NEUROPSYCHOLOGY

Neuroscience 2009
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Overview

- What is neuropsychology?
  - Sample tests
  - What is "normal"?
- Example: evaluation of dementia
  - Not always Alzheimer's disease: Case E
  - Goal is to help with correct diagnosis and assist with treatment

Definition

Neuropsychological testing uses **behavioral measures** to assess skills and abilities that relate to brain functioning. Most neuropsychological tests have been developed to measure "higher cerebral functioning," so they usually focus on **cognitive skills and abilities**.

These tests have been developed to help *diagnose* brain damage or brain dysfunction in some patients and to help ascertain the *behavioral effects* of brain damage in others. Such evaluation can provide information about cognitive strengths and weaknesses within an individual and the areas in which an individual's functioning may differ from that of the normal population. This type of evaluation is most commonly conducted on patients with neurologic disorders.

-- from "Neuropsychological Testing" by Laetitia L. Thompson, PhD (chapter 6 in *Psychiatric Secrets*)

Definition

- So, Neuropsychology assesses brain-behavior relations by means of (cognitive) tests for patients with neurological problems.
- Or, as one youngster understood it…

Nerdopsychology!

- Too nerdy to be a cool therapist
- But into data!
  - Quantitative orientation to behavioral neuroscience

Fluency

- You have one minute to list all the different things you can find at the supermarket.
- GO!

Attention

Tap your pencil as quickly as you can every time you see a letter <u>except</u> for “X”

How do we know what is normal?

Just like getting a lab test…

Ex: <u>prolactin level</u>

Result	Normal Range	
9 ng/mL	Low = 3	High = 29

Just like getting a lab test…

Ex: prolactin level, **39 yo female**

9 ng/mL (± .32) Low = 3 High = 29

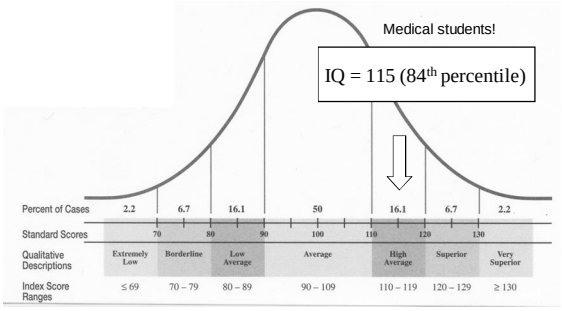
Reference range

- Male: 2.1 - 17.7
- Female non-pregnant: **2.8 - 29.2**
- Pregnant: 9.7 - 209.0
- Postmenopausal: 1.8 - 20.3

How do we know what is normal?

- Compare patient to him/herself
  - Premorbid functioning
    - Education, Occupation
    - Daily living: e.g., driving
- Lifespan databases for NP tests
  - Corrections for age, education, race/ethnic
  - Norms: age intervals ≈ 5 years

Normal Curve for IQ scores



Assessing dementias

- Get history and collateral information
- Set the premorbid "bar"
- Observe behavior
  - sensorimotor, speech, social
- Test cognitive domains
- Assess mood, interpersonal, judgment

Cognitive domains

- Attention (gatekeeper)
- Perception
- Language (speech and comprehension)
- Memory
  - Old memories usually spared
  - Problems forming new memories in some dementias
- Executive/frontal functions
    - Abstraction
    - Mental control (e.g., inhibition)

Dementia of the Alzheimer Type

- Deficits *for the age group* in memory
  - Can't form new memories
  - Contributes to disorientation, role changes
- Deficits in naming also common
  - Conversation somewhat stereotyped
- Sparing of social skills, other domains
  - Play golf, keep house, reminisce, socialize

Not always Alzheimer's

Case E video segments (Dr. Walsh)

- Introduction to patient
  - *This patient kindly consented to filming for educational purposes; complete confidentiality is understood.*
- Patient's vocal quality is part of the illness

Presenting Symptoms

- Came for psychotherapy
- Reporting symptoms of depression
  - Decreased appetite (lost 16 lbs over the year)
  - Reversal of sleep/wake cycle
  - Acknowledged sad mood
  - Passive suicidal ideation
  - Increasingly suspicious and paranoid

History

- 66 yo Caucasian female
- 13 y formal education
- Executive Assistant 9 y, Homemaker
- Married 38 y, 7 children
- No significant past medical history
- No psychiatric history/substance abuse

Family Medical History

- Father died age 82 -- stomach cancer
- Mother -- stroke in her 50's
  - plus "undiagnosed type of dementia," late 70's
- Four siblings all in good health

Video
Cognitive Exam ("Cognistat")

--Orientation (requires memory!)
--New learning (4 words)
--Attention (digit span)
--Language: repetition, naming
--Abstraction (how are a bicycle and a train alike?)
--Memory (recall 4 words)

Cognistat Results

Orientation	Good
New learning (4 words)	Good
Attention (6 digits)	Good
Language: repetition, naming	Good
Abstraction	4 out of 5 (concrete)
Memory (4 words)	3 out of 4 (√ cue)

Other Test Results

Impairments
- Low Reasoning/Abstraction
- Mental control impaired
  - Slow and perseverative on "Supermarket"
  - Problems with planning, inhibition
  - Could not do "Tap except for X"
  - Unable to "shift" on Trail Making B

Presenting Neurologic Symptoms
(2003)

- Progression of gait difficulties/falls
- Severe dysarthria
- Dystonic posturing of hands and feet
- Ataxic saccadic eye movements
- Poor voluntary upward + downward gaze
- Swallowing difficulties (liquids)

Neuroimaging Data

8/24/00 MRI

Essentially normal brain MRI

6/7/04 MRI

Mild diffuse cortical atrophy with no lobar predominance.

Epidemiology and course

Steele-Richardson-Olszewski syndrome

- Prevalence (M ≥ F)
  - 1.4 / 100,000 over age 60 (v. PD: 5/100,000)
- Etiology
  - Idiopathic: no familial, geographic, environmental, or ethnic patterns seen
  - Tauopathic: chromosome 17
- Average survival: 9.7 y
- Death secondary to falls or aspiration

PSP

- Characteristic features (+ in case E)
  - Broad based gait
  - Axial rigidity +
  - Toppling (backward) falls +
  - Nuchal dystonia
  - "Facial spasticity" (masked, apraxic) +
  - Dysarthria (apraxia of speech) +
  - ? Frontal release signs
  - ? Utilization behavior, pallilalia

Criteria

- NINDS-SPSP "Probable PSP"

Vertical supranuclear gaze palsy

+

Prominent postural instability with falls within first year of onset

=

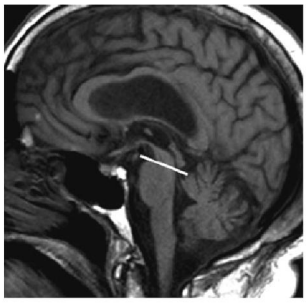
100% positive predictive value

Neuropathology

Neuronal loss
- esp. subthalamic nucleus, globus pallidus, superior colliculus, pretectal area, substantia innominata

- Neurofibrillary tangles
- Volumetric changes
  - midbrain (↓), 3rd ventricle (↑)
- ? Frontotemporal atrophy

Figure Midsagittal MRI of the brain demonstrates prominent midbrain atrophy without pontine atrophy (divided by white line), forming the silhouette of the "penguin" or "hummingbird" sign



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Neuropsychological profile

- Fronto-subcortical pattern in PSP
  - Language ok except for fluency (timed)
  - Perception ok
  - Memory generally preserved
  - Motor slowing and dyspraxia
  - *Executive dysfunction* very consistent

PSP versus Alzheimer's

Dementia profile (matched on severity)

- Better memory in PSP than AD
  - Mesial temporal structures OK
  - Also somewhat better memory than Parkinsons and Lewy Body dementias
- Worse initiation than AD
  - Basal ganglia and midbrain networks…

PSP versus Alzheimer's

- Affective symptoms
  - Apathy more frequent in PSP
  - Mild depression and anxiety (as in PD)
- Sleep disturbance worse than in AD
  - Insomnia and frequent awakening
  - Related to dysphagia, mobility, depression, nocturia

Lauterbach, 2004

Treatment

- Movement disorder (rigidity, bradykinesia)
  - Some patients respond temporarily to levodopa
  - **Donepezil (AChE) *worsened* self-care skills**
  - Botulinum toxin for blepharospasm
- Cognition
  - No benefit from AChE inhibitors that help AD
- Mood
  - Anticholinergics, SSRIs or tricyclics may help
- Apathy
  - Psychostimulant? in theory

Summary of Case E

- Affective disorder as presenting problem
- Dementia was mild
  - Executive dysfunction
  - Suspicion and reduced insight
- Dx Progressive Supranuclear Palsy
  - History, course, MRI, NPT typical for PSP
- Good family support and adaptation

QUIZ

How is "normal" determined?

A. If I can do it, it's normal.

B. Patient is normal if no *abnormal signs* are present.

C. Test results are compared to age group norms.

D. Normal means no change from past level of skills.

QUIZ

What unique information does the neuropsychological exam provide?

A. Test results quantify specific cognitive skills.

B. The tests measure mental status.

C. Test results can localize brain abnormality.

D. The exam determines the etiology of the brain disease.

QUIZ

How can the exam help determine whether an elderly patient is impaired or is just old?

A. Test norms are age-specific.
B. Medical and sensorimotor problems are taken into account.
C. The premorbid "bar" is set individually.
D. All of the above.

QUIZ

Which "frontal" symptoms did the patient exhibit?

A. witzelsucht
B. frontal release signs
C. utilization
D. perseveration

QUIZ

Which cognitive results distinguish PSP from Alzheimer's dementia?

A. memory is better in PSP
B. attention is better in Alzheimer's
C. abstraction is better in PSP
D. naming is better in Alzheimer's

References

- Aarsland D et al. (2003) Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. *J Neurol Neurosurg Psychi* 74: 1215-1220.
- Goetz C. *Textbook of Clinical Neurology*, 2nd ed., 2003.
- Lauterbach EC (2004) The neuropsychiatry of Parkinson's disease and related disorders. *Psychiatr Clin N Am 27* 801-825.
- Litvan & Agid. *Progressive Supranuclear Palsy: Clinical and Research Approaches*, 1992.
- Oba H et al. (2005) New and reliable MRI diagnosis for PSP. *Neurol 64* 2050-2055.

Neural development II

- ❖molecular genetics and neuroscience
- ❖CNS congenital malformations
- ❖Neurodegenerative diseases during aging

Relevant concepts

- Neural patterning (spatial ordering)
- Cellular determination
- Migration
- Connectivity
- Regressive events
- Activity-dependent processes

Nervous System organization begins in the neural plate stage

- **CNS develops as hollow tube**
- **Topographically flat sheet of cells = neural plate**
- **Process of CNS development called neurulation**
- **Gradual and continuous process**
- **Much of it occurs prenatally**
- **genetic determinants and experience**

Neurulation

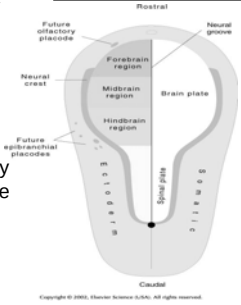
Neurodevelopment

Polarity
Bilateral symmetry
Regionalization

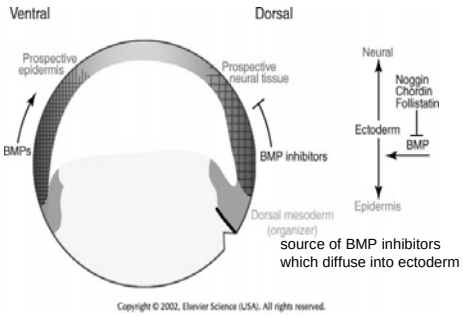
"requires complex processes of neural patterning that endow precursor cells with ability to give rise to correct type of neuron in the right location"

Right cell in the right place

Neural Plate



NEURAL INDUCTION



source of BMP inhibitors which diffuse into ectoderm

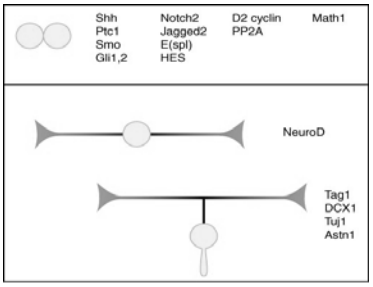
BMP= bone morphogenetic proteins (polypeptide growth factors) released by ectoderm

Changing patterns of gene expression

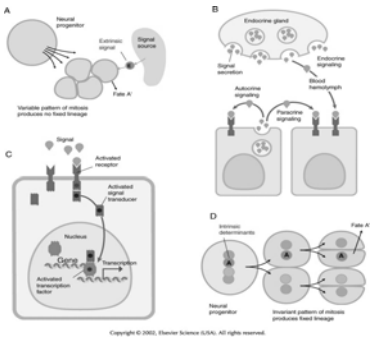
Proliferation

Differentiation

Migration



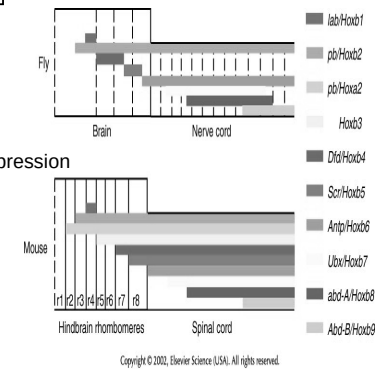
Neural fate controlled by: intrinsic and extrinsic determinants



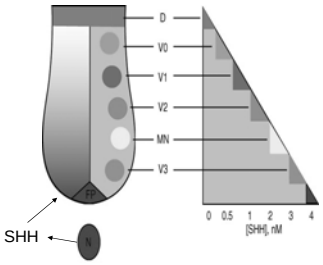
AP Migration

Drosophila-mouse

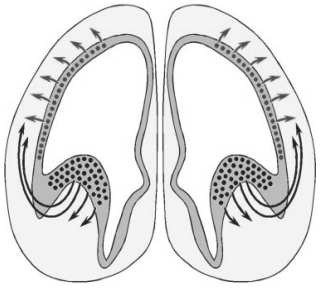
differential gene expression



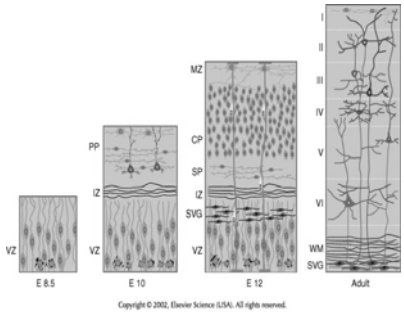
DV Migration



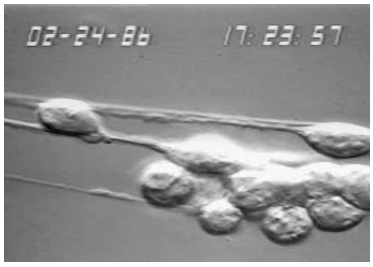
Radial migration



Radial pathway –major migratory route



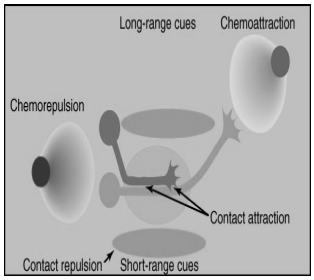
Radial migration



http://www.rockefeller.edu/labheads/hatten/mechanism.html

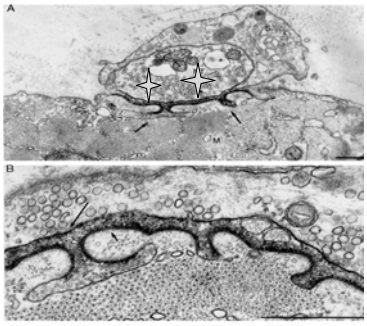
Hatten and Edmondson, 1987. (J. Neurosci.)

Axons guided to target by their responses to selectively distributed molecular signals



"push-pull-hem"

Synapse matching – molecular cues



= agrin

Agrin released by MN
AchR clusters

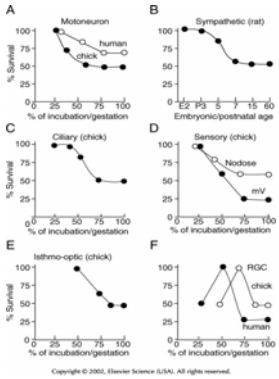
Programmed Cell Death:

spatiotemporal cell loss

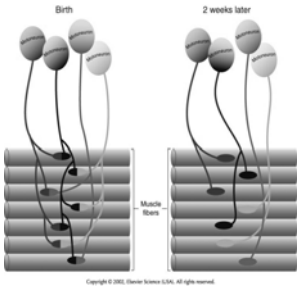
dependent on signals arising from cell:cell interactions

neurotrophic factor exposure

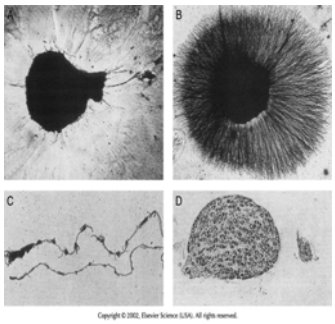
Aberrations in balance: cancer vs neurodegenerative diseases like ALS



Synapse elimination- transient synapse formation

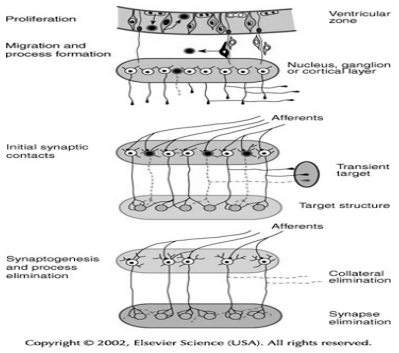


convert highly redundant, overlapping circuitry to unique functionally distinct circuit



PCD

Pruning



Neural Patterning (spatial ordering)

- Neural induction- BMPs
- Cellular determination –intrinsic vs extrinsic
- Migration- AP, DV, Radial
- Connectivity- functional networks
- Regressive events- pcd and pruning
- Influence of genetics vs activity-dependent processes

Early experience and critical period

- synaptic connections pass through a period in early life when the capacity to adjust is greater than in adulthood = “critical period”
- neurons are sensitive to modification by experience
- critical period – a pathway awaits specific instructions to develop normally
- Binocular vision, language, social imprinting

Relevance of understanding how the nervous system develops

- regeneration recapitulates development
- application to injury and repair
- intrinsic vs extrinsic

Neurodevelopment - neuroregeneration

- regeneration recapitulates development
- application to injury and repair
- intrinsic vs extrinsic
- traditional vs modern view of CNS repair

Neuroregeneration and Plasticity

- Regeneration = regrowth of damaged axon
- Plasticity = remodelling of spared, uninjured pathways

PNS Response to Injury: anterograde and retrograde

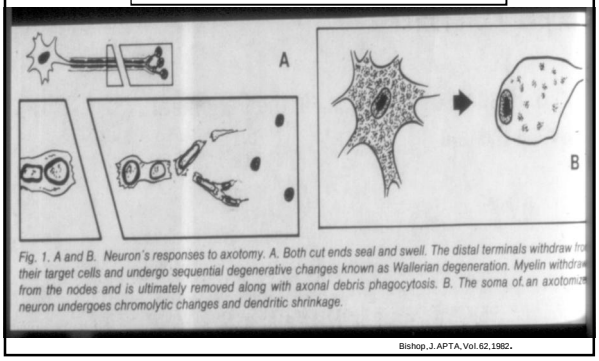
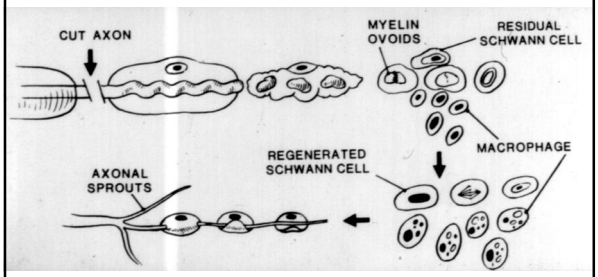


Fig. 1. A and B. Neuron's responses to axotomy. A. Both cut ends seal and swell. The distal terminals withdraw fro their target cells and undergo sequential degenerative changes known as Wallerian degeneration. Myelin withdra from the nodes and is ultimately removed along with axonal debris phagocytosis. B. The soma of an axotomiz neuron undergoes chromolytic changes and dendritic shrinkage.

Bishop, J. APTA, Vol. 62, 1982.



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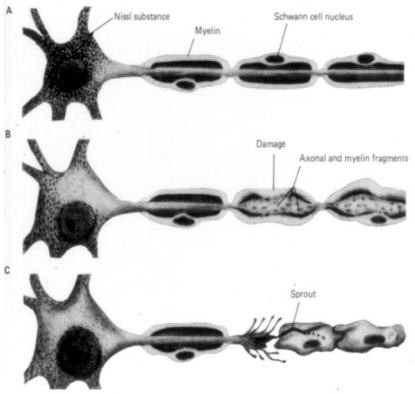

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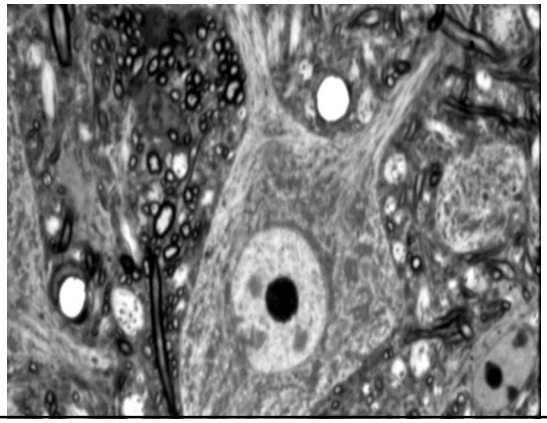

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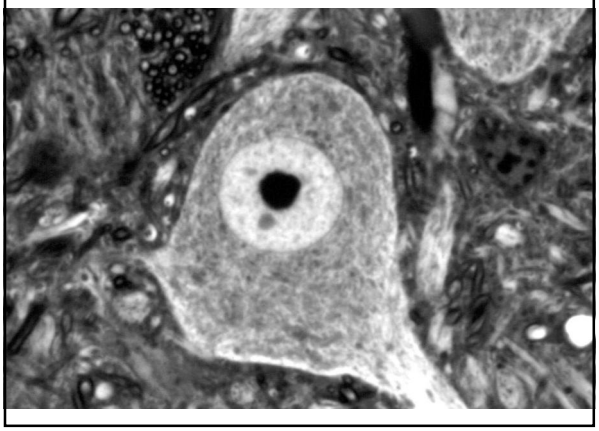


↑rRNA + mRNA

↓

↑Ribosomes + protein synthesis

↓

↑Production of regeneration-associated genes/proteins

↓

↑Axonal elongation and synaptogenesis

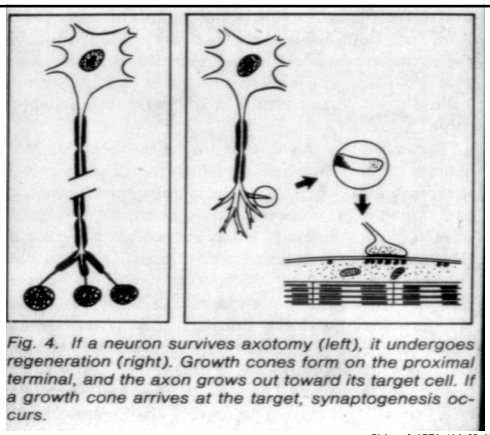
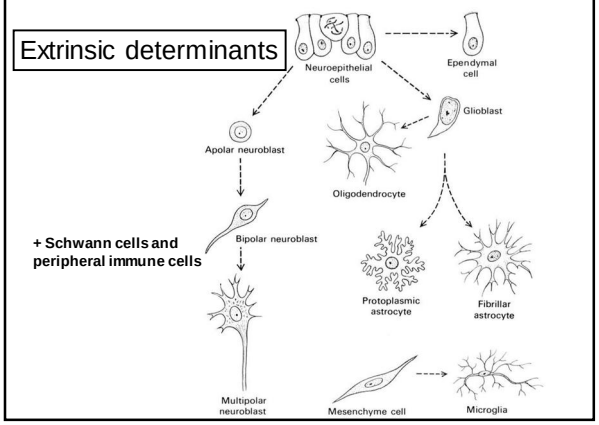


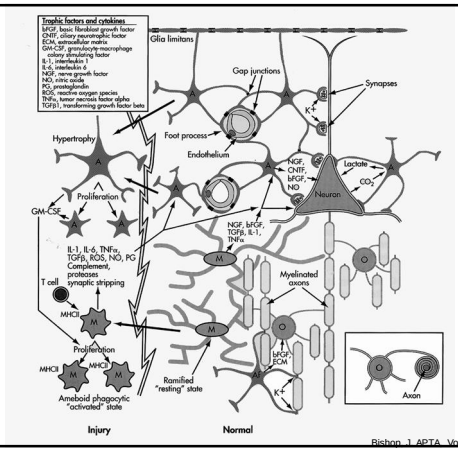
Fig. 4. If a neuron survives axotomy (left), it undergoes regeneration (right). Growth cones form on the proximal terminal, and the axon grows out toward its target cell. If a growth cone arrives at the target, synaptogenesis occurs.

Bishop, J. APTA, Vol. 62, 1982.

Extrinsic determinants

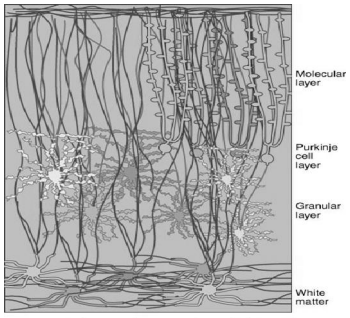


+ Schwann cells and peripheral immune cells

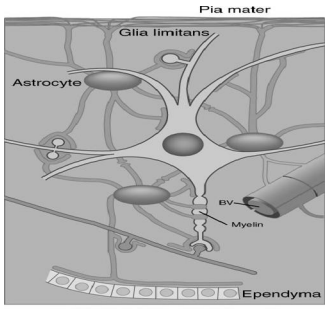


Bishop J APTA Vol 62 1982

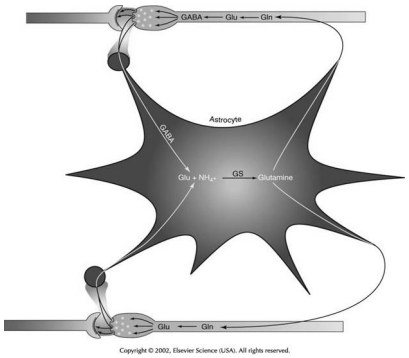
Astrocytes-can form glial scar



Astrocytes provide metabolic support

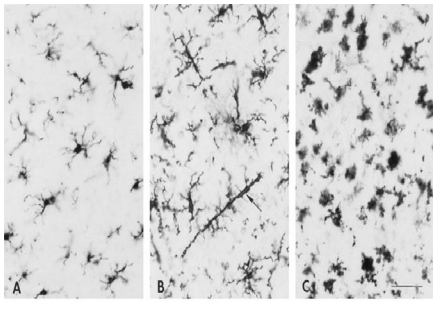


growth factors
adhesion molecules
spatial buffering

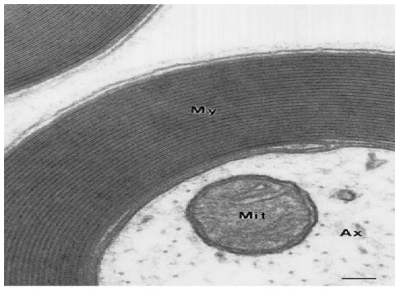


Protection from excitotoxicity

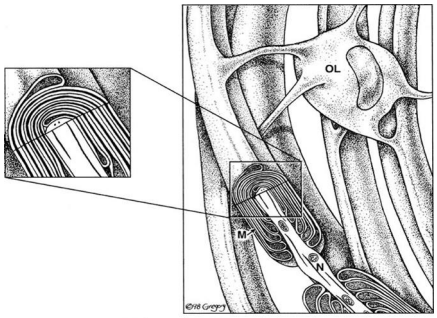
Microglia- mediate immune response

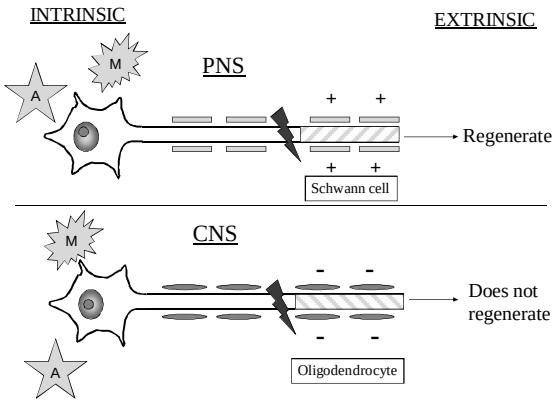


Schwann cells produce growth permissive environment



Oligodendrocytes-NoGoA





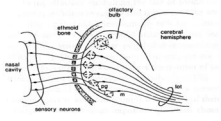
Spinal cord injury

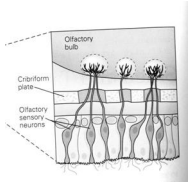
How to make a CNS motoneuron regenerate as effectively as a PNS motoneuron?

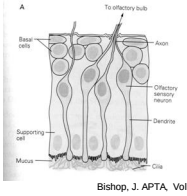
Olfactory Ensheathing Cells

- Unique type of macroglia found in the olfactory system
- Cross between PNS Schwann cells and CNS astrocytes
- In contrast to other CNS glia, provide growth permissive environment for regenerating CNS axons

PNS axons grow into CNS and establish synaptic contact with central neurons in the olfactory bulb







Bishop, J. APTA Vol. 62, 1982.

Factors influencing Regeneration

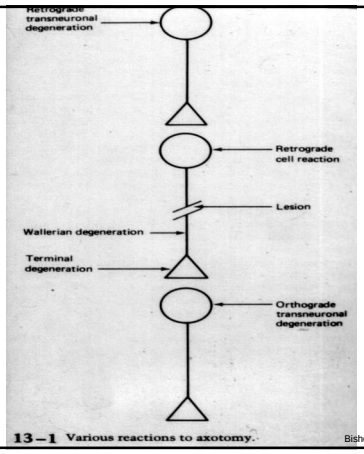
- PNS more likely to regenerate than CNS
- Intrinsic vs. extrinsic
- Age – immature more likely to die
- Site – proximal more severe

What is NEURAL PLASTICITY?

- Flexibility and adaptability of the nervous system
- Experience-related
- Adult CNS capable of plasticity

What LEVEL does NEURAL PLASTICITY occur at?

- Primarily at connectivity points
  - (i.e.- formation of synapses)
- Results in alternate pathways for various NS functions



13–1 Various reactions to axotomy.

Bishop, J. APTA, Vol. 62, 1982

PNS: Ia → αmn → muscle

CNS: Retina → LGN → visual cortex

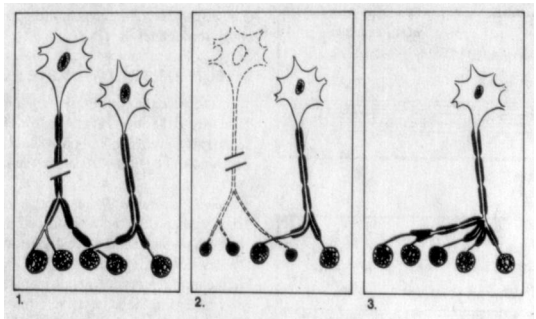
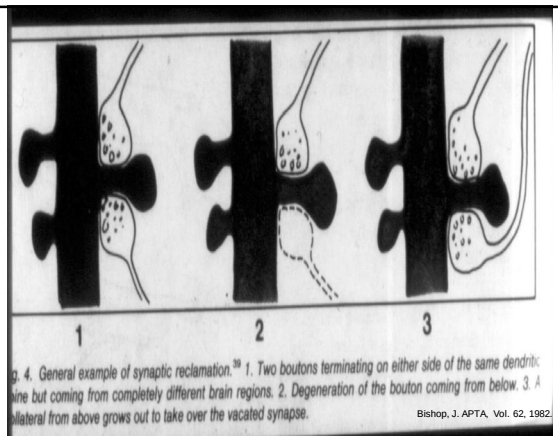


Fig. 3. Collateral sprouting of a viable motor axon. 1. Partial injury of a peripheral nerve severs one axon and leaves the other intact. 2. The severed axon degenerates, leaving its muscle fibers denervated. 3. Surviving neuron sends out collateral sprouts to reinnervate the denervated muscle fibers. The result is a giant motor unit.

Bishop, J. APTA, Vol. 62, 1982



g. 4. General example of synaptic reclamation.[39] 1. Two boutons terminating on either side of the same dendritic
pine but coming from completely different brain regions. 2. Degeneration of the bouton coming from below. 3. A
ollateral from above grows out to take over the vacated synapse.

Bishop, J. APTA, Vol. 62, 1982.

Recovery of function

- Regeneration vs plasticity
- Combinatorial treatment strategies
- Therapeutic staging
- Immune system involvement

Neuroplasticity and Neural Repair

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Edward Hines Jr. VA Hospital/Loyola University Medical Center
Chicago, USA
September 29, 2009

Neuronal Plasticity

- **Defined as the formation of new neuronal connections after CNS injury.**
- **Commonly seen following injury to the neonatal brain, and not after adult brain injury.**
- **This neuronal plasticity may be the anatomical substrate for functional recovery more commonly seen after brain injury in the young.**
- **Why doesn't the adult brain show such dramatic plasticity after injury…?**

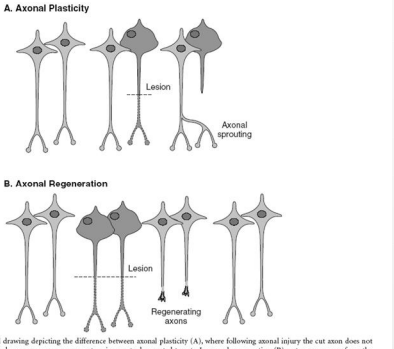
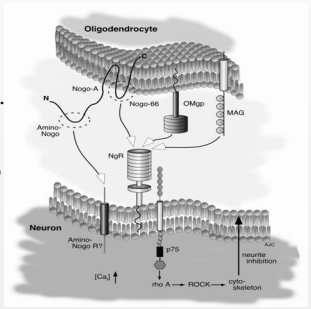


FIGURE 30-1 Simplified drawing depicting the difference between axonal plasticity (A), where following axonal injury the cut axon does not regrow, but other undamaged neurons grow new axons to reinnervate denervated targets. In axonal regeneration (B), cut axons regrow from the damaged sites and reconnect with denervated targets.

Taken from Basic Neurochemistry, Ed G.J. Siegel

Molecular Mechanisms of Neurite Inhibition

- **Three myelin inhibitory proteins have been found, Myelin Associated Glycoprotein (MAG), Oligodendrocyte myelin glycoprotein (OMgp), and Nogo-A.**
- **One receptor, Ng-66R, binds with all three.**
- **This receptor interacts with p75 to activate down- stream molecules that cause growth cone collapse.**
- **Other inhibitory factors are present in glial scars, i.e. proteoglycans.**



by AJC

Adapted from Schwab, Current Opinion in Neurobiology, 2004

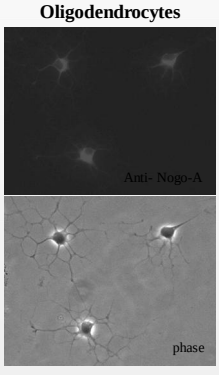
Swiss Alps, Interlaken

by G..K.

Nogo-A

- **A neurite inhibitory protein expressed primarily by oligodendrocytes.**
- **This protein is known to cause growth cone collapse and thereby inhibit new neuronal connections, i.e. block neuronal plasticity.**

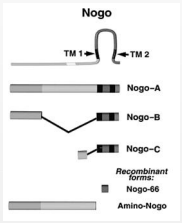
Oligodendrocytes



by G..K.

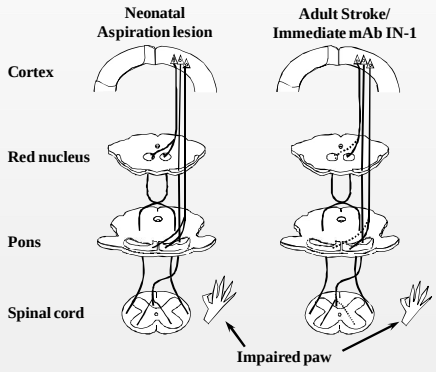
Molecular Structure of Nogo-A

- One of three protein products from the Nogo gene, ie Nogo-A, B and C
- M.W. 250,000 kD.
- All isoforms share a common c-terminal domain of 188 amino acids.
- Blocking antibody IN-1 (mAb IN-1) neutralizes Nogo-A and promotes neurite outgrowth in culture and after spinal cord injury, so will mAb IN-1 result in plasticity when given to adults after stroke?



Brittis and Flanagan, Neuron, 2001

Hypothesis



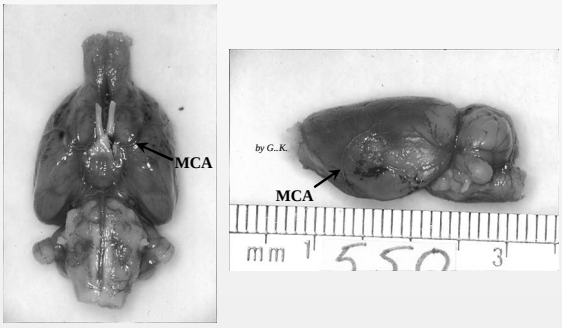
by G..K.

Behavioral Testing

- The skilled forelimb reaching test is a sensorimotor test that requires accurate limb placement and fine digital control for the manipulation of small food pellets.
- The corticospinal and corticorubral-spinal pathways are essential to complete this task.
- Animals are trained to reach through the opening and retrieve food pellets.
- 20 pellets are placed one at a time on the outside platform.

by G..K.

Rodent Brain Vasculature



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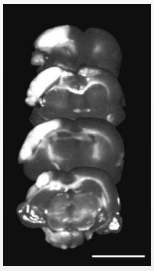
TTC Staining



TTC (2,3,5-triphenyl-2H-tetrazolium chloride)-stained coronal brain sections at 3 days after permanent MCAO demonstrates a representative stroke size and location in the ispilateral sensorimotor cortex. Viable tissue appears red as a result of the reduction of the dye by functional mitochondrial enzymes; the area of the ischemic infarction appears white.

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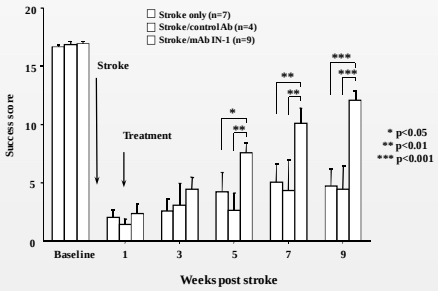
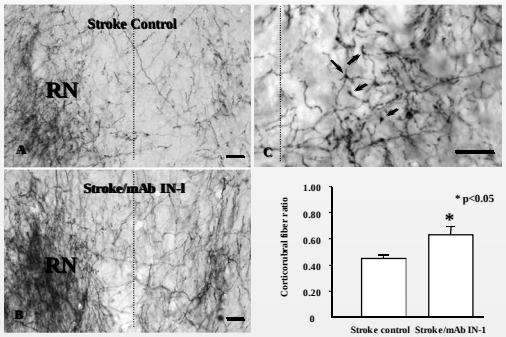
Functional Recovery Following Stroke/ One Week Delayed mAb IN-1 Treatment



(Seymour et al 2005, J Cerebral Blood Flow Metabolism)

Corticorubral Plasticity



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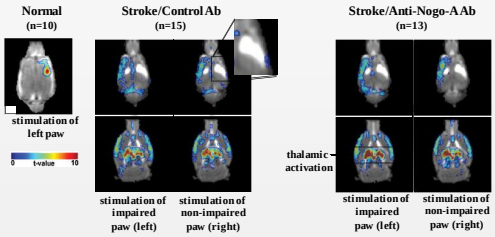
fMRI

Anti-Nogo-A treatment enhances thalamic activation after stroke and anti-Nogo-A treatment



by G..K.

Aged Rat at Baseline

Right-handed

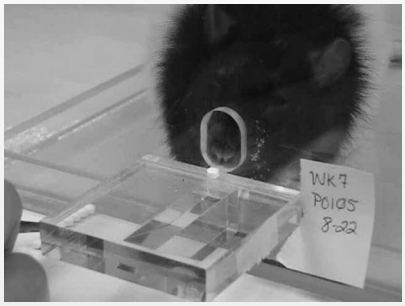
by G..K.

Aged Rat after Stroke/No Treatment
Initial Deficit

Right-handed/Left MCAO

by G..K.

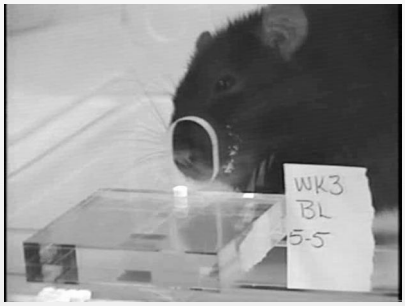
Aged Rat 15 Weeks after Stroke/No Treatment
No Improvement



Right-handed/Left MCAO

by G..K.

Aged Rat at Baseline



Left-handed

by G..K.

Aged Rat after Stroke/Anti-Nogo A Treatment

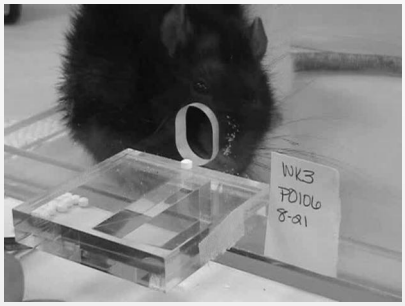
Initial Deficit

Left-handed/Right MCAO

by G..K.

Aged Rat after Stroke/Anti-Nogo A Treatment

(15 Weeks Post-Tx): Showing Marked Improvement

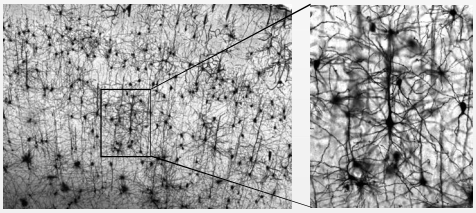


Left-handed/Right MCAO

by G..K.

Does mAb IN-1 Treatment Enhance Dendritic Arborization In Spared Neurons After Stroke ?

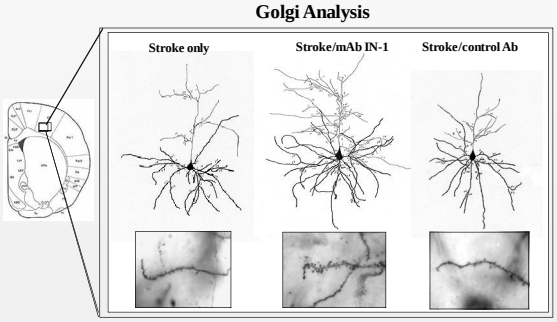
Golgi-Cox Stain of Neurons in Unlesioned Forelimb Cortex



by G..K.

Dendritic Sprouting Following Stroke and mAb IN-1 Treatment

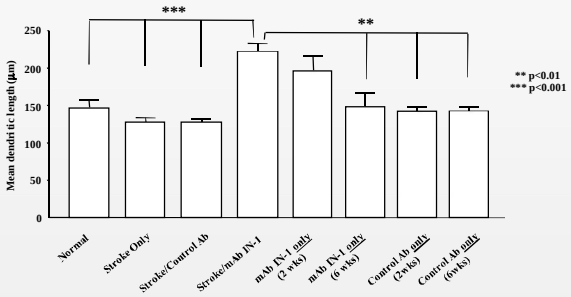
Golgi Analysis



(Papadopoulos et al 2006, Cerebral Cortex)

Golgi Analysis

Total Dendritic Length



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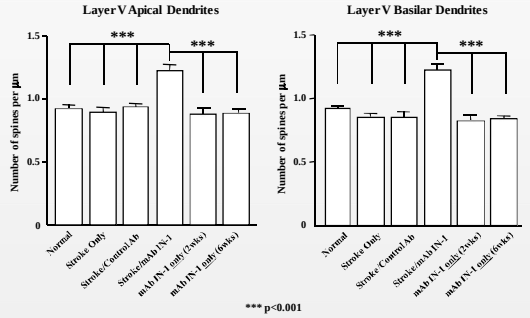
Golgi Analysis-Spine Density



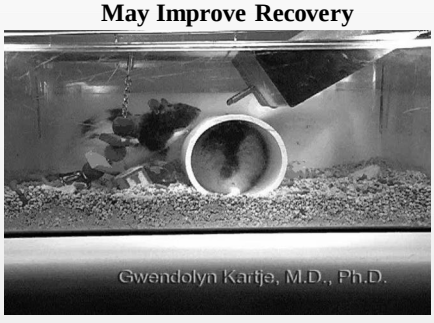
*** p<0.001

by G..K.

Environmental Enrichment May Enhance Neuronal Plasticity and Improve Functional Recovery

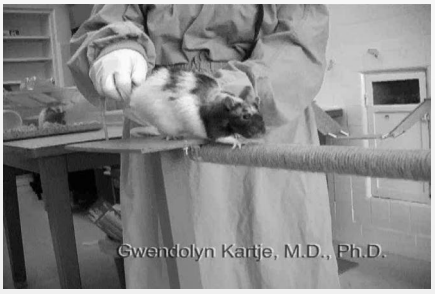
- Social interactions
- Complex housing
- Regimented physical therapy

Environmental Enrichment May Improve Recovery



- Social interaction
- Complex housing

Environmental Enrichment May Improve Recovery



- Regimented physical therapy

Summary

1. Cortical reorganization can occur after brain injury.
2. This reorganization, called Neuroplasticity, results in functional recovery.
3. Molecules responsible for creating an inhibitory environment in the adult CNS include Nogo-A, MAG, Omgp, and Proteoglycans.
4. Blocking the protein Nogo-A results in new axonal sprouting after stroke, as shown by recent experiments.