Lesson (3)

The cellular organization of the nervous system III (neuroglia & myelin)

The neuroglia: structure and functions

There is a debate on their actual number (formerly 10 times): now 2-3 times the number of the neurons

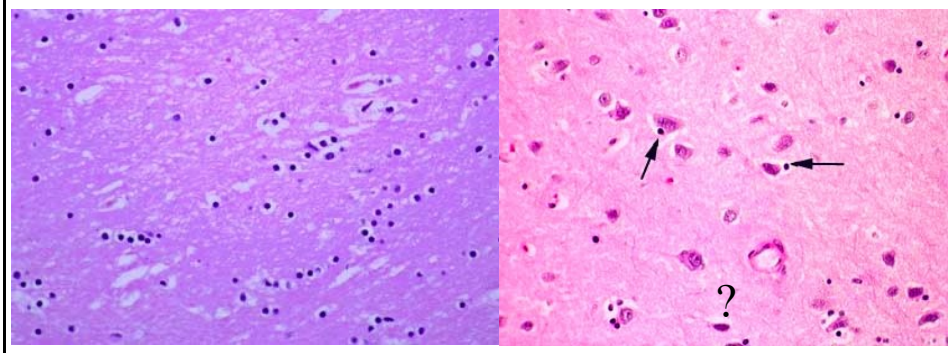
6 main types:

- **Astrocytes**
- **Microglia**
- **Ependimal cells**
- **Radial glia**
- **Oligodendrocytes**
- **Schwann cells**

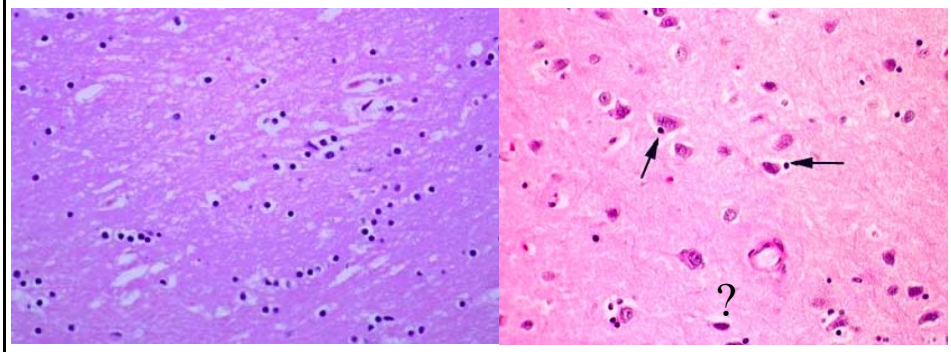
Functions:

-Filter (Blood-Brain Barrier)
-Physical support
-Protection (sequestration of ion or neurotransmitters in excess; resident immune system)
-Trophic and metabolic support
-Signal transduction (transcytosis, myelin formation)
-Regeneration and degeneration/scar formation (neural stem cells)

?



Oligodendroglia (CNS)



Oligodendroglia (CNS)

- "few-branch" glia
- Discovered by del Rio-Hortega, using metallic impregnation techniques in 1921
- one oligo myelinates many CNS axons
- CNS myelinators (white matter)
- Target of autoimmune attack in MS
- Specific oligodendrocyte myelin proteins:
  - PLP
  - DM20
  - MBP

Oligodendroglia

1 glial cell forms myelin around many axons

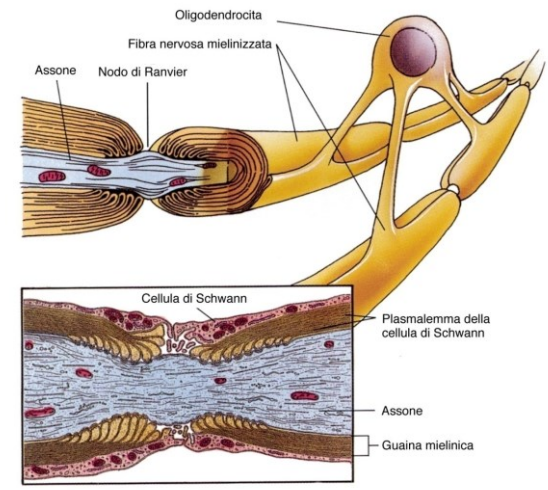
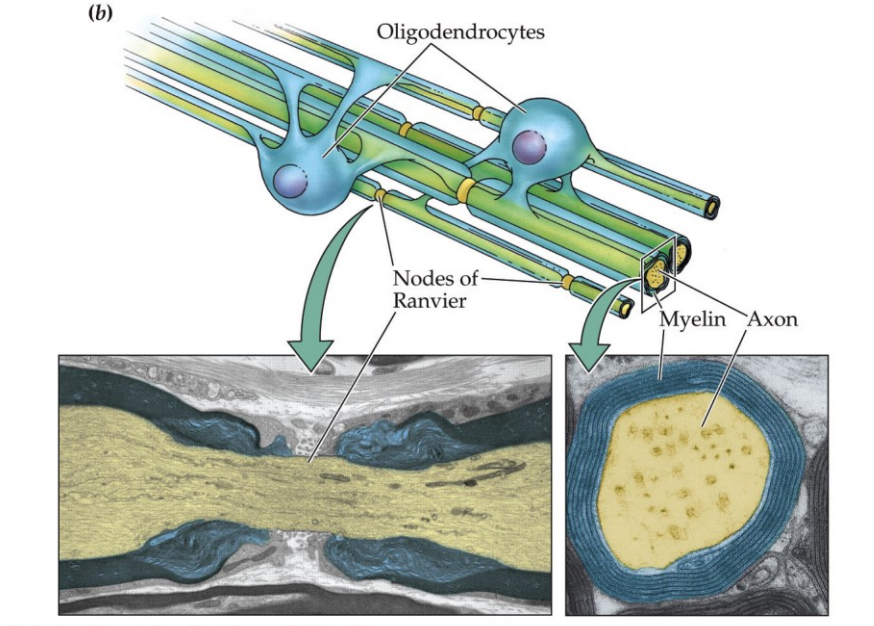


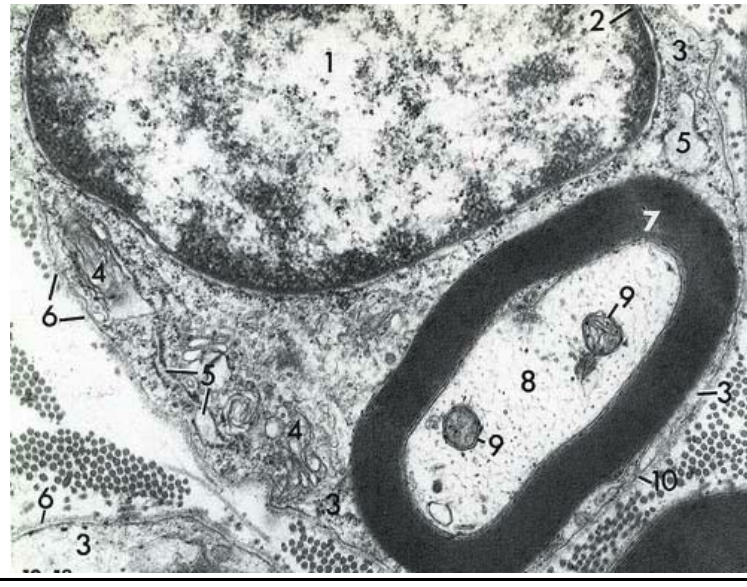
Figura 9–13

Figure 2.6 Representative Glial Cells (Part 2)

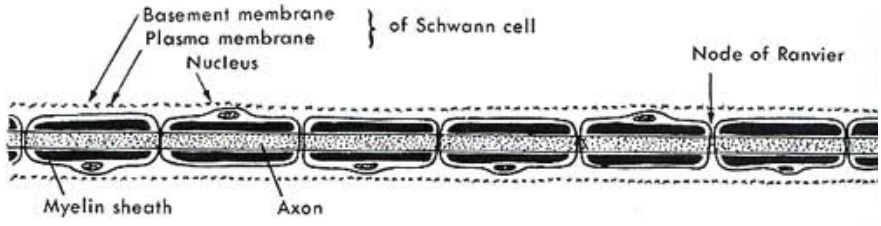


Biological Psychology 5e, Figure 2.6 (Part 2)

Schwann Cell (PNS)



Schwann Cell



Theodore Schwann (19th cent. German anatomist; a key founder of cell theory)
Each Schwann cell wraps a portion of a single peripheral axon

Figure 26.3B Sensory neuron

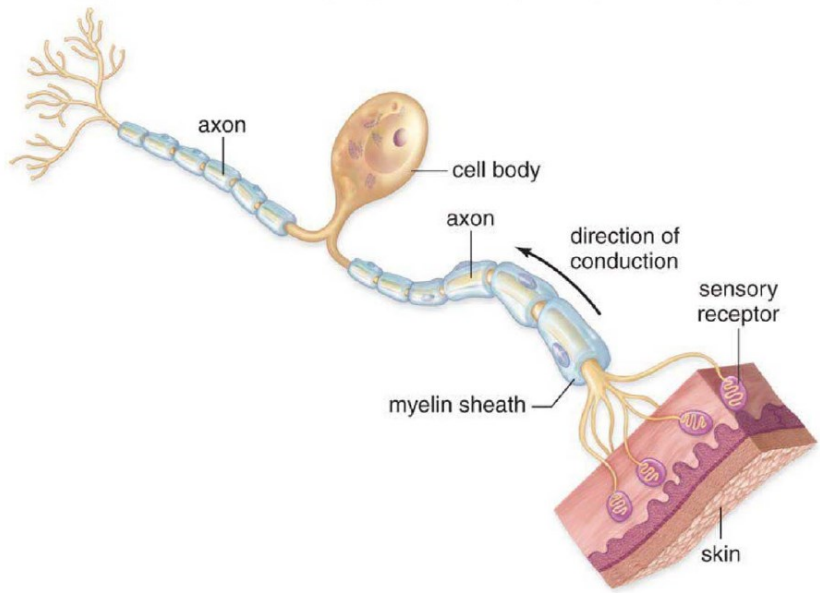
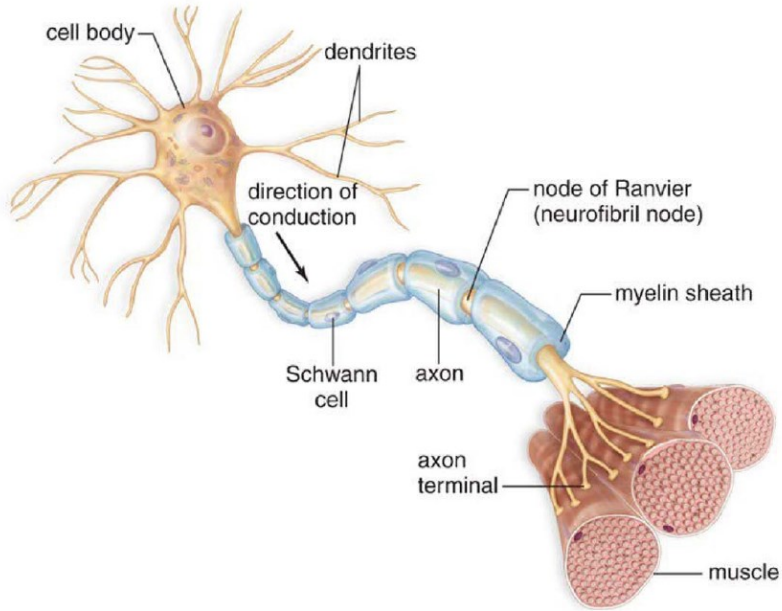
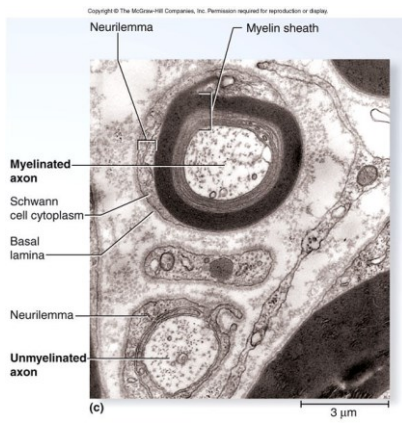
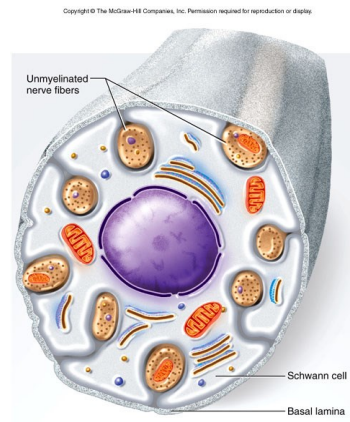


Figure 26.3A Motor neuron



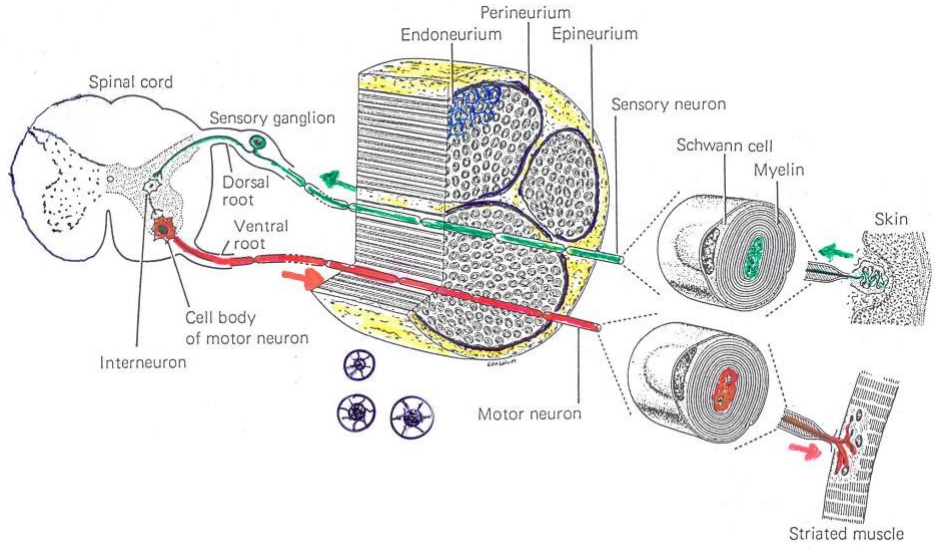
Unmyelinated Axons of PNS





- Schwann cells hold small nerve fibers in grooves on their surface with only one membrane wrapping

Peripheral nerve



Myelinated perypheral axons

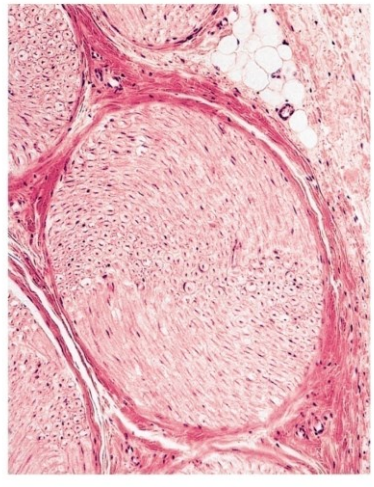


Figura 9–21

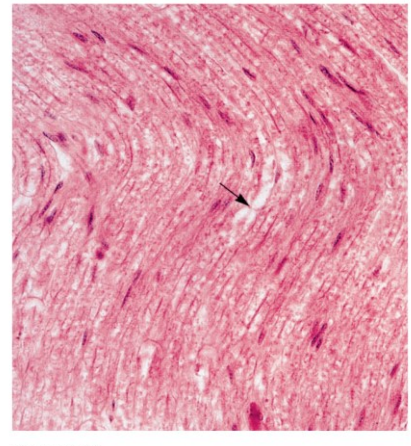
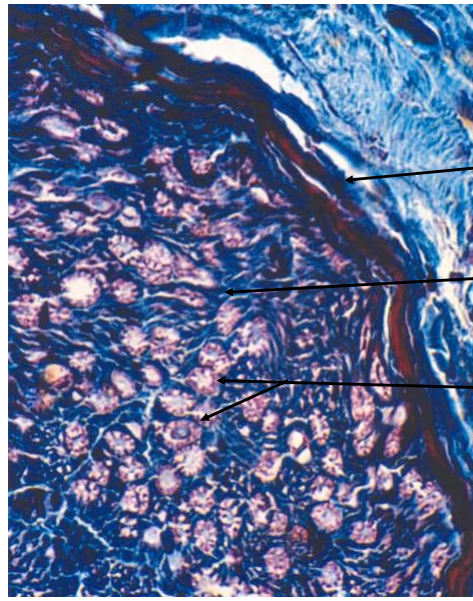
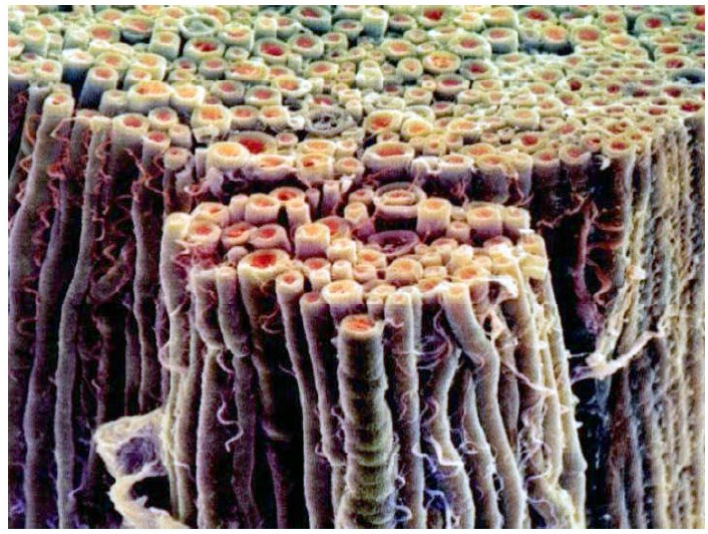


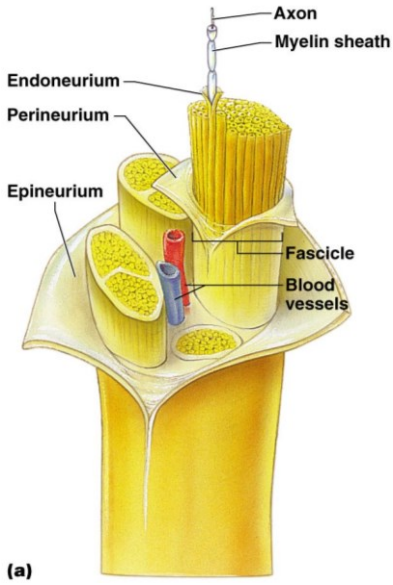
Figura 9–20

Peripheral Nerve (Fascicle)



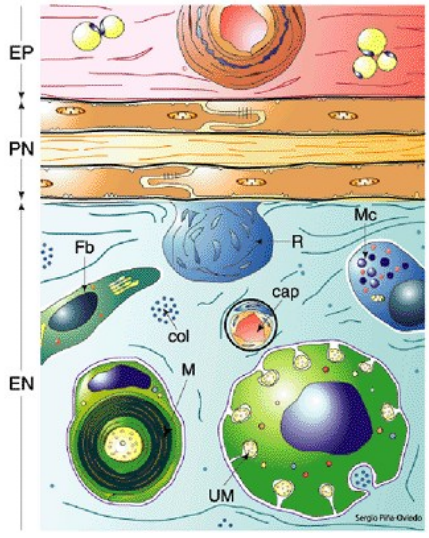


Structure of a Nerve



- **Endoneurium** – layer of delicate connective tissue surrounding the axon
- **Perineurium** – connective tissue wrapping surrounding a nerve fascicle
  - **Nerve fascicles** – groups of axons bound into bundles
- **Epineurium** – whole nerve is surrounded by tough fibrous sheath

Diagram of peripheral nerve components



L'epinevrio (EP) contiene fibre di collagene, vasi sanguigni e tessuto adiposo. Le cellule appiattite del perinevrio sono tenute assieme da giunzioni strette e formano dei foglietti separati dalle fibre di collagene. I corpi di Renaut (R) sono posizionati all'interno dell'endonevrio (EN). Le cellule di Schwann formano delle lamelle di mielina(M) che sorreggono gli assoni più grandi . Le fibre non mielinizzate (UM) creano delle invaginazioni sulla superficie di una cellula di Schwann.

Other elements: fibroblasts (Fb), mast cells (Mc), capillaries (cap) and collagen (col).

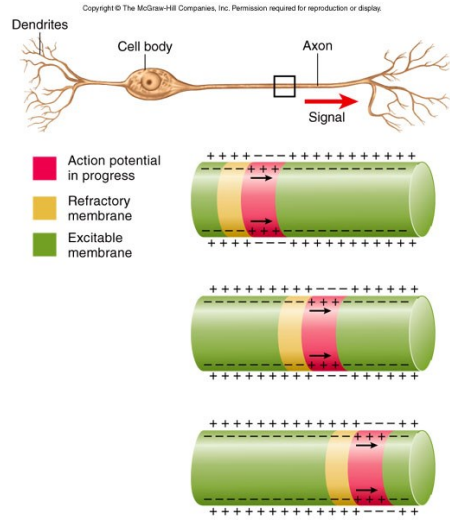
Myelin main features

- **Myelin acts as an insulator for vertebrate nerve cells**
  - oligodendrocytes in CNS and Schwann cells in PNS
  - formed from wrappings of plasma membrane
  - 20% protein and 80 % lipid (looks white)
  - all myelination completed by late adolescence
- **Cellular structure - myelin is composed of alternating layers of protein and lipid**
  - Very little cytoplasm between layers
- **Myelin represents a major vertebrate feature**
  - Not a major factor in invertebrates nervous systems
  - Major advantages
    - ***faster conduction (10x)***
    - ***smaller sized neurons (10x)***

Speed of Nerve Signal

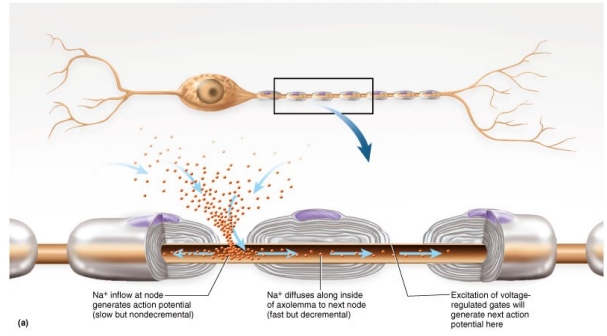
- Diameter of fiber and presence of myelin
  - large fibers have more surface area for signals
- Speeds
  - small, unmyelinated fibers = 0.5 - 2.0 m/sec
  - small, myelinated fibers = 3 - 15.0 m/sec
  - large, myelinated fibers = up to 120 m/sec
- Functions
  - slow signals supply the stomach and dilate pupil
  - fast signals supply skeletal muscles and transport sensory signals for vision and balance

Impulse Conduction - Unmyelinated Fibers

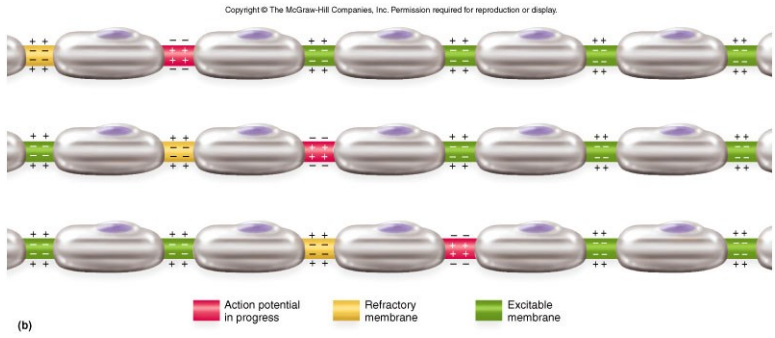


Saltatory Conduction - Myelinated Fibers

- Voltage-gated channels needed for APs
  - fewer than 25 per μm^2 in myelin-covered regions
  - up to 12,000 per μm^2 in nodes of Ranvier
- Fast Na^+ diffusion occurs between nodes

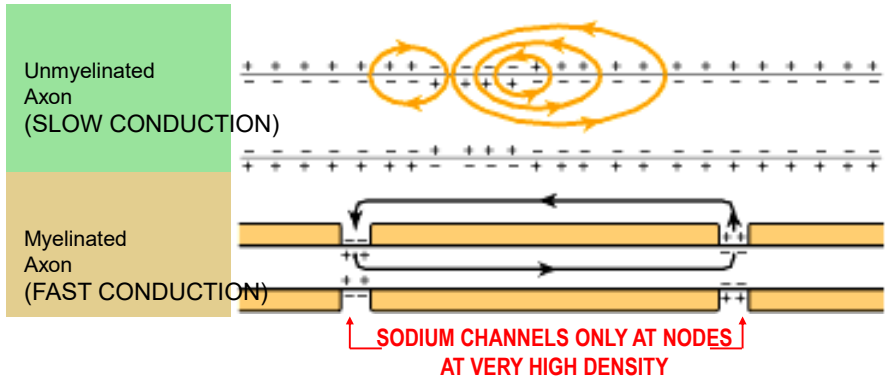


Saltatory Conduction



- Notice how the action potentials jump from node of Ranvier to node of Ranvier.

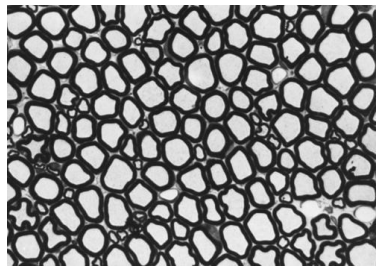
ROLE OF MYELIN IN FAST ELECTRICAL TRANSMISSION



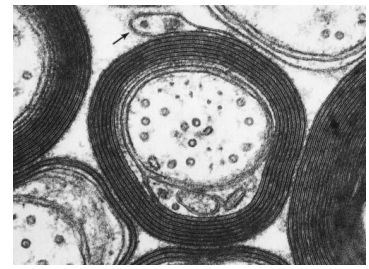
Action potential at one point along unmyelinated axon produces current that only propagates short distance along axon, since current is diverted through channels in axon membrane. So action potential can only next occur at short distance away

Myelin reduces effective conductance and capacitance of internodal axon membrane. (how???)
Action potential at node of Ranvier produces current that propagates 0.5-5 mm to next node of Ranvier, generating next action potential

MYELINATED FIBERS VIEWED IN CROSS-SECTION

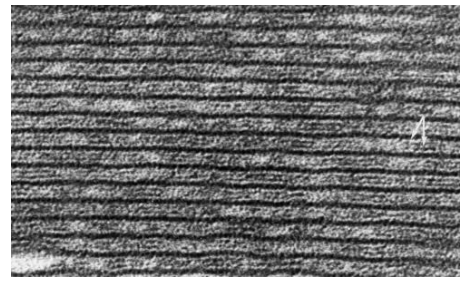


Low magnification
Light microscopy

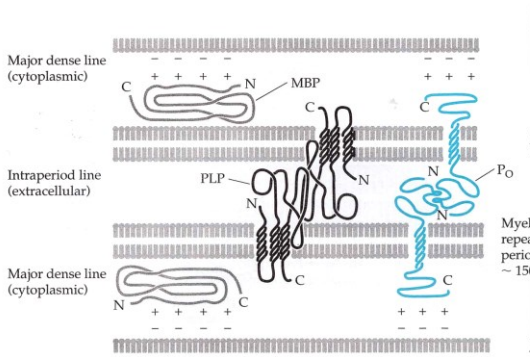


High magnification
electron microsopy

Electron microscopy at very high magnification reveals alternating major dense lines and intraperiod lines

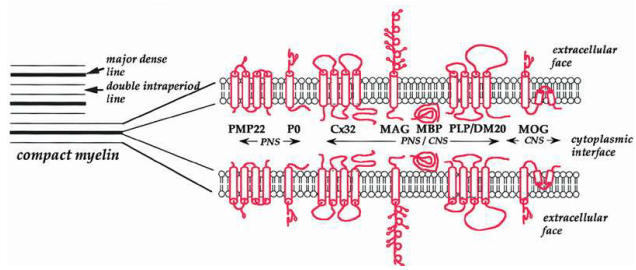


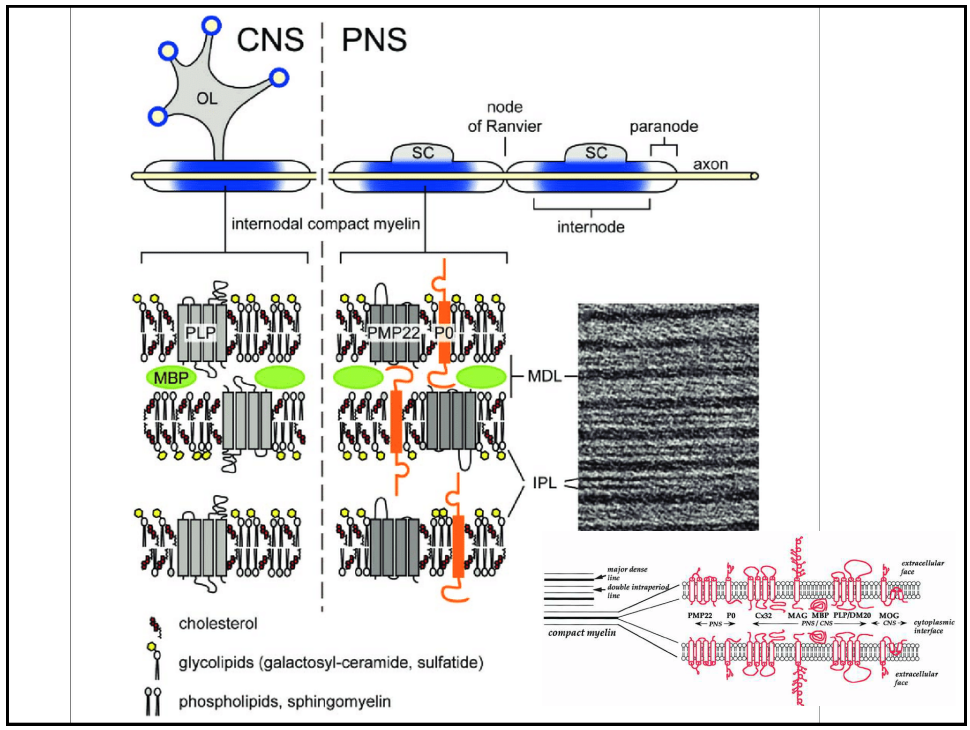
ORGANIZATION OF THE MYELIN REPEAT PERIOD



PLP is the most abundant protein in CNS myelin

P0 is the most abundant protein in PNS myelin

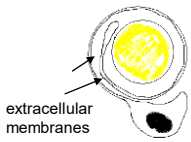




Major proteins found in Myelin

- **P0 (protein zero**) intraperiod line formation
  - a glycoprotein only in myelin-forming Schwann cells (50%)
  - similar to CAMs, but bifunctional (in PNS)
- **proteolipid protein (PLP)** intraperiod line formation
  - only in Oligodendrocytes (50%) (in CNS)
- **myelin basic protein (MBP)**
  - expressed in both, involved in compaction
  - very antigenic, can be used to induce experimental multiple scelerosis, (T-lymphocyte inv. of CNS and PNS
  - *shiverer* in mice
- **NCAM**
  - Cellular adhesion

Myelin protein P0 is a cell adhesion molecule in Schwann cells



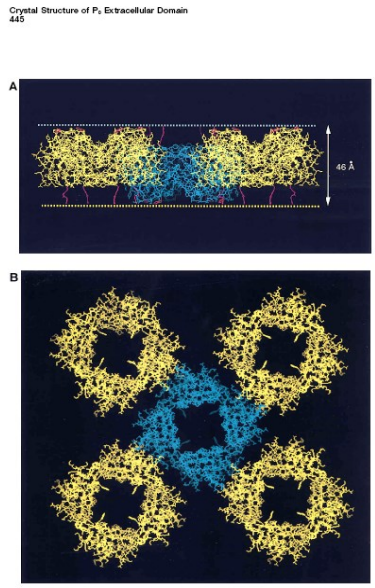


Figure 6. Combined P_0 Interactions Observed in the Crystal Lattice

(A) P_{0ex} tetramer structures joined by twofold symmetric putative adhesive interfaces. These tetramers are depicted here as they might emanate from their respective membrane surfaces (schematically indicated with dotted lines) at the C-termini, with the blue-colored tetramers protruding from the blue surface, and the yellow-colored tetramers from the yellow surface. The Trp-28 side chains, which may intercalate into the opposite membrane bilayer, are shown in red, and a model for main chain atoms for the five residues of the disordered linker to the membrane are shown in purple. The c axis is vertical and the a axis horizontal.

(B) Perpendicular view of this layer of the crystal lattice.

Neuron, Vol. 17, 435–449, September, 1996, Copyright ©1996 by Cell Press

Crystal Structure of the Extracellular Domain from P_0, the Major Structural Protein of Peripheral Nerve Myelin

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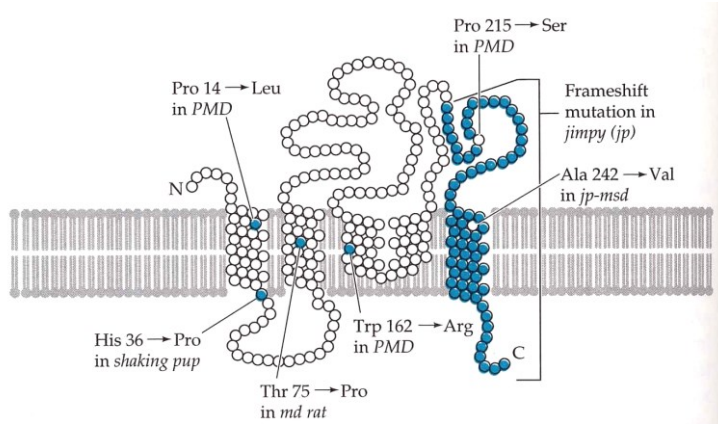
King of Prussia, Pennsylvania 19406

which the P_0 gene was disrupted by homologous recombination (Giese et al., 1992). Schwann cells in these animals can contact and ensheath axons, but membrane compaction is severely impaired. It has also been shown that expression of P_0 antisense RNA in Schwann cells prevents normal myelination of axons in culture (Owens and Boyd, 1991). Furthermore, some instances of the dysmyelinating diseases Charcot-Marie-Tooth (CMT) type 1 and Dejerine-Sottas syndrome (DSS) have been attributed to mutations in the human P_0 protein, encoded by the MPZ gene (Patel and Lupski, 1994; Warner et al., 1996 [this issue of *Neuron*]).

P_0 is a single-pass transmembrane glycoprotein with a highly basic 69-residue intracellular domain and a 124-

MUTATIONS IN PLP GENE CAUSING HYPOMYELINATION IN CNS

Myelin proteolipid protein (PLP or lipophilin) is the major myelin protein from the central nervous system

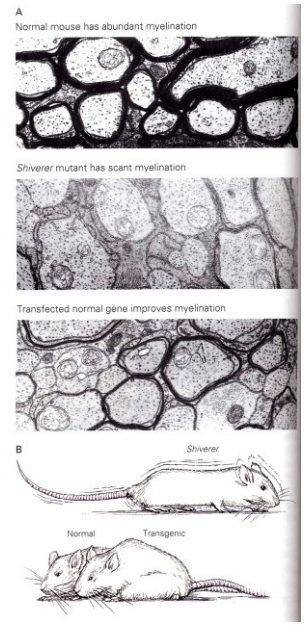


Similarly, structural mutations in PNS myelin protein genes cause defective myelination of the PNS

MUTATIONS CAN CAUSE MINOR OR MAJOR MYELIN LOSS

"SHIVERER" mutant mouse has almost complete absence of myelination, due to a failure of precursor cells to differentiate into oligodendrocytes
Mice homozygous for the autosomal recessive mutation *shiverer* (shi) lack **myelin basic protein (MBP)** and were obtained from Dr. Alan Peterson (McGill University)

Other mutations which impair myelination are mutations in the major protein components of the myelin sheath



Schwann Cells and Peripheral Neuropathies

- Schwann cells also perform trophic functions (NGF production in regeneration).
- Myelin proteins
  - **Schwann cells (PNS): P0, PMP22** ***(Peripheral myelin protein 22)***

  PMP22 is a small glycoprotein involved in correct myelination during development of peripheral nerves, the stability of myelin, and the maintenance of axons

  - Charcot-Marie-Tooth disease type 1A (CMT1A) =duplication of PMP22
  - Hereditary Neuropathy with liability to Pressure Palsies (HNPP), and a subtype of Dejerine-Sottas Syndrome (DSS) =deletion of PMP22

(surprisingly, deletion causes milder phenotype than CMT1A duplication)

Summary of structure

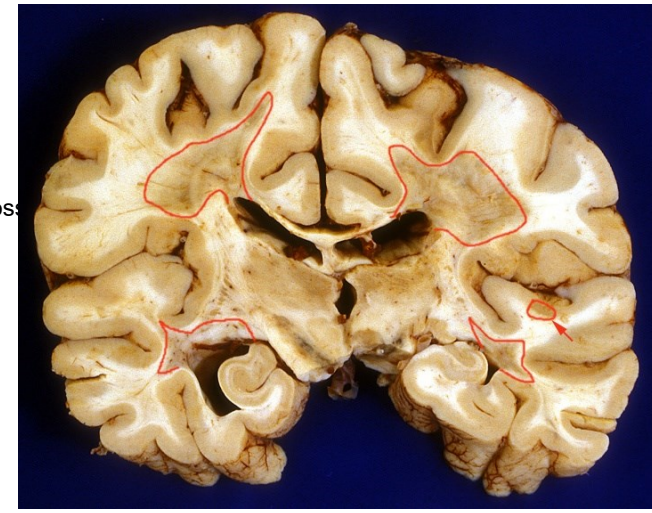
- Myelinating cells in CNS and PNS differ
- Axon-satellite cell interaction is crucial for the formation of nodes of Ranvier e.g interaction of gliomedin in Schwann cells and NF186 is an important factor in Na^+ channel clustering
- Myelinated axon membrane incorporates domains typically expressing certain ion channels and cell adhesion molecules (CAMs)
- Sheath contains characteristic CAMs eg P0, and these stabilize myelin

D.P. Schafer and M.N. Rasband (2006) Current opinion in Neurobiology 16: 508-514. (Review) READ THIS

Neuropathological note

- Tumors of the nervous system are largely Glial tumors:
- Peripheral: Schwannoma, Neurofibroma
- Central:
  - astrocytomas (includes benign pilocytic astrocytic and most common and most malignant: glioblastoma multiforme)
  - Oligodendrogliomas
  - ependymomas

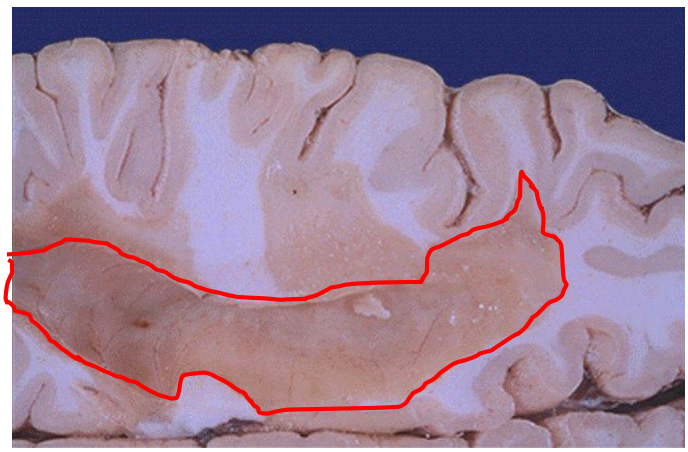
Cross

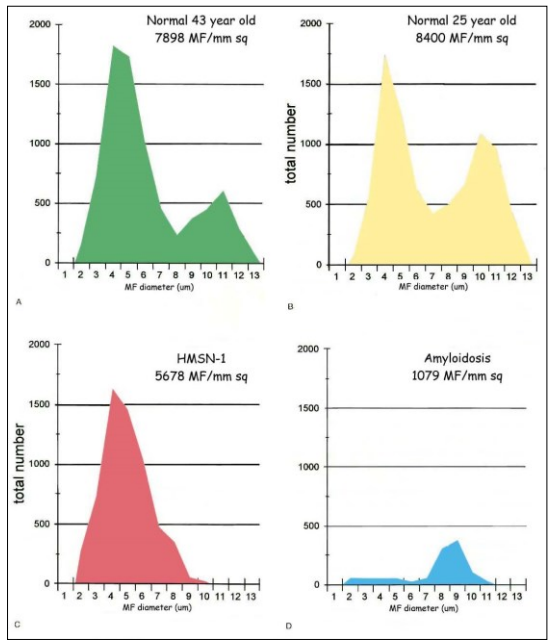


) gene

Demyelinating disease: Multiple sclerosis in humans

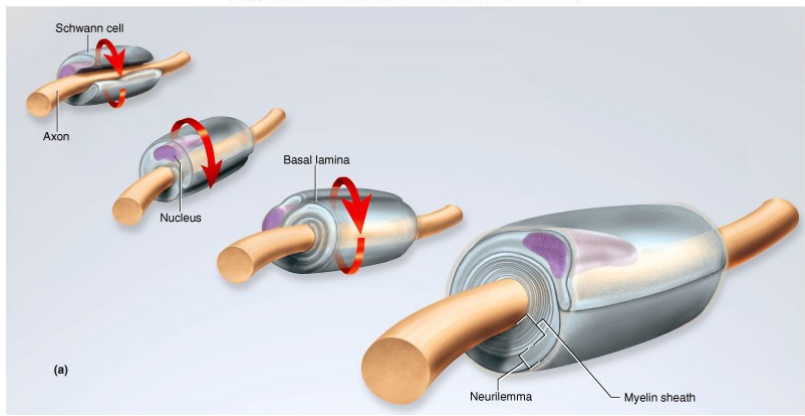
Multiple Sclerosis is an autoimmune attack on white matter





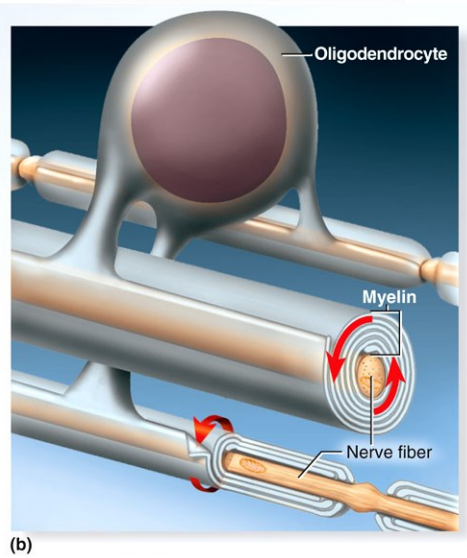
- There is normally a bimodal distribution of myelinated fiber diameters.
- The thickness of the myelin sheath is generally proportional to the axon diameter.
- In some forms of polyneuropathy, such as hereditary motor sensory neuropathy type I, the large myelinated fibers may be preferentially affected, while in amyloidosis, for example, the small myelinated fibers may be preferentially affected.

Myelination in PNS

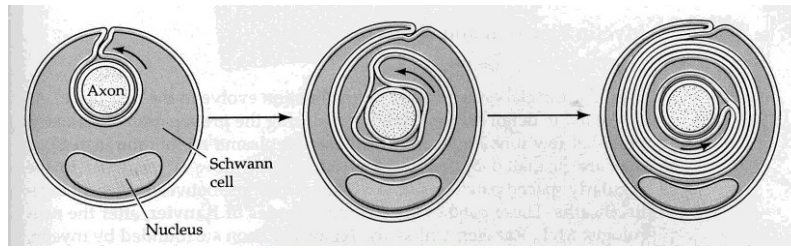


- Myelination begins during fetal development, but proceeds most rapidly in infancy.

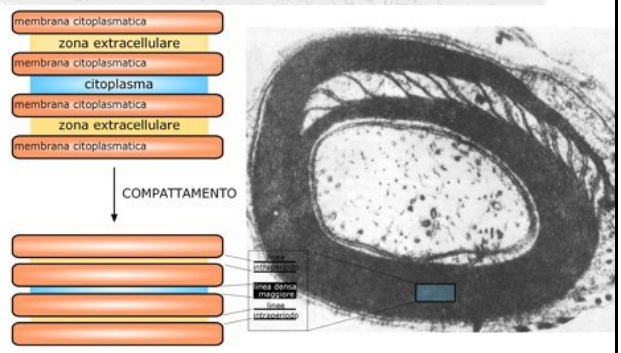
Myelination in CNS

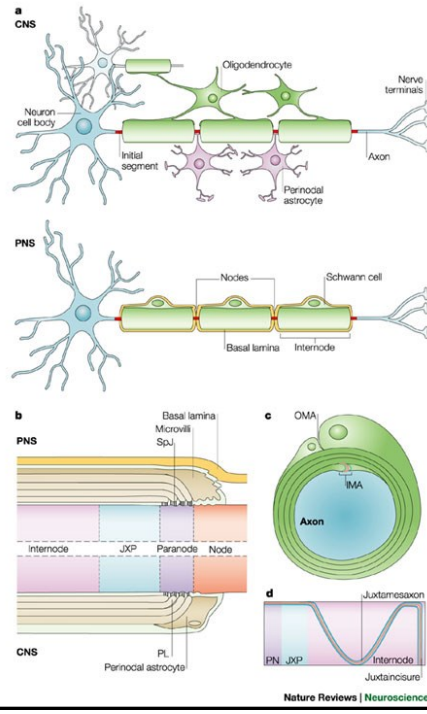


MYELIN SHEATH GENERATED BY CONTINUED MIGRATION OF PROCESS LEADING EDGE AROUND AXON



While the leading glial process continues to encircle the axon, the earlier-formed loops undergo compaction to form the contact myelin sheath





From Poliak and Peles 2003

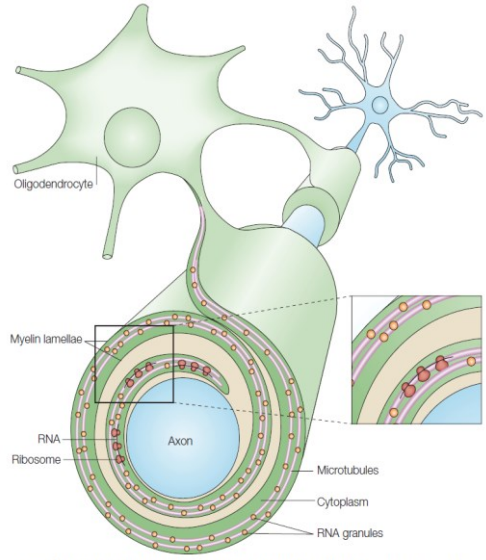


Figure 1 | **Ensheathment of an axon by oligodendrocytes.** An oligodendrocyte extends and surrounds neighbouring axons and the myelinating process develops a distinct protein and lipid composition. The synthesis of some myelin proteins — and presumably the assembly of new membrane — occurs at sites distal to the cell body as a result of microtubule-based transport of RNA granules (orange circles) that contain mRNA (blue lines) and ribosomes (red circles) from the nucleus to the paranodes.

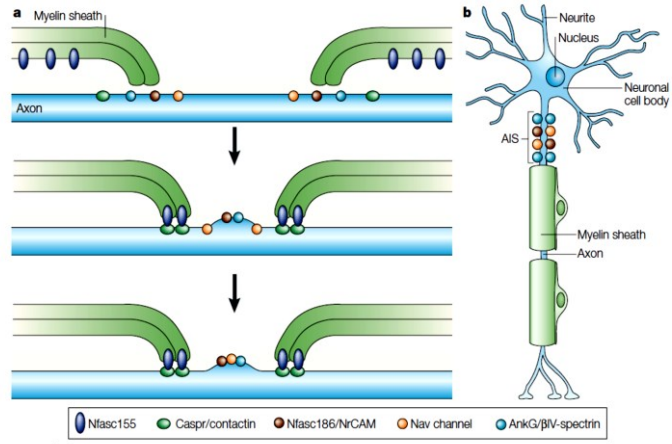


Figure 2 | **Myelination causes clustering of the sodium channel complex at nodes of Ranvier and axon initial segments. a** | Initially the adhesion molecules of the future paranodal region and the components of the node are distributed diffusely along the axon and myelinating process. Establishment of paranodal axo–glial junctions between glial neurofascin 155 (Nfasc155) and axonal contactin-associated protein (Caspr) and contactin coincides with the clustering of some of the nodal components, such as Nfasc186, NrCAM, ankyrin G (AnkG) and βIV-spectrin, which is followed by the clustering of voltage-gated sodium (Nav) channels. **b** | The axon initial segment (AIS) is the site at which action potentials are initiated as a result of various synaptic inputs arriving at the neuron. The composition of the AIS is similar to that of the node, which indicates that there could be similar mechanisms for the assembly of the sodium channel complex.

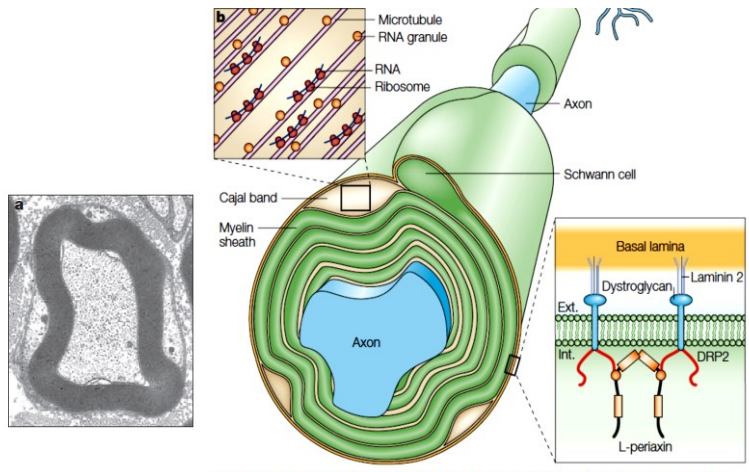
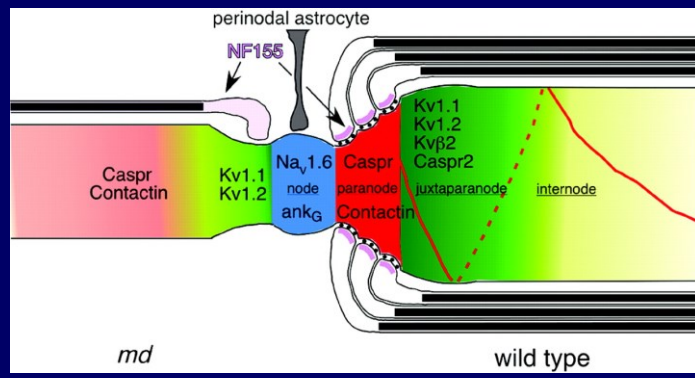


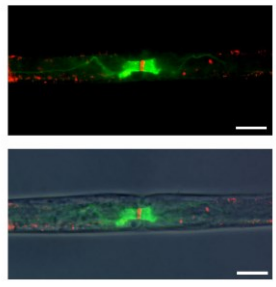
Figure 3 | **Cajal bands form channels for mRNA transport in Schwann cells. a** | Electron micrograph of a transverse section of the quadriceps nerve. **b** | Cajal bands are cytoplasm-filled channels that lie underneath the plasma membrane of the Schwann cell. The cytoplasm is squeezed between appositions that form between the outer surface of the myelin sheath and the cytoplasmic face of the Schwann cell plasma membrane, and contains the periaxin–dystrophin-related protein 2 (DRP2–dystroglycan complex; see right inset). Cajal bands contain microtubules that participate in the delivery of mRNA from the nucleus to distal sites at which it is translated, as occurs in oligodendrocytes (see FIG. 1). Importantly, intact Cajal bands seem to be vital for the transport function of microtubules in Schwann cells. Disruption of the periaxin–DRP2–dystroglycan complex that is responsible for forming the Cajal bands also prevents microtubule-based mRNA transport. Panel **a** modified, with permission, from REF. 25 © (2004) Macmillan Magazines Ltd.

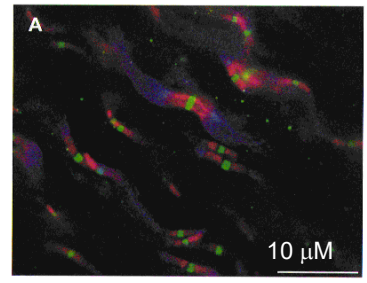
Figure 10.

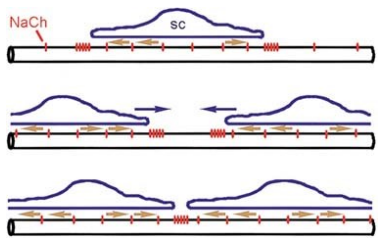


Arroyo, E. J. et al. J. Neurosci. 2002;22:1726-1737

Rudolf Martini



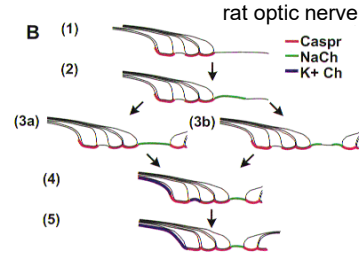




Formation of nodes of Ranvier
by Schwann cells

Peter Shrager

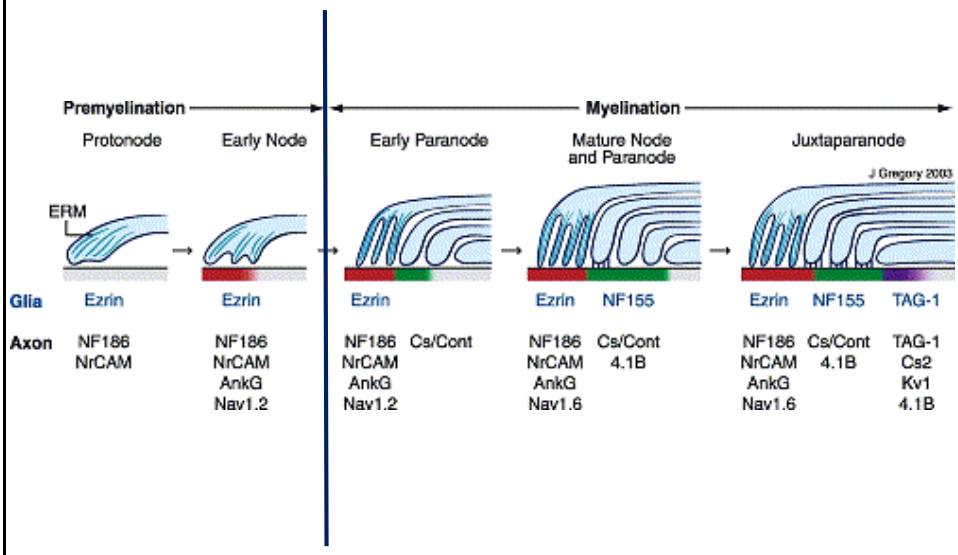
rat optic nerve



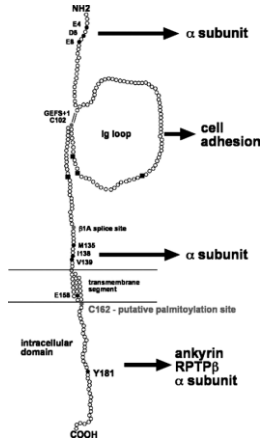
Na^+ channels (green) Caspr 1 (red)
Fast K^+ channels (blue)

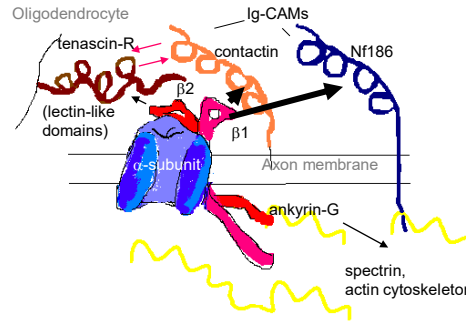
Matthew Rasband
and Peter Shrager 2000

Adhesion molecules at Nodes of Ranvier during myelination



β-subunits interact with both intracellular and extracellular proteins, controlling Na^+ channel localization and contributing to the control of channel density





β1 is crucial

McEwen j. Biol Chem 279: 16044-16049 (2004)

Construction of myelinated nerve

Myelinating cells cause clustering of Na^+ and K^+ channels and induce large axonal diameters

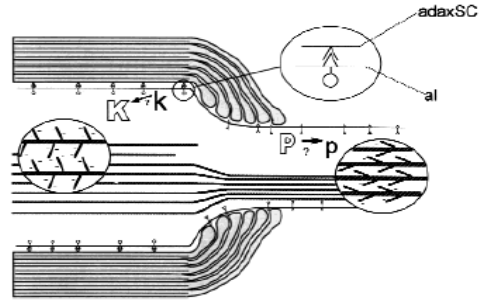
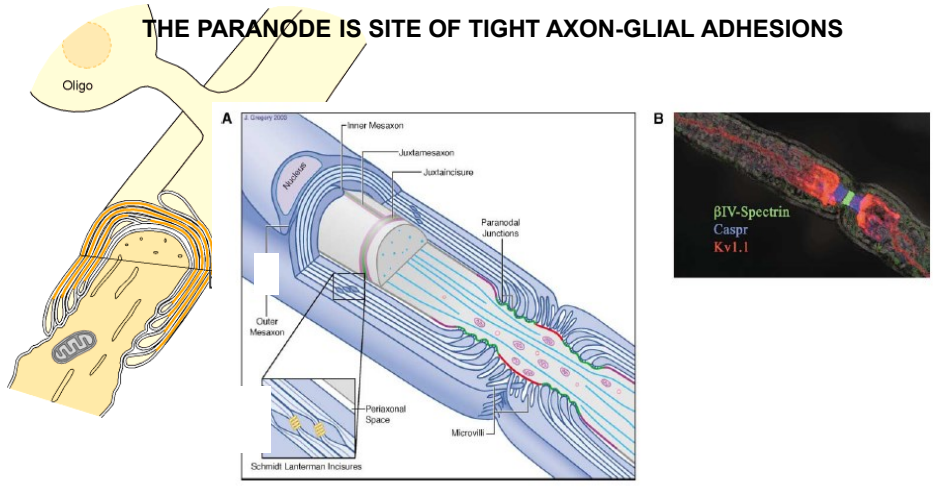
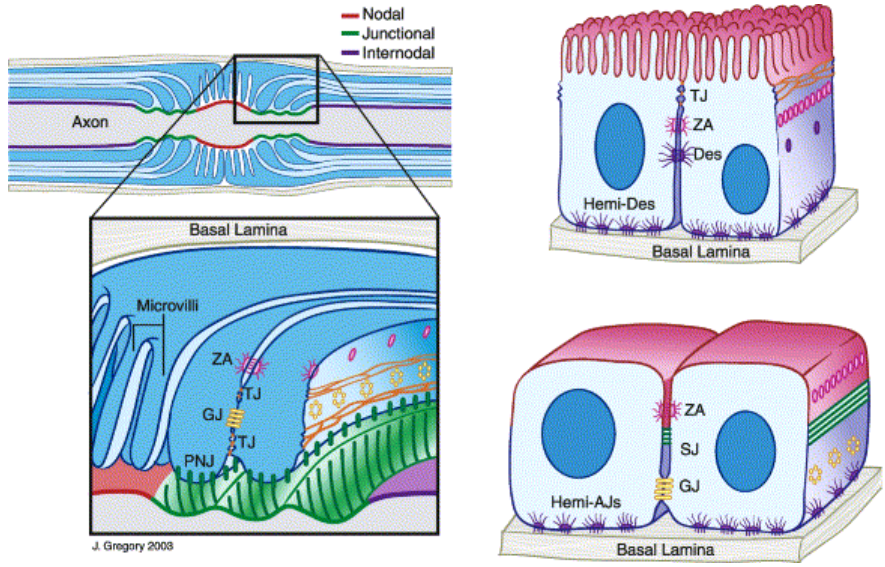


FIGURE 1. Diagram of the putative mechanisms modifying axonal caliber as a response to axon–Schwann cell interactions. In the myelinated part of the axon (left), more neurofilaments are present. In addition, the neurofilaments show a higher phosphorylation state that leads to repulsion of the highly phosphorylated side arms from the filamentous cores by negative charges. This leads to an increase in space between the neurofilaments and, eventually, to an increase in axon caliber. Conversely, in the nonmyelinated part of the axon (or at the node of Ranvier), fewer neurofilaments are present and their phosphorylation state is reduced, leading to a smaller axon caliber. The modulation of the

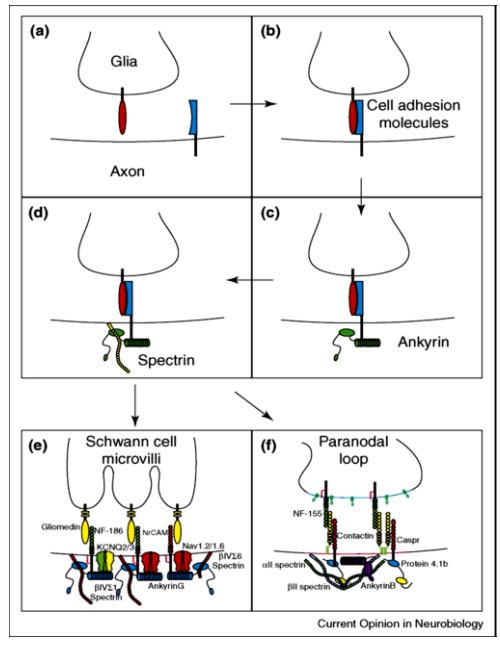
THE PARANODE IS SITE OF TIGHT AXON-GLIAL ADHESIONS



Cell-cell junctions in myelin



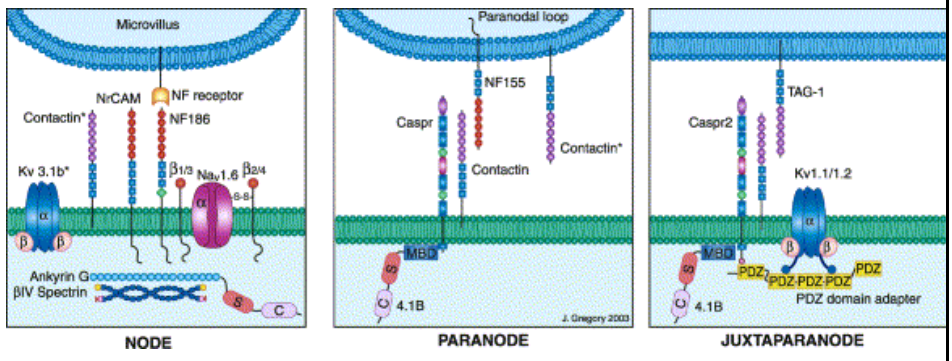
Glial CAMs recruit axonal CAMs at points of contact



Axonal CAMs are attachment sites for cyto-skeletal proteins

D.P. Schafer and

M. N. Rasband (2006)



	Node	Paranode	Juxtaparanode	Internode
Membrane complex	Na_v, AnkG, Spectrin, NF, NrCAM	Caspr, Contactin, 4.1B	K_v1, Caspr2, TAG-1, 4.1B	?
Axon diameter	reduced	reduced	expanded	expanded
NF phosphorylation	decreased	decreased	increased	increased
Axon transport	reduced	reduced	rapid	rapid
Organelles	increased	increased	slow	slow

Review by James Salzer *Neuron* (2003) 40:297