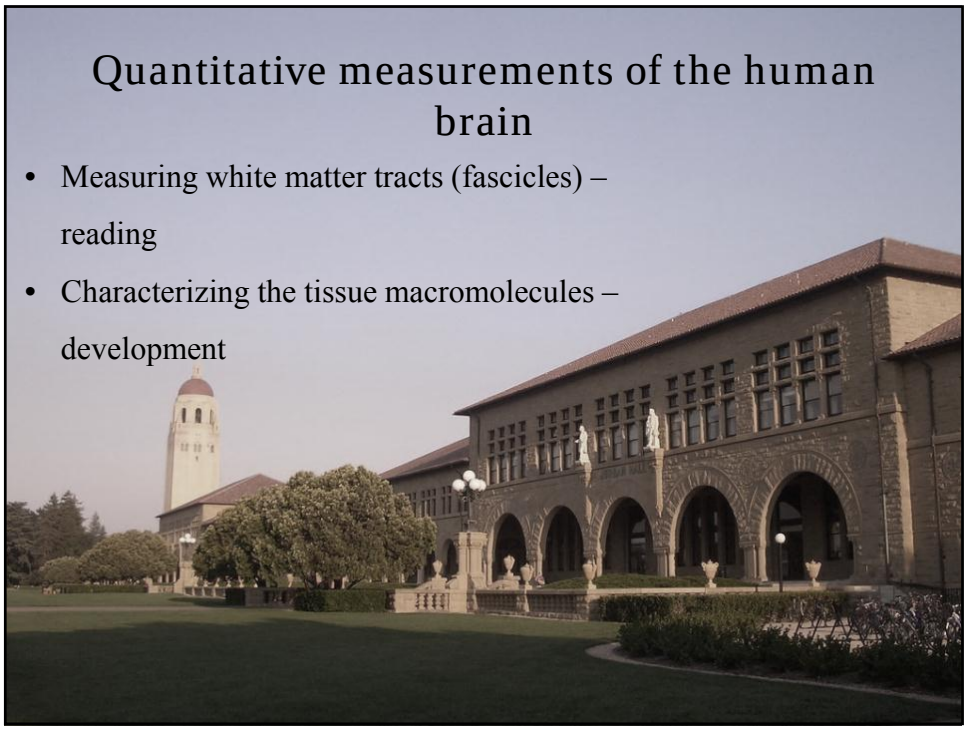
Junhee Seok[a,1], H. Shaw Warren[b,1], Alex G. Cuenca[c,1], Michael N. Mindrinos[a], Henry V. Baker[c], Weihong Xu[a], Daniel R. Richards[d], Grace P. McDonald-Smith[e], Hong Gao[a], Laura Hennessy[f], Celeste C. Finnerty[g], Cecilia M. López[c], Shari Honari[f], Ernest E. Moore[h], Joseph P. Minei[i], Joseph Cuschieri[j], Paul E. Bankey[k], Jeffrey L. Johnson[h], Jason Sperry[l], Avery B. Nathens[m], Timothy R. Billiar[j], Michael A. West[n], Marc G. Jeschke[o], Matthew B. Klein[j], Richard L. Gamelli[p], Nicole S. Gibran[j], Bernard H. Brownstein[q], Carol Miller-Graziano[k], Steve E. Calvano[r], Philip H. Mason[e], J. Perren Cobb[s], Laurence G. Rahme[t], Stephen F. Lowry[r,2], Ronald V. Maier[j], Lyle L. Moldawer[c], David N. Herndon[g], Ronald W. Davis[a,3], Wenzhong Xiao[a,t,3], Ronald G. Tompkins[t,3], and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program[4]

[a]Stanford Genome Technology Center, Stanford University, Palo Alto, CA 94305; Departments of [b]Pediatrics and Medicine, [s]Anesthesiology and Critical Care Medicine, and [t]Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114; [c]Department of Surgery, University of Florida College of Medicine, Gainesville, FL 32610; [d]Ingenuity Inc., Redwood City, CA 94063; [e]Department of Surgery, Massachusetts General Hospital, Boston, MA 02114; [f]Department of Surgery, Harborview Medical Center, Seattle, WA 98195; [g]Shriners Hospitals for Children and Department of Surgery, University of Texas Medical Branch, Galveston, TX 77550-1220; [h]Department of Surgery, University of Colorado Anschutz Medical Campus, Denver, CO 80045; [i]Department of Surgery, Parkland Memorial Hospital, University of Texas, Southwestern Medical Center, Dallas, TX 75390; [j]Department of Surgery, Harborview Medical Center, University of Washington School of Medicine, Seattle, WA 98195; [k]Department of Surgery, University of Rochester School of Medicine, Rochester, NY 14642; [l]Department of Surgery, University of Pittsburgh Medical Center Presbyterian University Hospital, University of Pittsburgh, PA 15213; [m]Department of Surgery, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada M5B 1W8; [n]Department of Surgery, San Francisco General Hospital, University of California, San Francisco, CA 94143; [o]Division of Plastic and Reconstructive Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada M4N 3M5; [p]Department of Surgery, Stritch School of Medicine, Loyola University, Chicago, IL 60153; [q]Department of Anesthesiology, Washington University, School of Medicine, St. Louis, MO 63110; and [r]Department of Surgery, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ 08903

Contributed by Ronald W. Davis, January 7, 2013 (sent for review December 6, 2012)

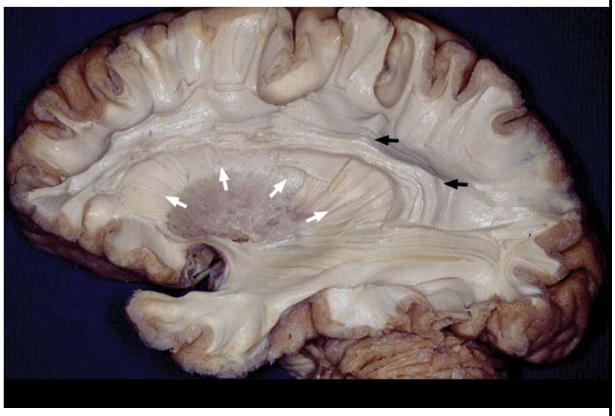
Quantitative measurements of the human brain

- Measuring white matter tracts (fascicles) – reading
- Characterizing the tissue macromolecules – development



Human fascicles (tracts)

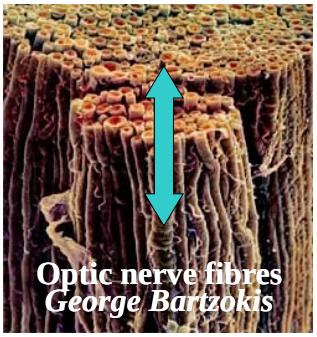
- There are many long-range connections
- These connections are not passive – they change their properties in response to use
- A system with active wires

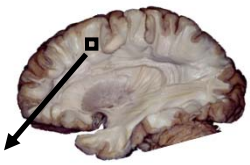


Courtesy Professor Ugur Ture

Diffusion probes brain microscopic structure

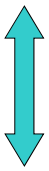
Along the axon, within the cytoskeleton, water diffuses easily; the **Apparent Diffusion Coefficient (ADC)** is relatively large

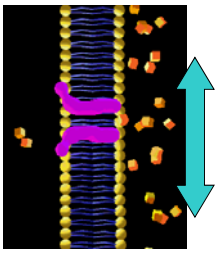




5 um

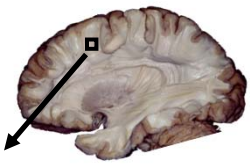
Longitudinal diffusivity ($\mu m^2/ms$)





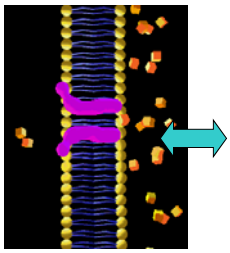
Diffusion probes brain microscopic structure

Bi-lipid cell membranes limit diffusion. Hence, perpendicular to axons the **ADC** is relatively small



5 um

Radial Diffusivity ($\mu m^2/ms$)

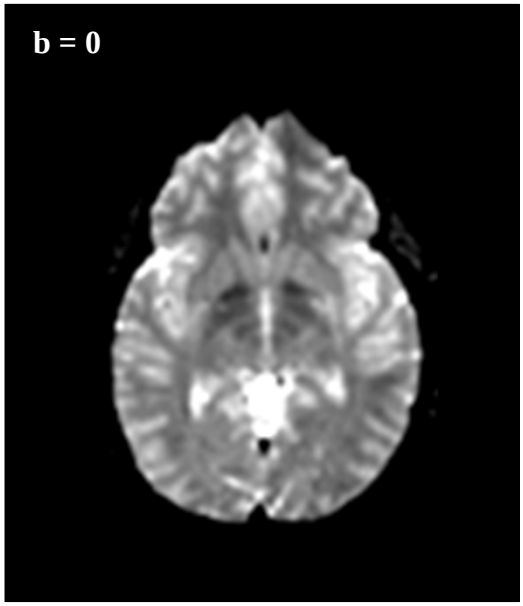


Raw Diffusion MR Images

Dark means:
Low signal
High ADC

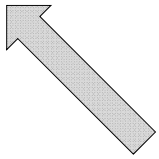
The diffusion signal in a direction, θ, is related to the apparent diffusion coefficient in that direction, A(θ), by

$$S(\theta) = S_0 \, e^{-bA(\theta)}$$

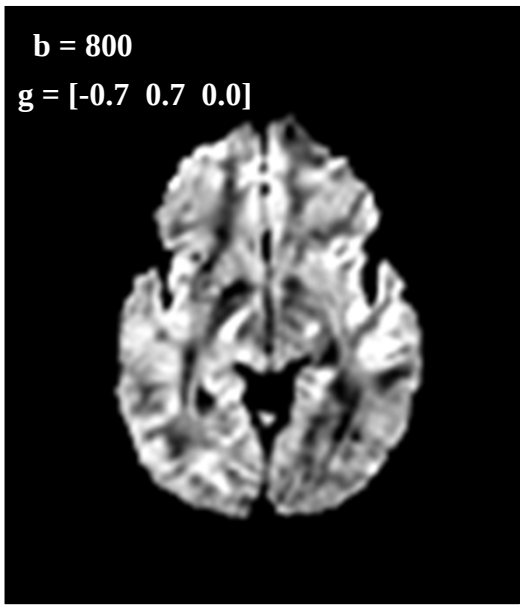


Diffusion weighted images

Dark means:
Low signal
High ADC

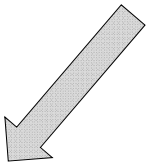


$$S(\theta) = S_0 \, \mathrm{e}^{-bA(\theta)}$$

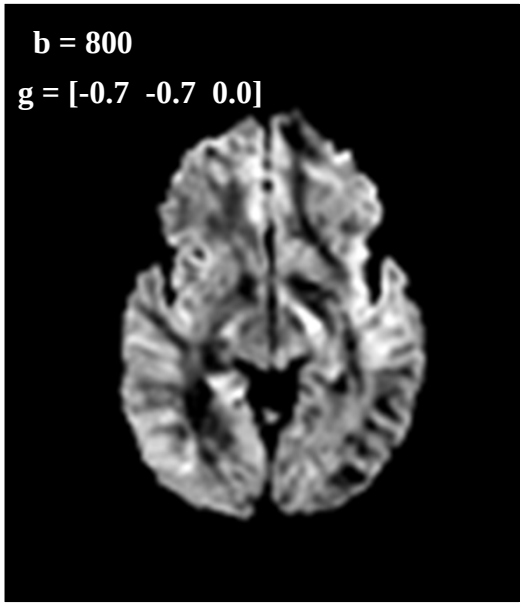


Diffusion weighted images

Dark means:
Low signal
High ADC

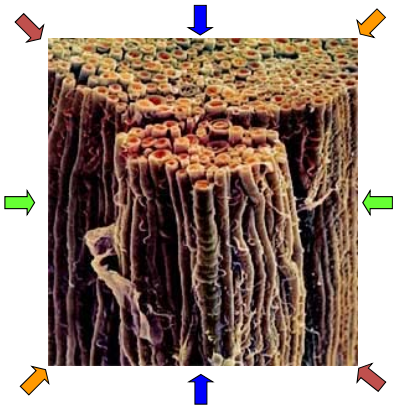


$$S(\theta) = S_0 \, \mathrm{e}^{-bA(\theta)}$$



Diffusion Tensor Imaging (DTI)
A summary of the ADC at low b-values

5 um



$1 = v' Q^{-1} v,$

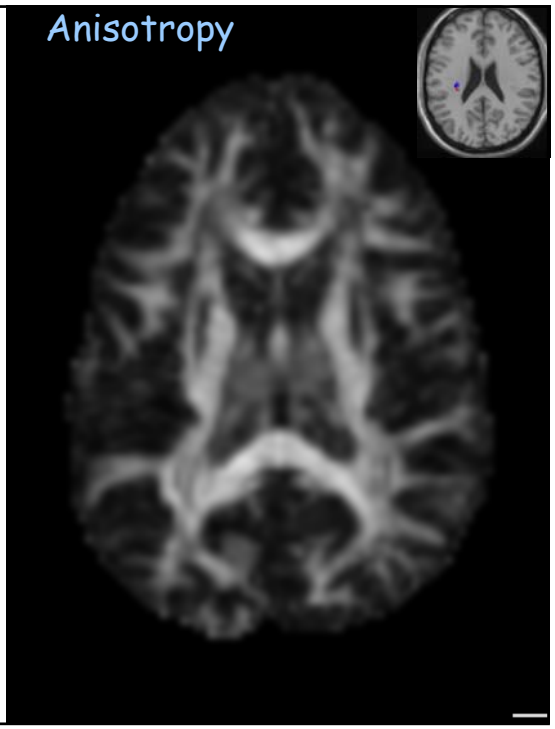
v is a 3d-vector

The **mean** distance a typical water molecule will diffuse in a unit of time

$A = u' Q u$

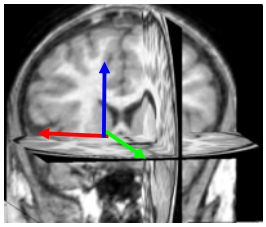
DTI summary measures of white matter microstructure

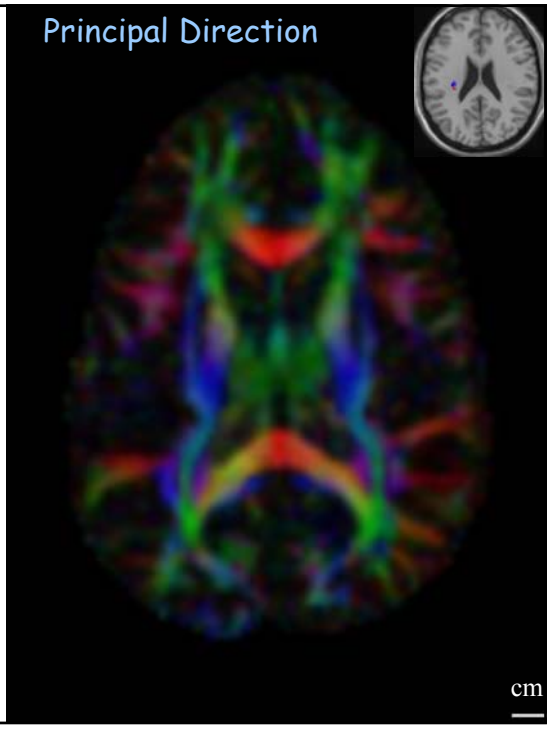
Fractional anisotropy



DTI summary measures of white matter microstructure

Principal diffusion direction

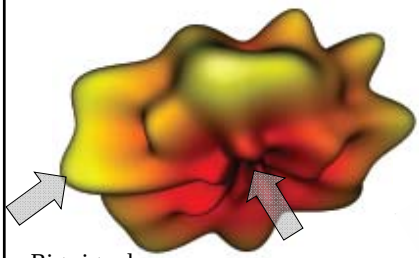




Diffusion data analysis

High angular resolution diffusion imaging (HARDI)

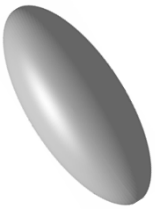
MRI diffusion signal



Big signal, small ADC

Small signal, large ADC

$$S(\theta) = S_0 \, e^{-bA(\theta)}$$

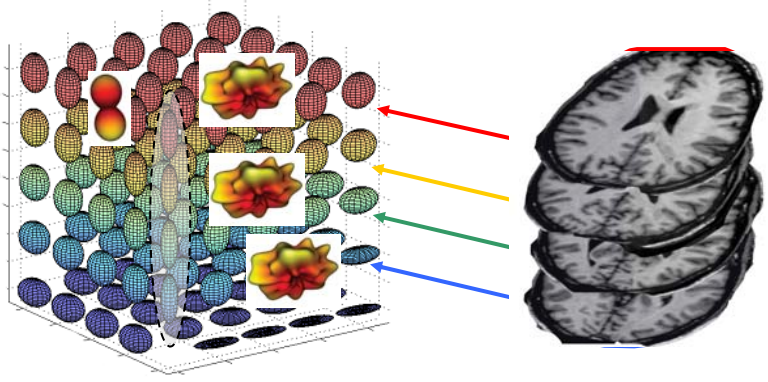


Diffusion distance, monotonic with ADC

Tractography

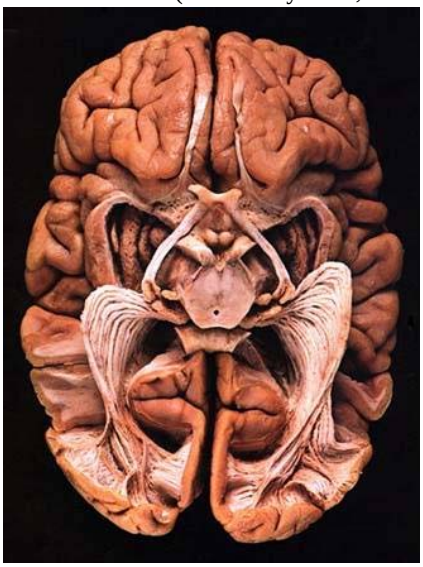
Use the local (voxel) diffusion data to estimate known fascicles and identify new fascicles – living human brain

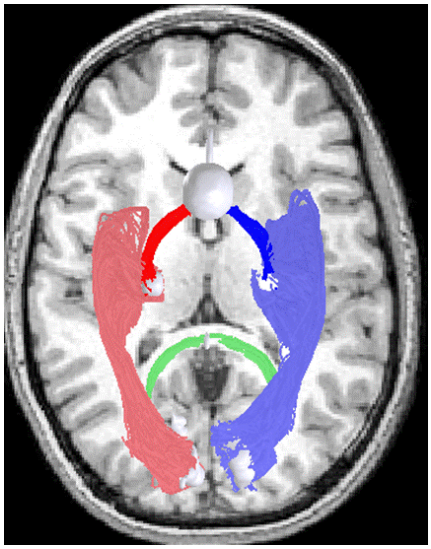
Diffusion data are surfaces



Estimating pathways of known tracts (Contrack)

(Sherbondy et al., 2008; N. Levin, et al., Neuron, 2010)

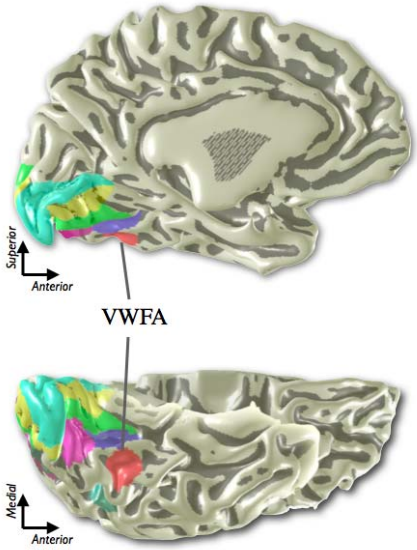


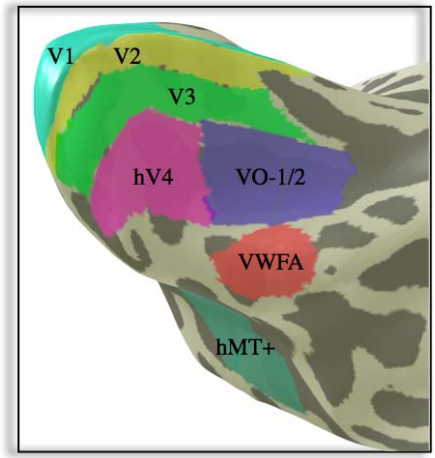


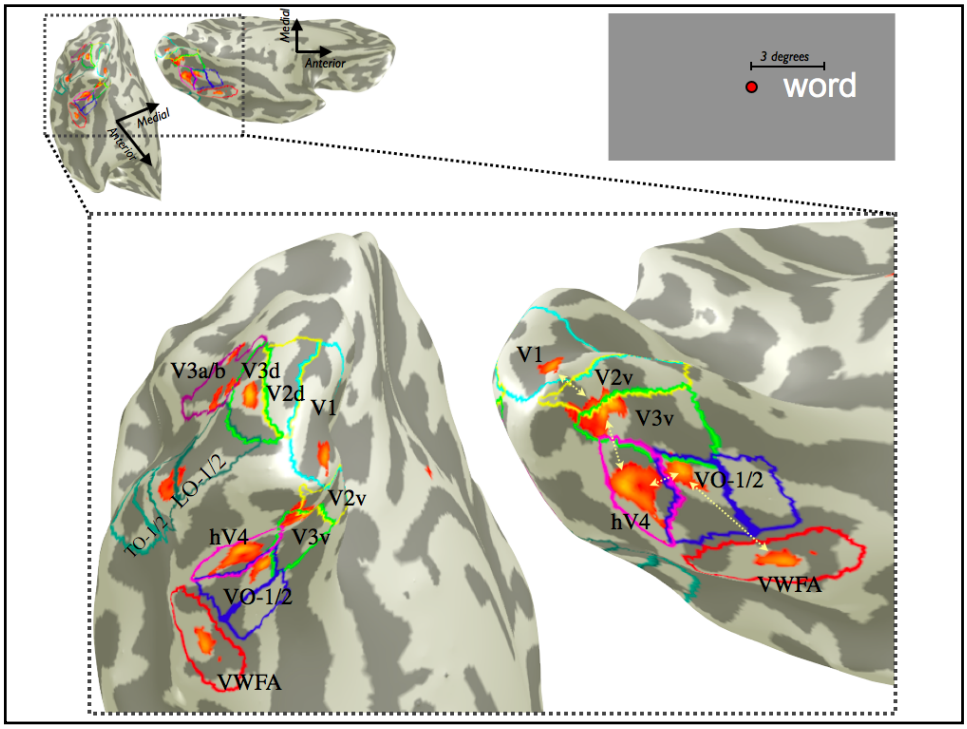
Cellular changes that matter for thought: tracking down reading

Functional and tract-based measures of the reading circuitry in the developing child's brain

Locating reading circuits and maps

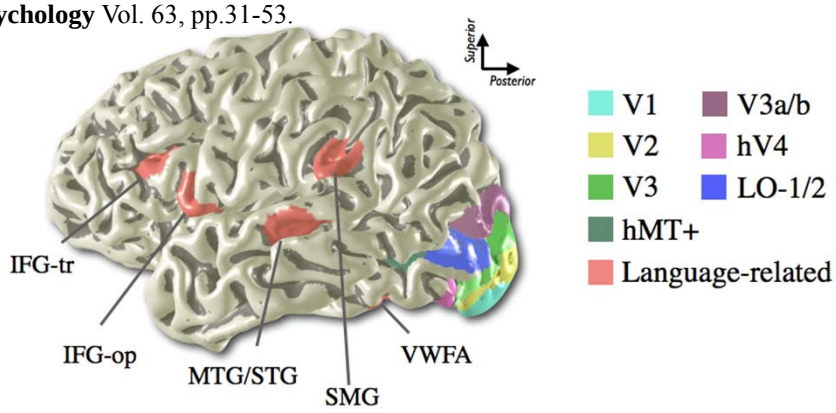






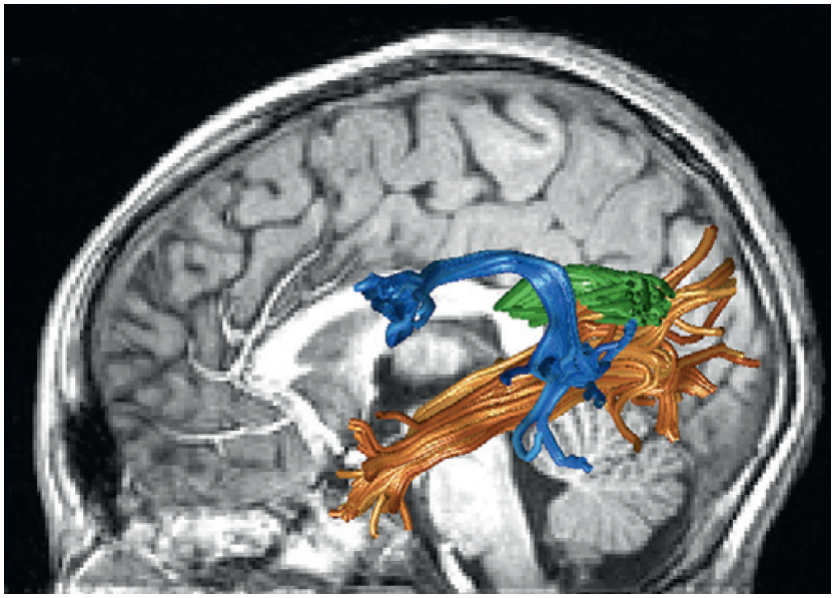
The cortical reading network

Learning to See Words
B.A. Wandell, A. Rauschecker
and J. Yeatman (2012).
Annual Review of
Psychology Vol. 63, pp.31-53.



White matter reading tracts

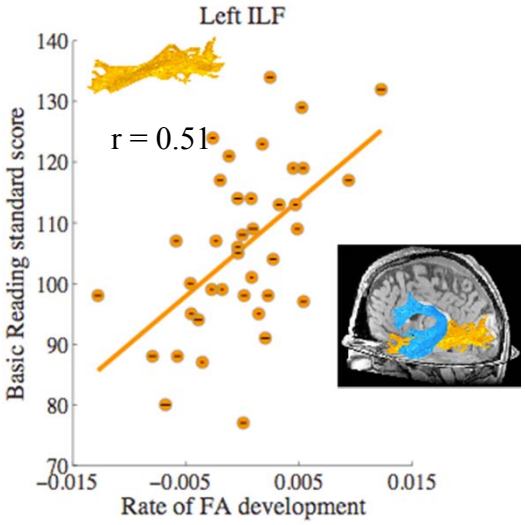
(Wandell and Yeatman, 2013)



Strong associations between tract FA development and reading

(Yeatman et al., 2012)

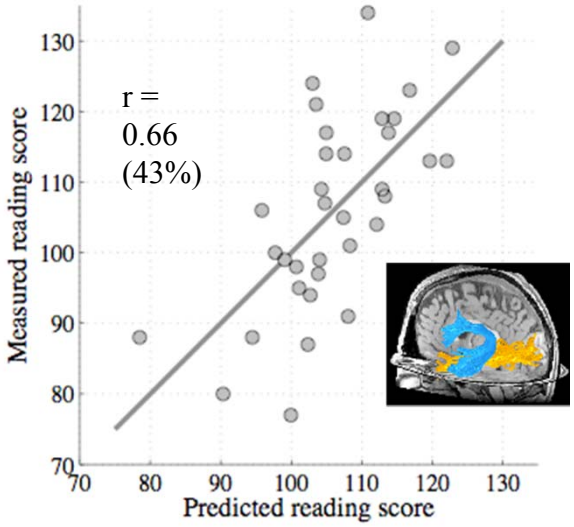
- Diffusion development within certain tracts, but not others, correlates with the ability to see words
- This is one reason we think that the wires are active, changing in response to learning and memory



Predicting reading scores from white matter maturity

(Yeatman et al., 2012)

- With even very simple models we can make predictions of reading skill from diffusion
- The predictions are not yet useful, but they are statistically significant



Brief introduction to MR signals

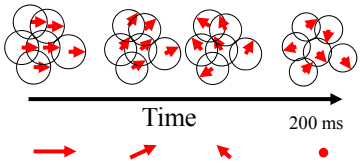
Spin-lattice interactions (T1)
A few facts

There are two MR relaxation mechanisms

High energy

Low energy

Anti-parallel gives up energy to lattice and returns to lower energy parallel state (T1)



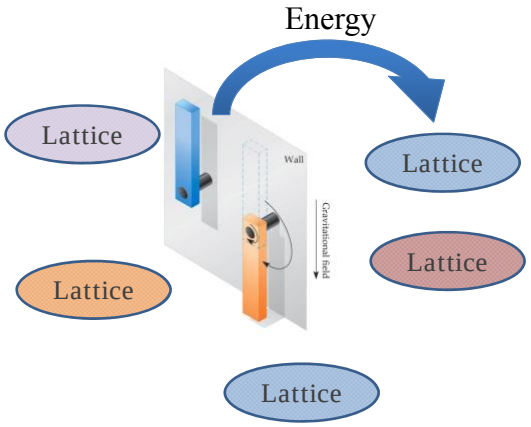
The spins dephase (T2)

Analyzing spin-lattice exchange (T1)

Energy from anti-parallel spins is absorbed by the macromolecules in the environment (lattice)

How efficient is this energy exchange?

I am glad you asked.

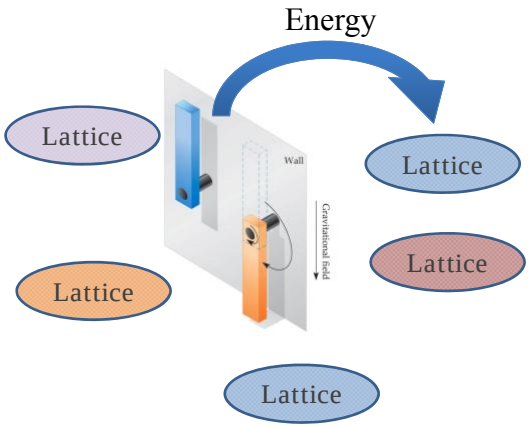


Analyzing spin-lattice exchange (T1)

Spin-lattice energy exchange rate (T1) depends on

- How much material is present
- The type of material

If you could measure this in the brain, these are pretty good things to know (noninvasively)

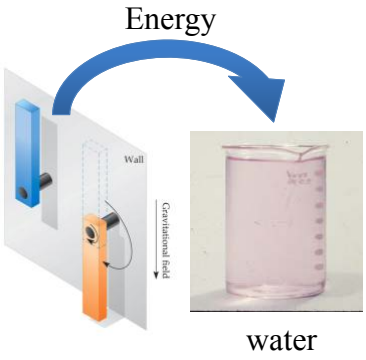


Analyzing spin-lattice exchange (T1)

Suppose the only nearby material is water.

There are two interesting properties

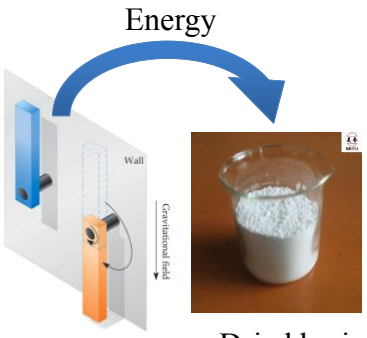
- T1 is the same for all magnetic field strengths
- T1 is 4.5 s (body temp)



Analyzing spin-lattice exchange (T1)

Suppose the only nearby material is dried brain

- T1 varies with magnetic field strength
- T1 is much shorter than 4.5 s
- The T1 also depends on the stuff in the dried brain

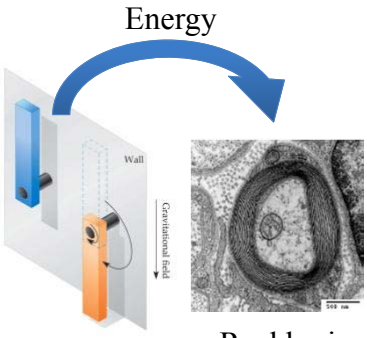


Dried brain

Analyzing spin-lattice exchange (T1)

Real brain is a mixture of water and dried brain. We want to know

- How much stuff is present in each voxel?
- What type of material is it, in the sense of how efficiently does this material exchange energy with the water protons?

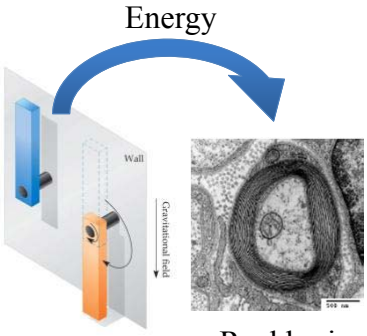


Real brain

Analyzing spin-lattice exchange (T1)

We use MR to quantify how much and type

- How much– The volume of each voxel that is NOT water is the Macromolecular Tissue Volume (MTV)
- The type – How many protons were exchanged with the lattice per second per unit stuff? We call this number the Surface Interaction Rate (SIR)



Real brain

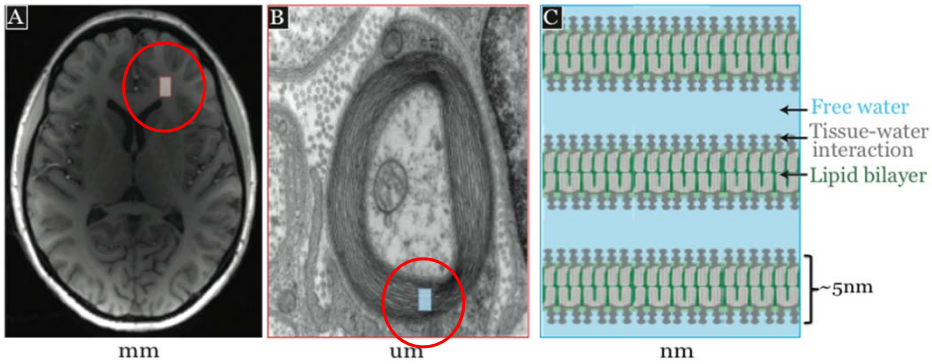
Quantitative MRI of human tissue development

(Mezer et al., Nature Medicine, in press)

Macromolecular tissue volume (MTV)

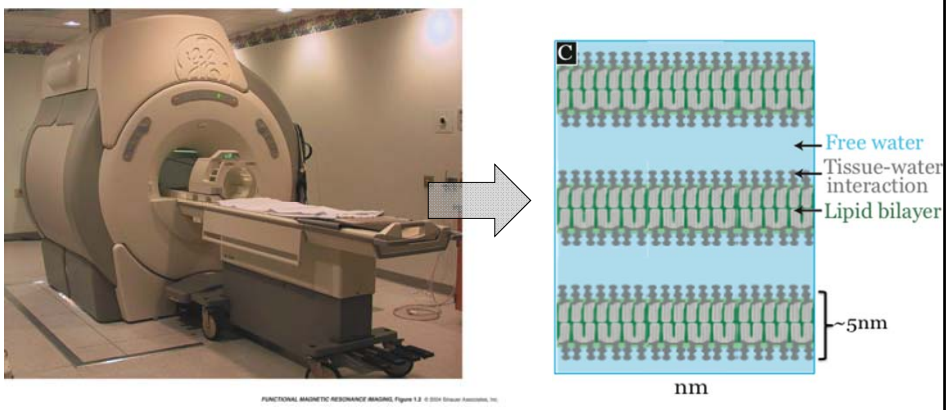
Surface interaction rate (SIR)

Human brain processes can be analyzed at many different length scales



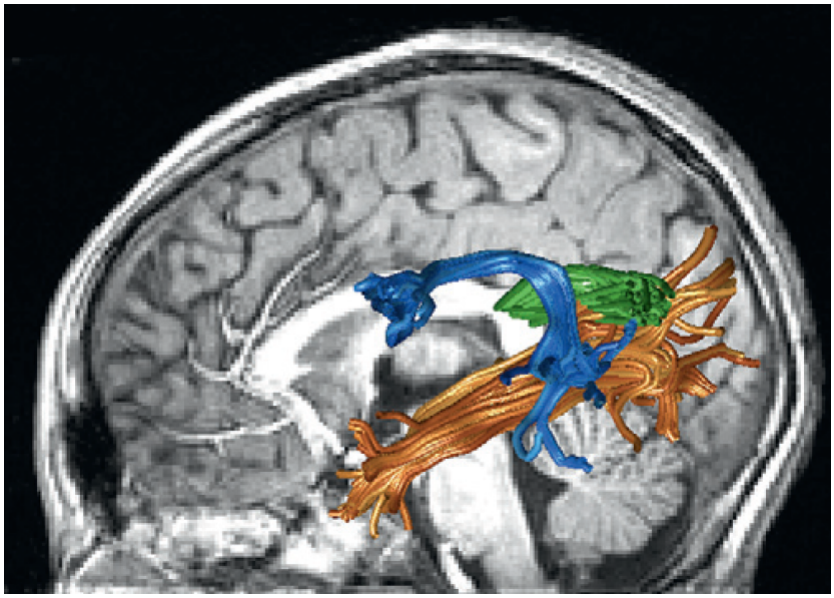
MR measures interactions between water and brain molecules at the nanometer scale

Mezer et al., Nature Medicine (in press)



White matter reading tracts

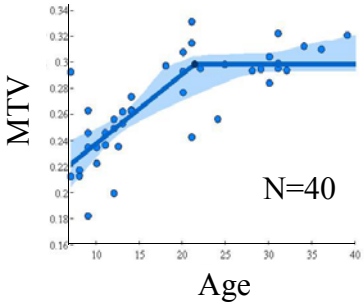
(Wandell and Yeatman, 2013)



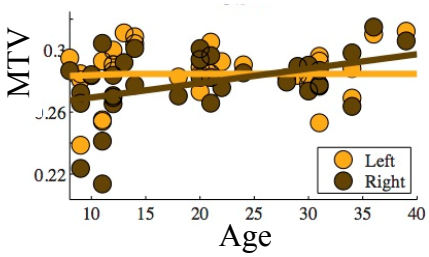
MTV development

Fascicle rates differ

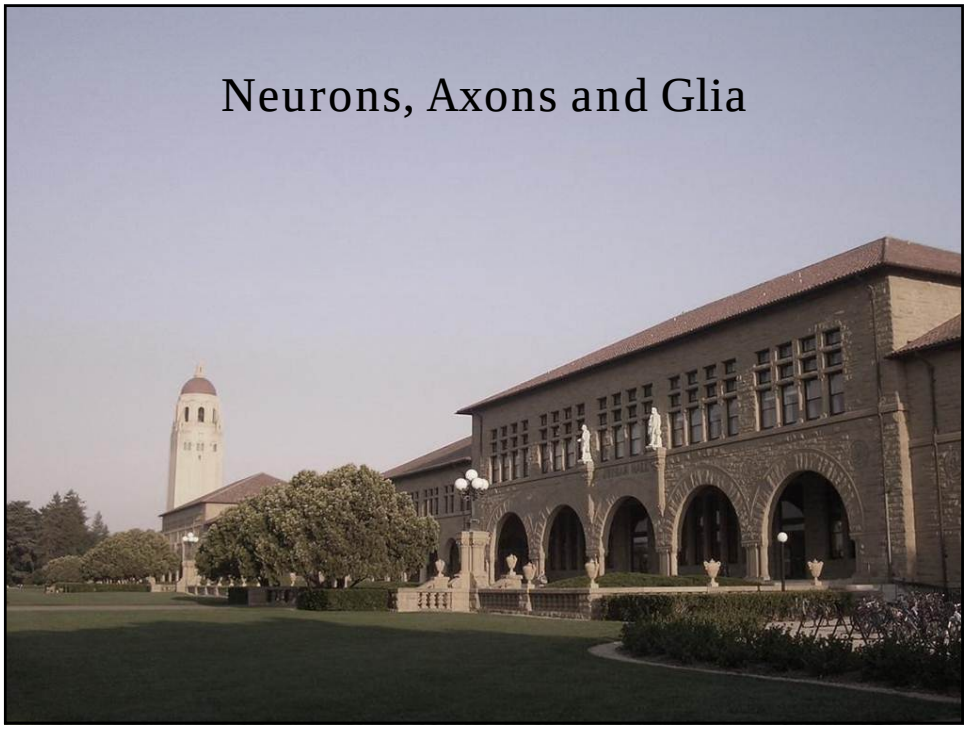
Arcuate fasciculus



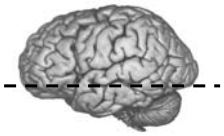
Cortical spinal track

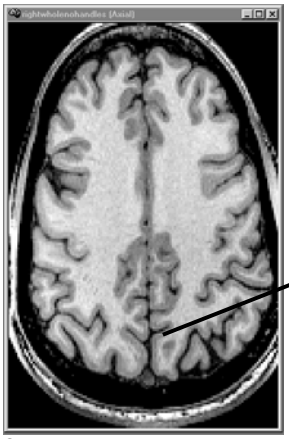


Neurons, Axons and Glia



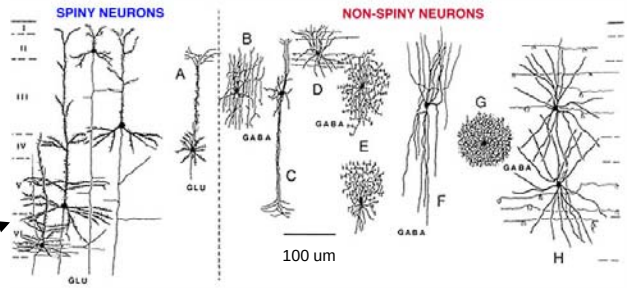
Many types of neurons





Primary visual cortex

- Spiny pyramidal – excitatory
- Spiny stellate – excitatory
- Smooth or sparsely spiny - inhibitory



Structures

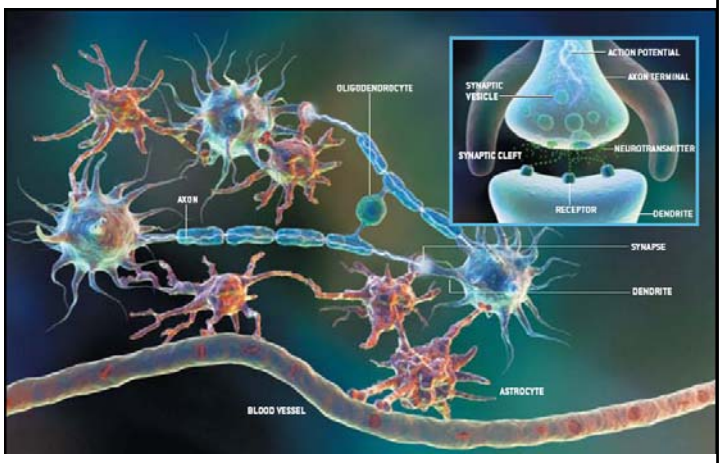
Types of Glia

Microglia *(20%) scavenging for infections, plaques, damaged neurons; regulating healthy neurons*

Astrocytes *bring nutrients to neurons as well as surround and regulate synapses. (50%)*

Oligodendrocyte glia *produce myelin that insulates axons.*

Schwann cells *perform myelination duties in the body's peripheral nervous system.*



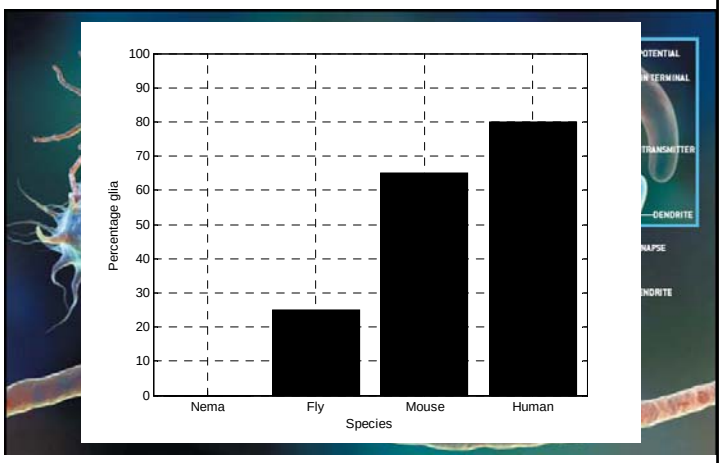
Types of Glia

Microglia *(20%) scavenging for infections, plaques, damaged neurons; regulating healthy neurons*

Astrocytes *bring nutrients to neurons as well as surround and regulate synapses. (50%)*

Oligodendrocyte glia *produce myelin that insulates axons.*

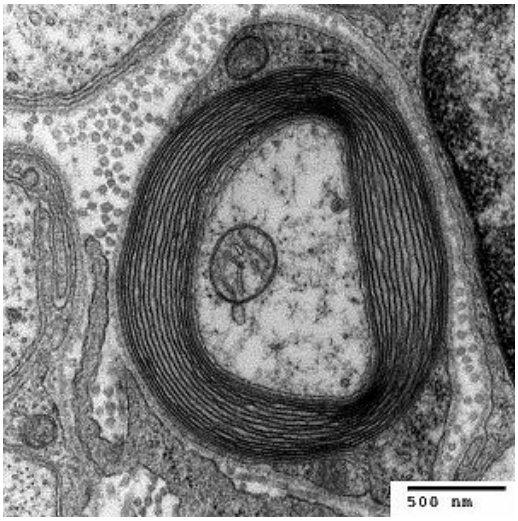
Schwann cells *perform myelination duties in the body's peripheral nervous system.*



Myelin sheath

Electron micrograph showing the myelin sheath

Type of glial cell: Oligodendrocyte



Astrocytes play a role in neuronal signaling in the hippocampus

NATURE REVIEWS | NEUROSCIENCE VOLUME 6 | AUGUST 2005

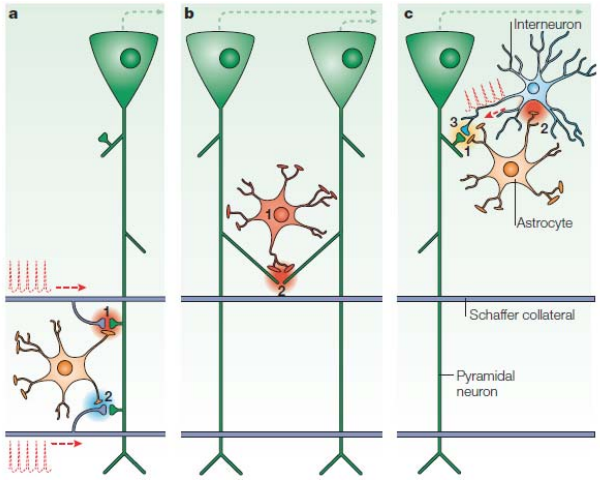
Andrea Volterra and Jacopo Meldolesi‡*

Three astrocyte actions during signaling are illustrated between pyramidal and Schaffer collaterals

Heterosynaptic depression of synapses

Excitation and synchronization of adjacent PNs

Potentiation of inhibitory synapses



Neuron Doctrine

www.sciencemag.org SCIENCE VOL 310 4 NOVEMBER 2005

This proposition, developed primarily by the great Spanish anatomist and Nobel laureate Santiago Ramón y Cajal, holds that a neuron is an anatomically and functionally distinct cellular unit that arises through differentiation of a precursor neuroblast cell.

PERSPECTIVES

NEUROSCIENCE

The Neuron Doctrine, Redux

Theodore H. Bullock, Michael V. L. Bennett, Daniel Johnston, Robert Josephson, Eve Marder, R. Douglas Fields

After a century, neuroscientists are rethinking the Neuron Doctrine, the fundamental principle of neuroscience. This proposition, developed pri-

synaptic switch regulating information flow through neural circuits. The synaptic cleft went unseen until a half-century later, when in 1954 the electron microscope pro-

rather than all-or-nothing electrical spikes that propagate regeneratively (*2*). It was also determined that evoked electrical responses often occur on a background of spontaneous changes in membrane potential (i.e., produced without input from other neurons) and that some parts of the neuron are incapable of producing all-or-nothing action potentials (*3*). Today, it is apparent that information processing in the nervous system must operate beyond the

Neuron Doctrine, Redux

www.sciencemag.org SCIENCE VOL 310 4 NOVEMBER 2005

Neuron Doctrine

At the same time, physiological studies established that conduction of electrical activity along the neuronal axon involved brief, all-or-nothing, propagated changes in membrane potential called action potentials. It was thus often assumed that neuronal activity was correspondingly all-or nothing and that action potentials spread over all parts of a neuron. The neuron was regarded as a single functional unit: It either was active and “firing” or was not.

Today, it is apparent that information processing in the nervous system must operate beyond the limits of the Neuron Doctrine as it was conceived.

Neuron Doctrine, Redux

www.sciencemag.org SCIENCE VOL 310 4 NOVEMBER 2005

- Gap junctions – widespread in mammals; synchronize neural firing (M.V. L. Bennett, R. S. Zukin, *Neuron* **41**, 495, 2004)
- Controlled in various ways by chemical synapses; plastic as well; and these connections are made with astrocytes (V. Alvarez-Maubecin, F. Garcia-Hernandez, J. T. Williams, E. J. Van Bockstaele, J. *Neurosci.* **20**, 4091 (2002).)
- Dendrites contain a mosaic of voltage-gated ion channels, so that signal integration can be quite complex ().

Neuron Doctrine, Redux

www.sciencemag.org SCIENCE VOL 310 4 NOVEMBER 2005

- Polarized communication between neurons by action potentials is heavily influenced by non-neuronal cells
- Unexpectedly, chemical synapses have recently been detected between neurons and a class of glia (oligodendrocyte precursor cells), undermining a defining feature of neurons (Bergles et al., 2000)
- Axon-glial communication violates the *Neuron Doctrine* in two ways.
    - Signals arise between cells outside chemical synapses, and
    - Propagate through cells that are not neurons

Special role for glia in human

Oberheim, N. A. *et al*. Uniquely hominid features of adult human astrocytes. *J. Neurosci.* **29**,3276–3287 (2009).

For example, the human brain contains several more populations of astrocytes than the rodent brain, and human astrocytes are up to threefold larger and more ramified than their rodent counterparts