
dstein

Perspectives on Plasticity and Repair after Brain Injury

Donald G. Stein, Ph.D.

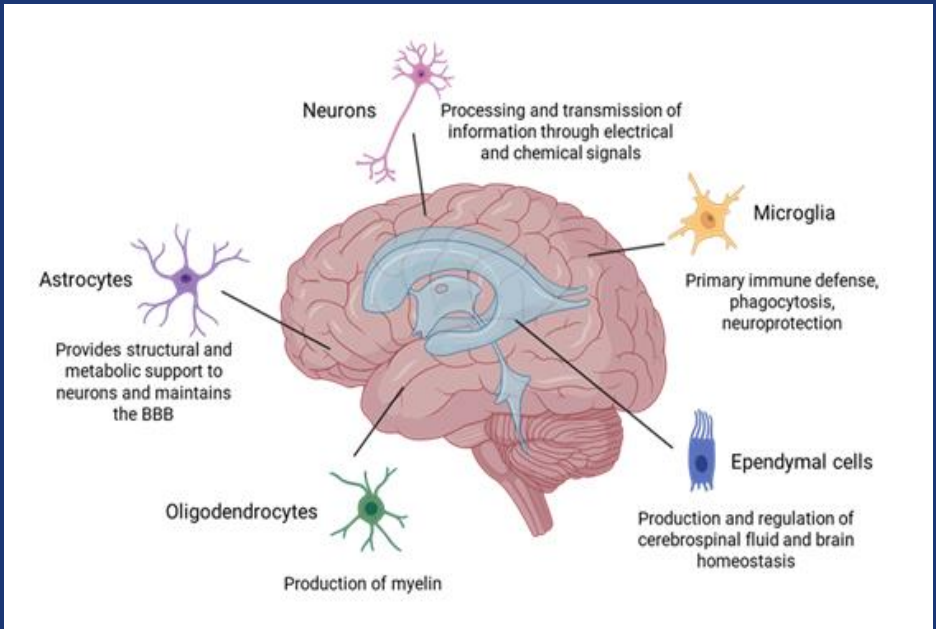
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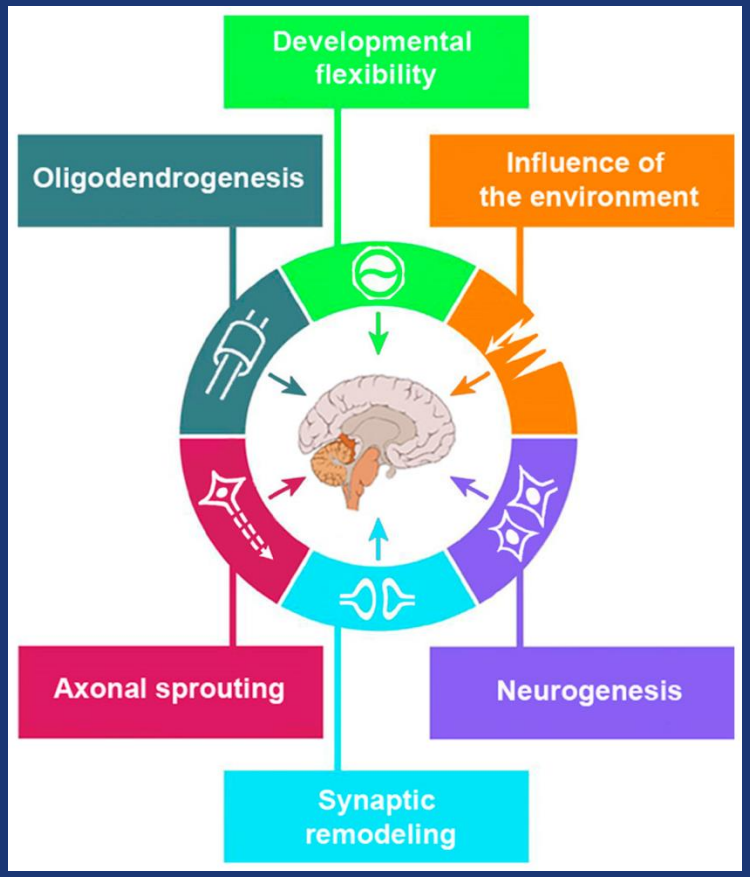
A Major Issue For Restorative Neuroscience: How Is "Plasticity" Defined?

- How do we define "function" and "plasticity"?
- How do we specify what is required to promote plasticity and execute function?
- How do you conclusively show which part of the brain specifically controls a particular function?
- Can functions become maladaptive as a result of experience or injury (e.g. learned disuse)? Is it still 'plasticity' if it's harmful?

The Major Components of Plasticity



Plasticity Is A Series of Complex Actions



A Few Examples Of How Functions/Results Are Often Described

- Results 'may' be *interpreted to suggest*….
- Our findings *can be taken to indicate* that…
- The hippocampus is *implicated* in….
- The frontal cortex is *'associated with'*...
- The caudate nucleus *'mediates'*....
- The visual cortex *'is the center'* of visual processing.
- The reticular formation *'regulates'* consciousness/.

Some Definitions of Neuroplasticity
Britannica, 2024

- **Neuroplasticity**, the capacity of neurons and neural networks in the brain to change their connections and behaviour in response to new information, sensory stimulation, development, damage, or dysfunction.

- Although some neural functions appear to be hard-wired in specific, localized regions of the brain, certain neural networks exhibit modularity and carry out specific functions while also retaining the capacity to deviate from their usual functions and to reorganize themselves.

- Other 'types' of neuroplasticity, such as compensatory masquerade, *can simply be described (?)* as the brain figuring out an alternative strategy for carrying out a task when the initial strategy cannot be followed due to impairment.

- When one function is carried out frequently enough through repeated behaviour or stimulus, the region of the cortical map dedicated to this function grows and shrinks as an individual "exercises" this function.

How Dogma Can Block Discovery



not seeing—even when it's right in front of your eyes



Figure 3.26. Santiago Ramón y Cajal (1852–1934), winner of the 1906 Nobel Prize for his extensive contributions to neuroanatomy.

"Once development was ended the fonts of growth and regeneration of the axon and dendrites dried up irrevocably. In adult centers, everything may die, nothing may be regenerated."

-Santiago Ramon y Cajal

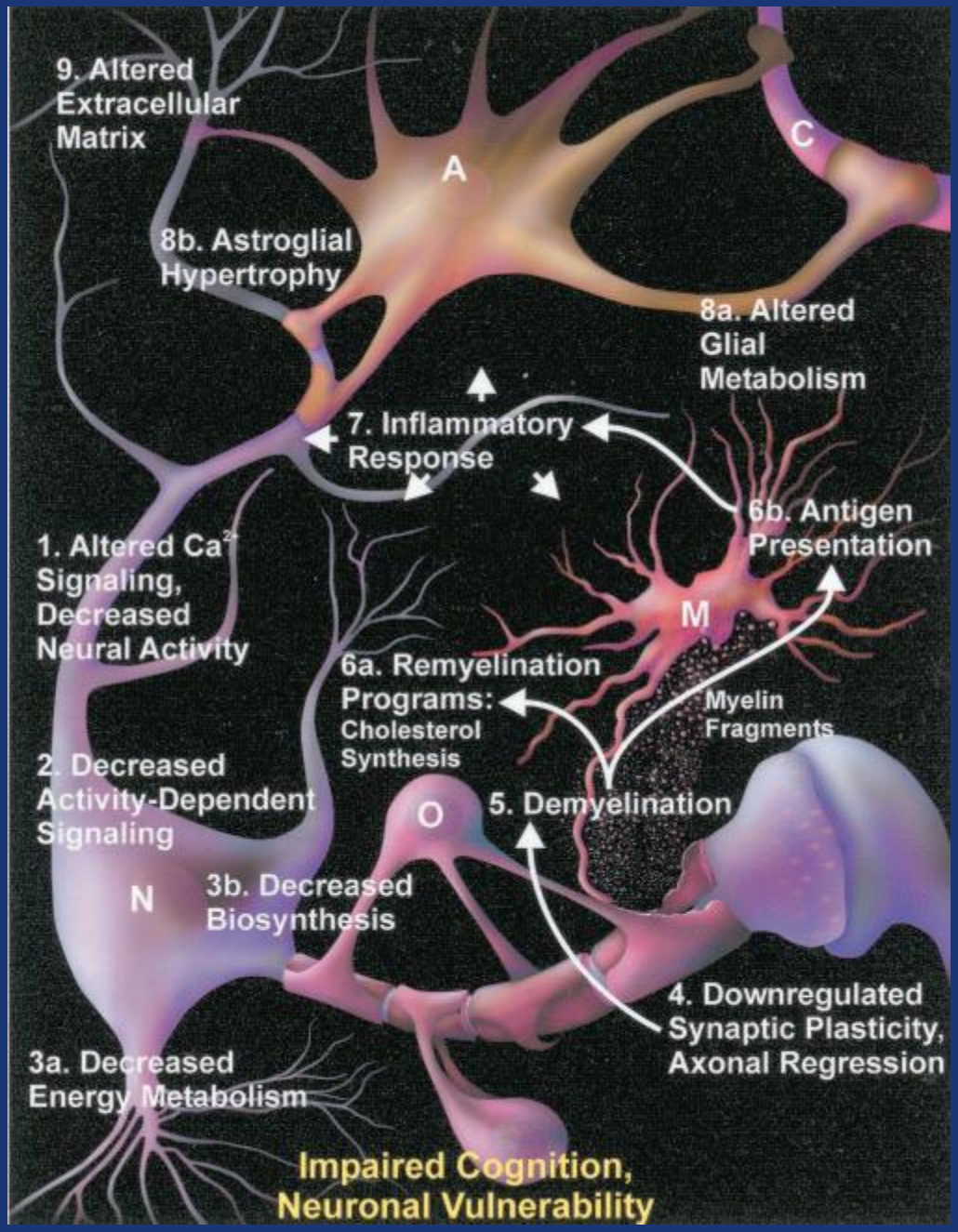
A Short True-false Test On Plasticity And Repair After Damage To The Brain

- Neurons in the adult nervous system do not regenerate!
- Only replacement of specific nerve connections will lead to recovery of function!
- Only neurons play a role in repairing brain functions!
- Once a brain structure is lost, its specific functions are lost forever!
- If functional recovery does not occur in the first few months after injury—it will never occur!
- Any recovery observed is just a "trick" used to compensate for the loss of function.

What Opportunities Are There To Enhance Plasticity In The Damaged Brain?

Early Work On Neural Regeneration & Repair

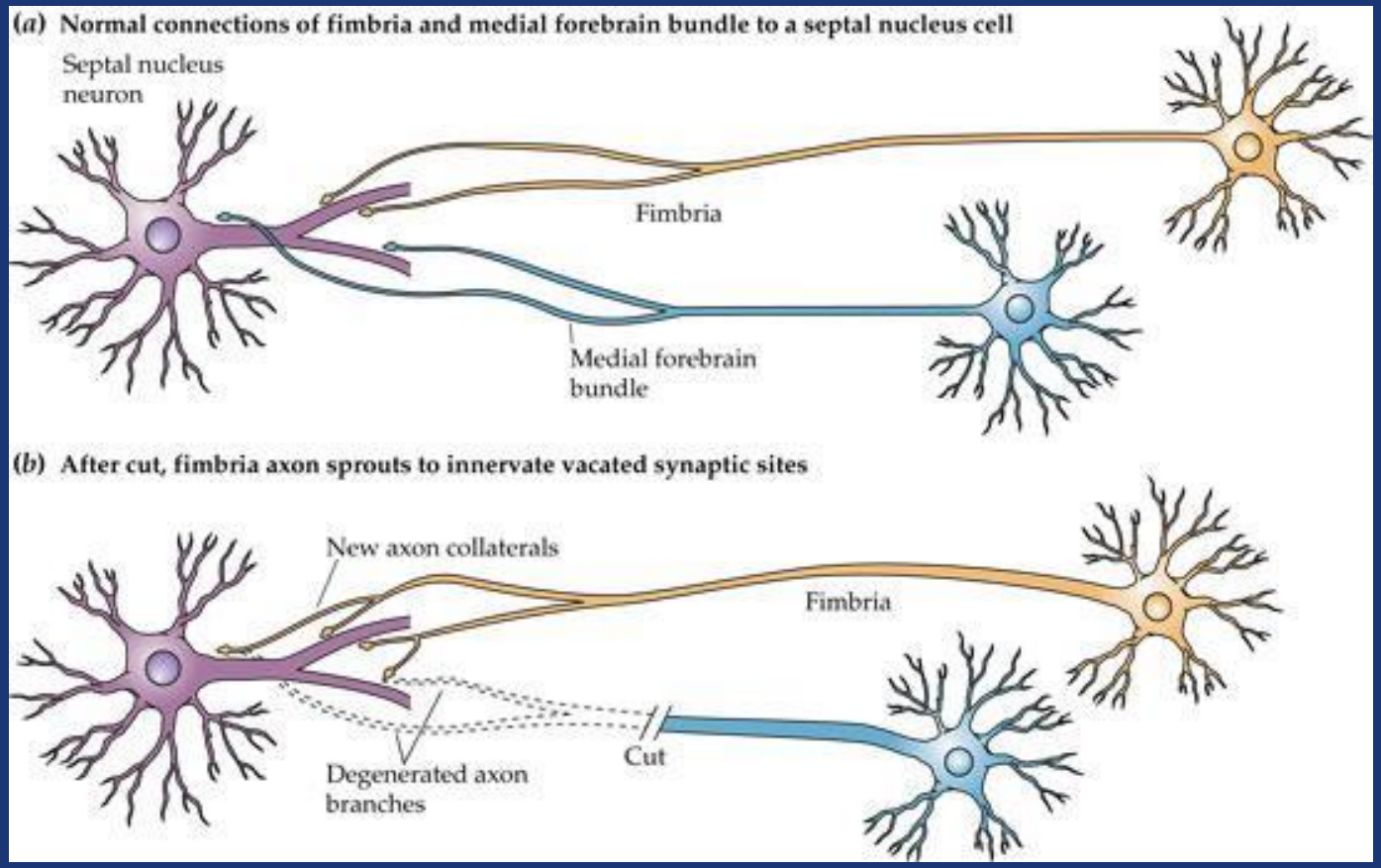
Collateral Sprouting & Regeneration


9. Altered Extracellular Matrix
A
C
8b. Astroglial Hypertrophy
8a. Altered Glial Metabolism
7. Inflammatory Response
6b. Antigen Presentation
1. Altered Ca^{2+} Signaling, Decreased Neural Activity
M
6a. Remyelination Programs: Cholesterol Synthesis
Myelin Fragments
2. Decreased Activity-Dependent Signaling
O
5. Demyelination
N
3b. Decreased Biosynthesis
4. Downregulated Synaptic Plasticity, Axonal Regression
3a. Decreased Energy Metabolism
Impaired Cognition, Neuronal Vulnerability

First Steps: Geoff Raisman Helped Change The Story



Collateral Sprouting After Injury 1968

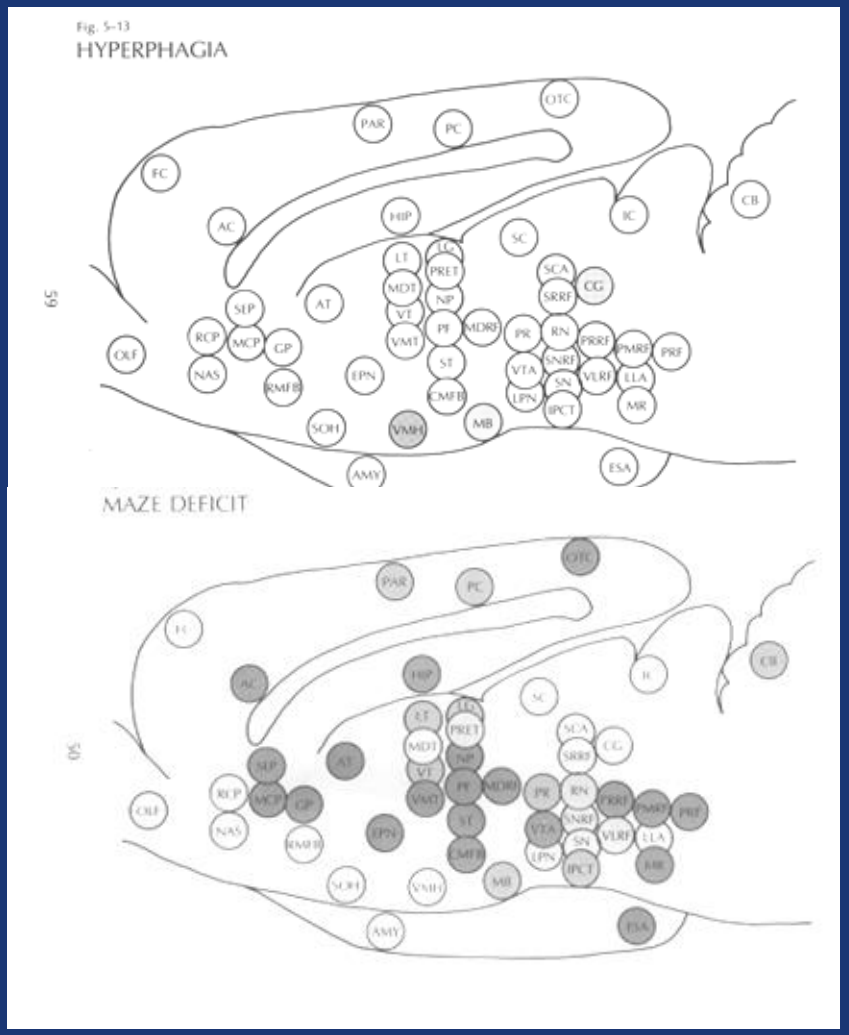


An Important Question

If Plasticity And Recovery Occur, How Does This Fit With The Idea That Functions Are Hardwired And Localized

?

MAPPING THE BRAIN: LOCALIZATION OF MAZE AND EATING DISORDERS AFTER BRAIN LESIONS IN A RAT BRAIN ATLAS



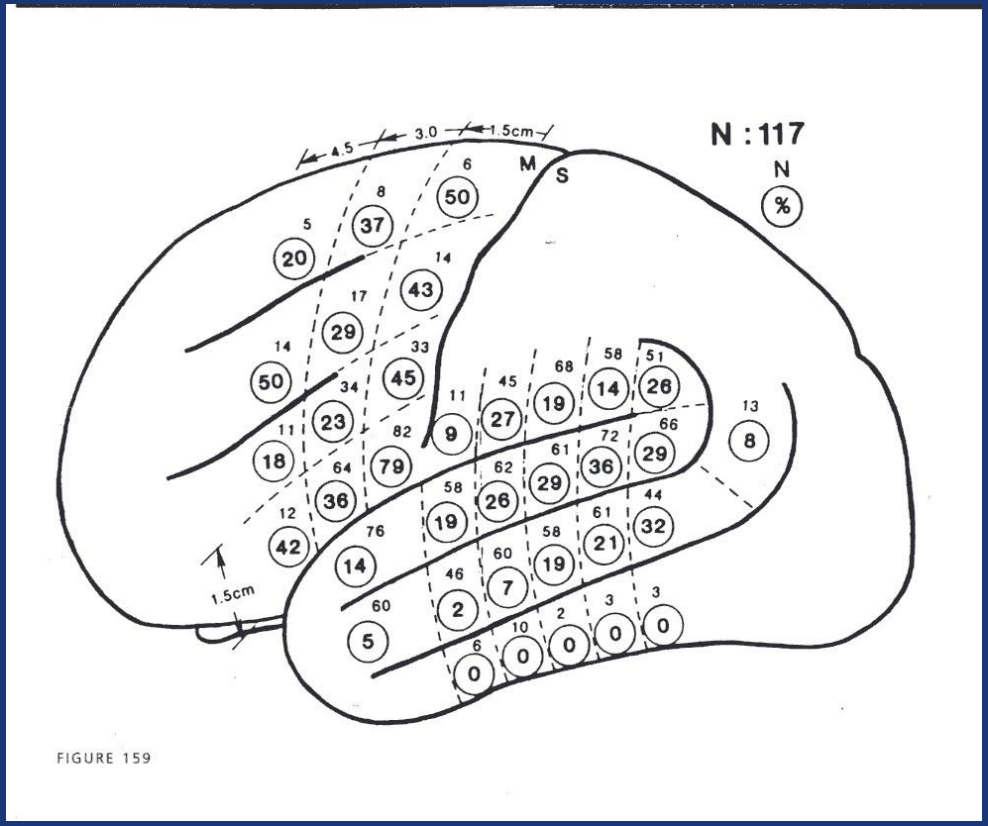


FIGURE 159

LOCALIZATION OF LANGUAGE FUNCTIONS BY ELECTRICAL STIMULATION OF THE CORTEX IN 117 PATIENTS

(reveal substantial variability)

Ojemann G, et al., 1999, J Neurosurg 71:316

The Serial LESION Effect. Why Is It Important In Understanding Brain Function And Repair

70 Years Ago, A Cautionary Note

- "A disturbance of a particular complex function does not in fact arise in association with a narrowly circumscribed lesion of one part of the cortex."
- "The performance of a given function necessitates the integrity of far more extensive and far more structurally varied zones of the cortex than is assumed by classical neurology."
- "We must conclude that there is no evidence for isolated cerebral 'centers' for any of the complex forms of mental activity."

Alexander Luria, Human Brain & Psychological Processes, 1966

Brain Mapping Project

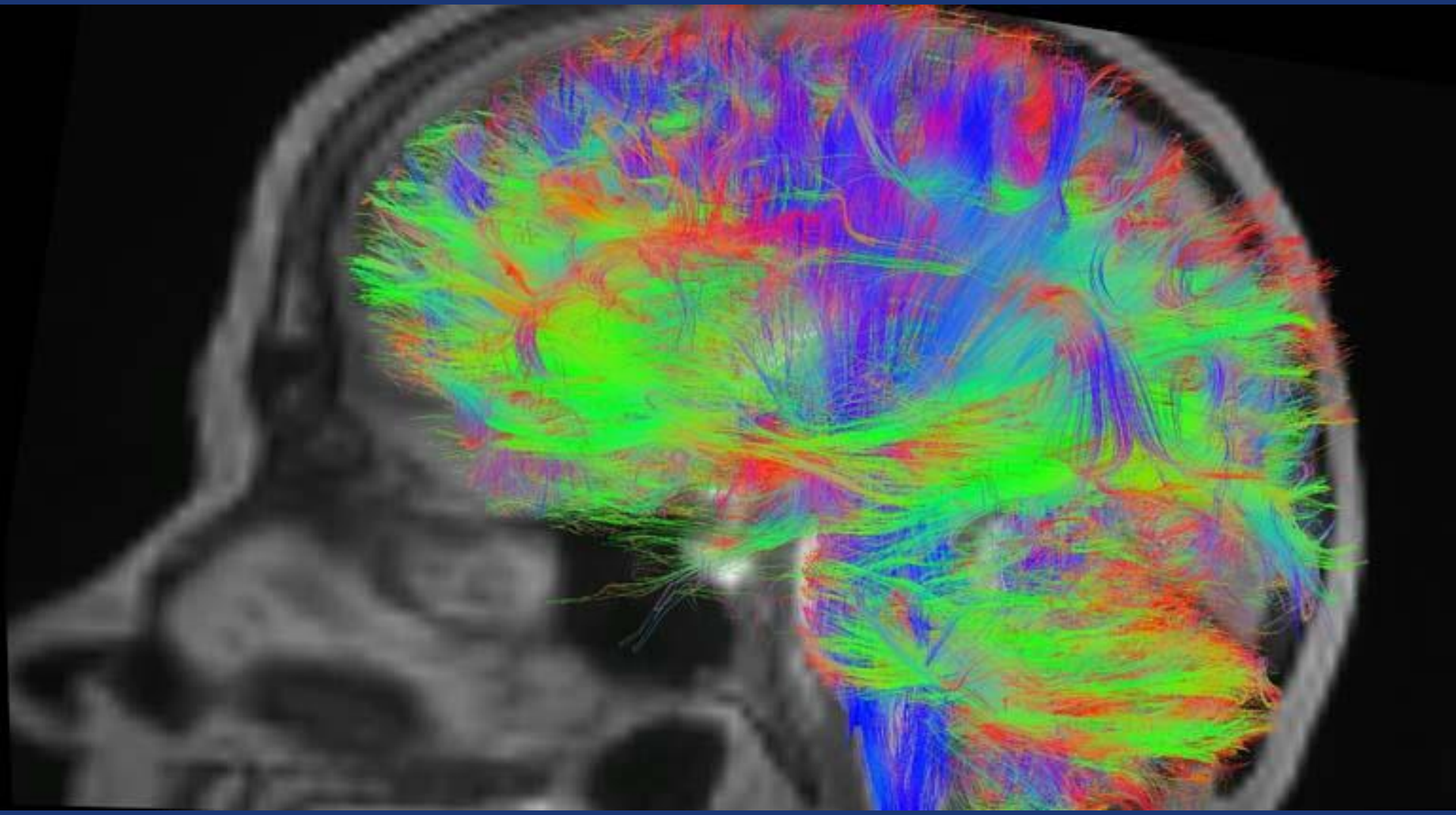


Fiber Tract Mapping

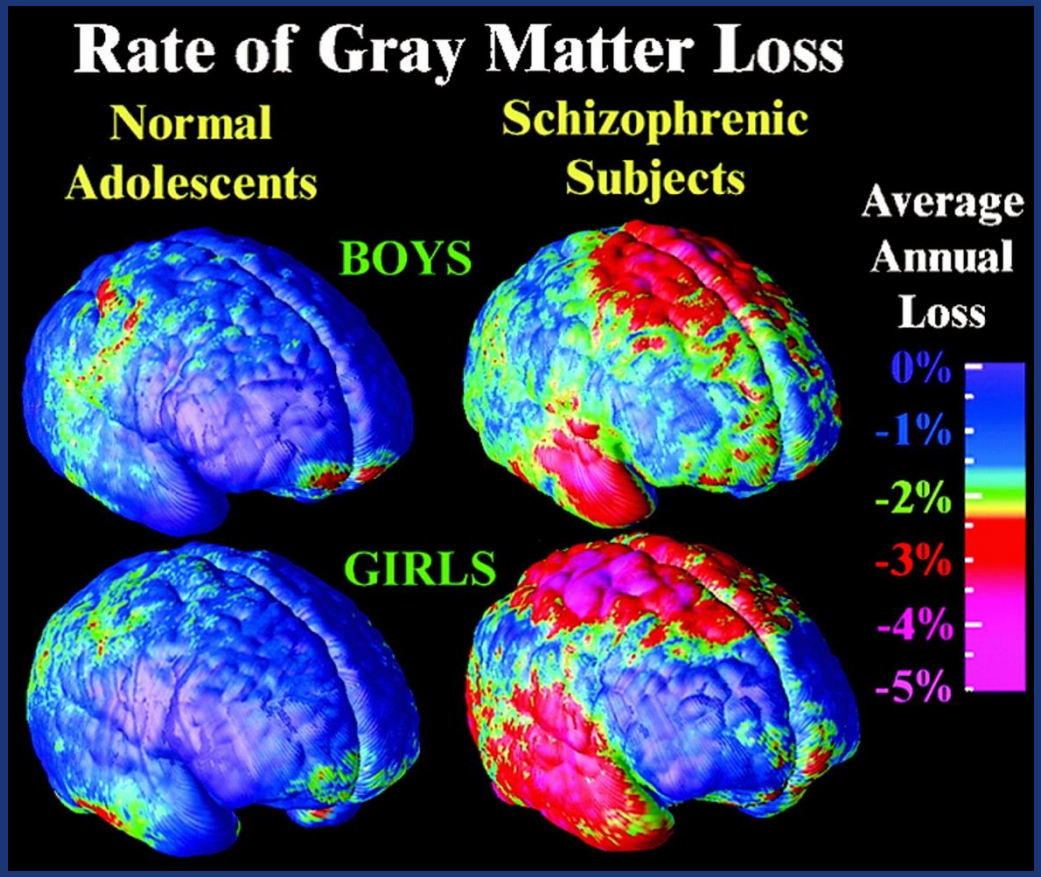




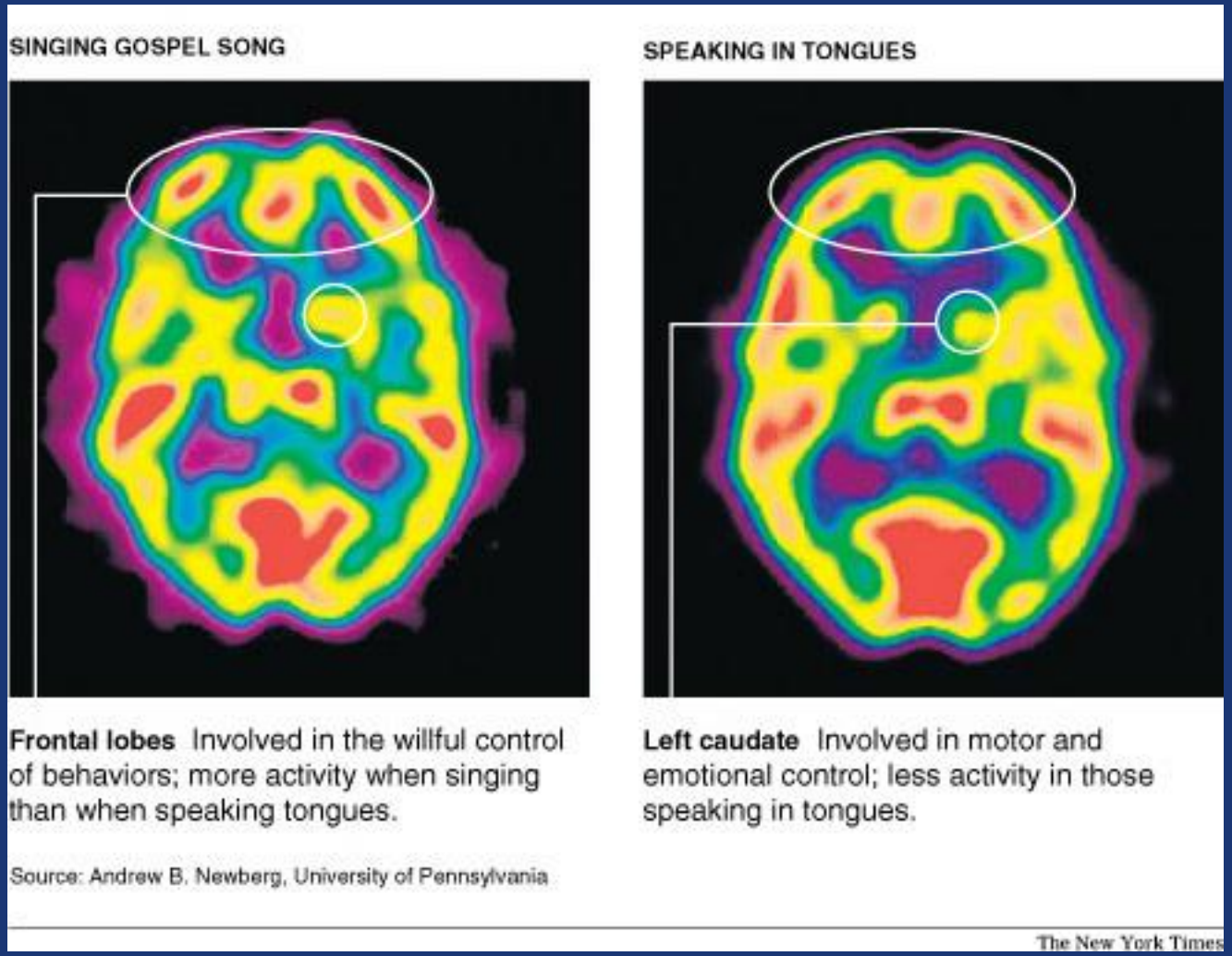
Mapping The Connections



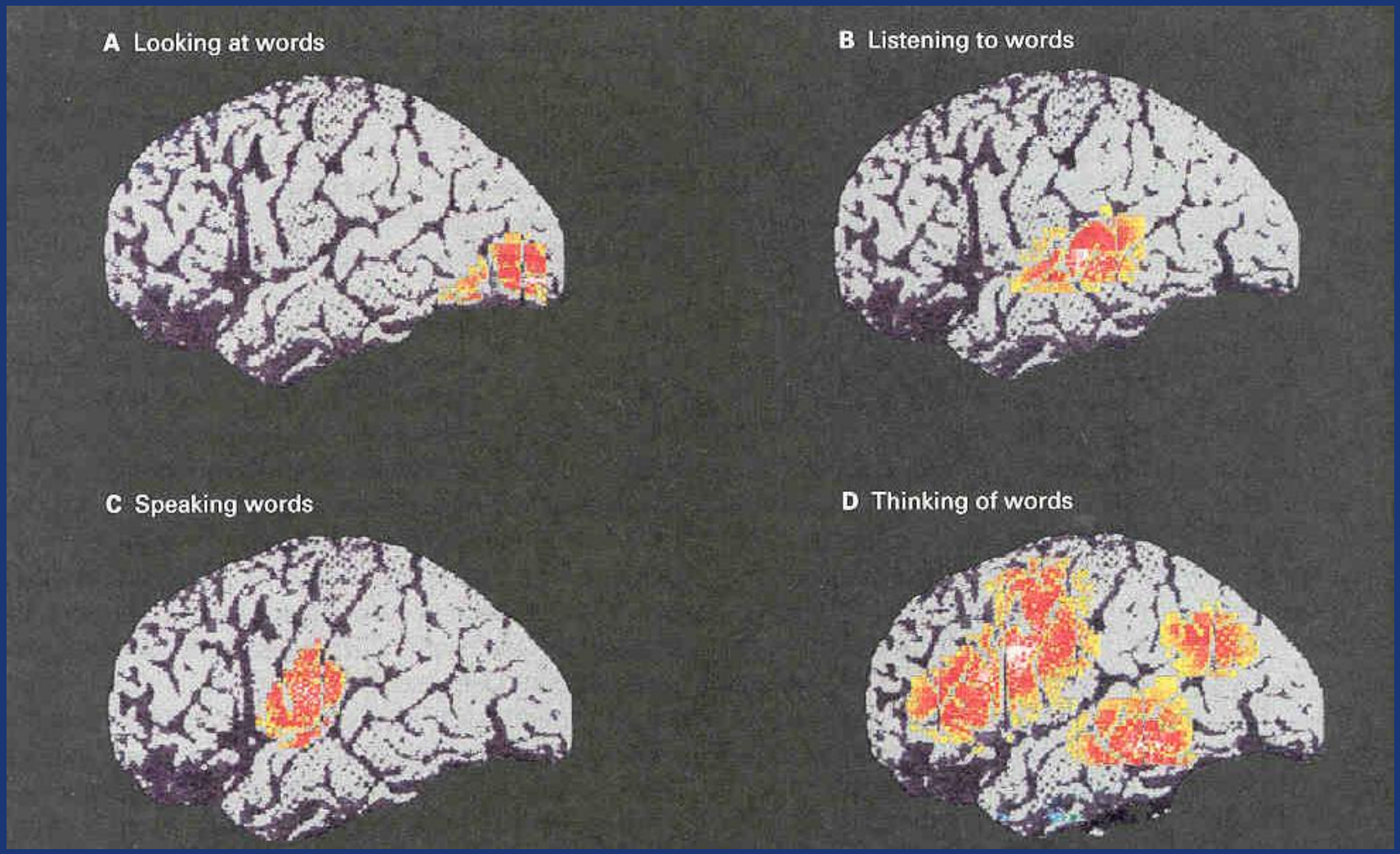
Mapping Schizophrenia



Mapping "Functional" Localization



Metabolic Assessment Of Cognitive Functions: How Does It Tie Together - Where Does The Actual Perception Occur?



Do Brain Scans Reveal Mechanisms?

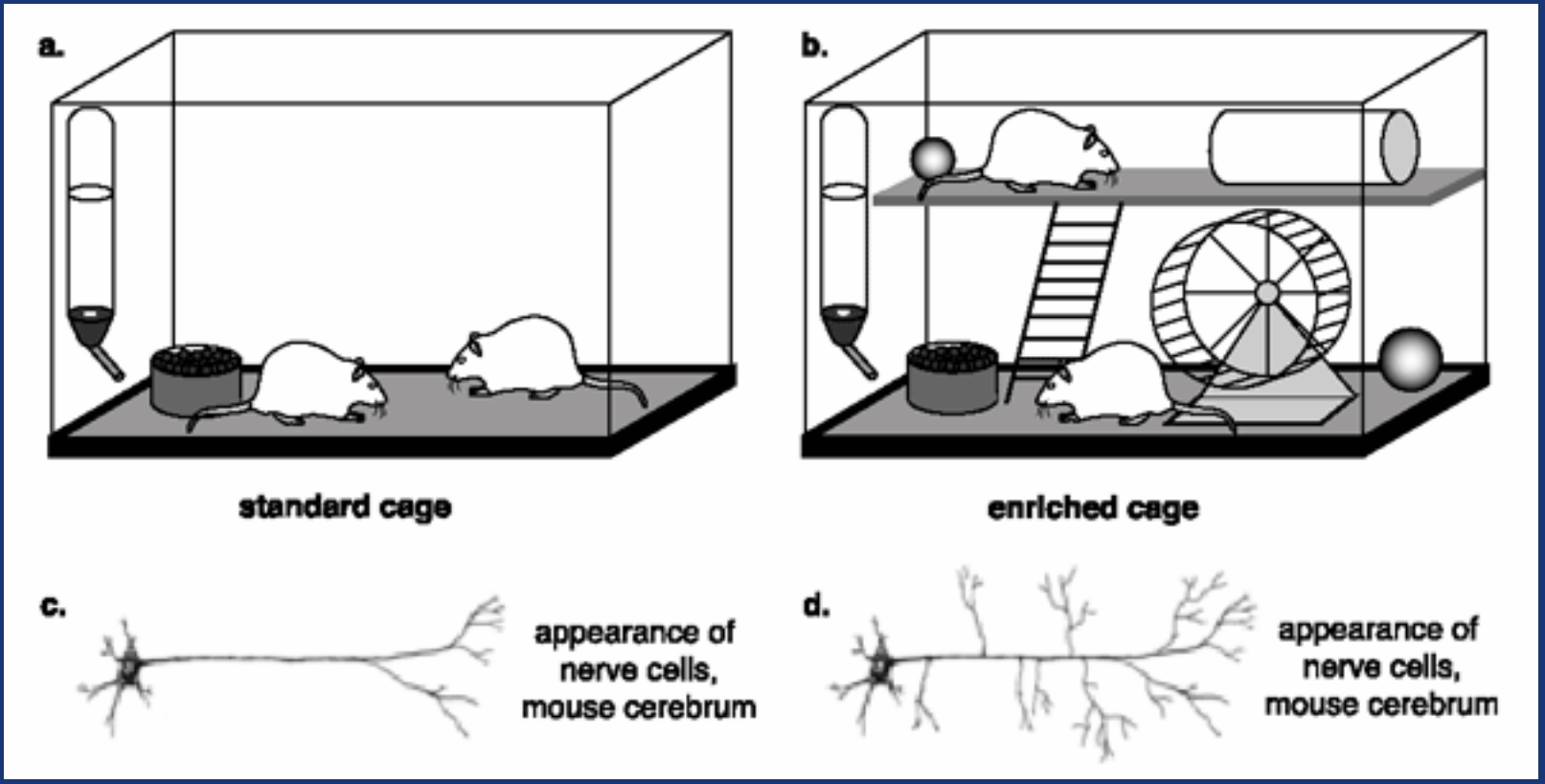
- They cannot explain recovery or sparing of function after injury.
- They **associate** brain structures with psychological and behavioral functions but *associations are not explanations*.
- The difference between phrenology and modern brain imaging is that brain scans more accurately identify brain structures that are active when someone is doing something.
- They do not provide any information on mechanisms because they do not explain how those neural networks generate behaviors that are supposedly dependent on that structure.

"Normal science, the activity in which most scientists inevitably spend almost all their time, is predicated on the assumption that the scientific community knows what the world is like. Much of the success of the (scientific) enterprise derives from the community's willingness to defend that assumption even at considerable cost. Normal science often suppresses fundamental novelties because they are necessarily subversive of its basic commitments."

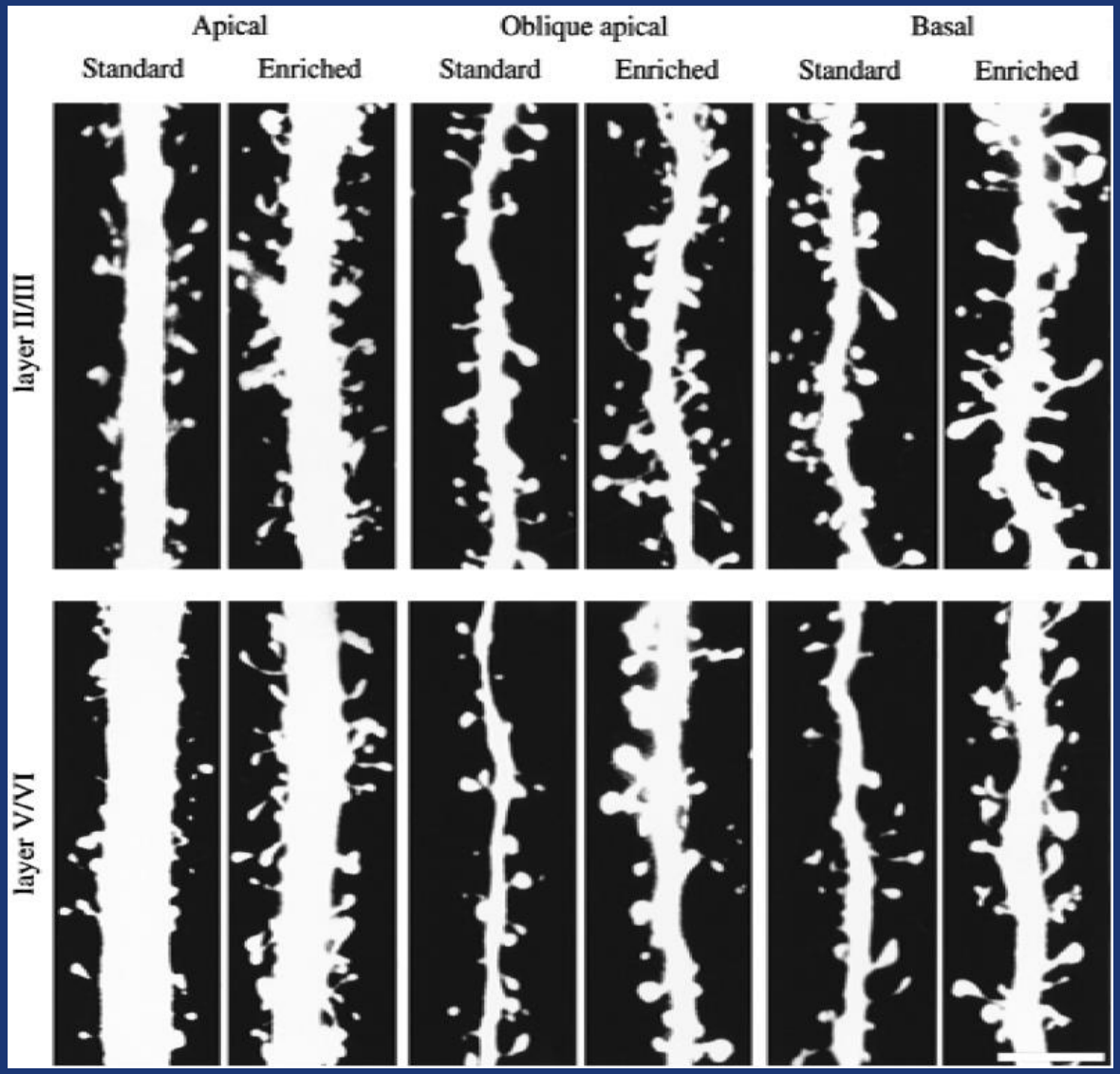
-Kuhn, T.S. "The Structure of Scientific Revolution"
2nd Edition, 1970 Univ. Chicago Press

You Don't Need A Brain Injury To See/Produce Plasticity: Environment And Experience Can Alter Cells Even In The Adult Brain

Studies From The 1950's

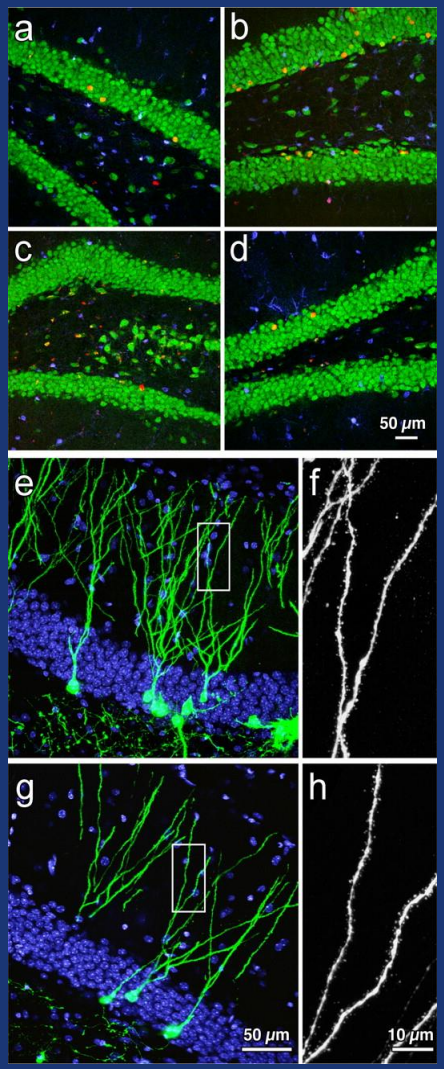


Effects Of Enrichment On Dendritic Growth



Neurogenesis Induced By Exercise In The Young And Aged Dentate Gyrus

*Note that number of new cells is very small (red dots)



van PraagH et al., J Neurosci 2005;25:8680-8685

Neurogenesis in the adult hippocampus of the monkey

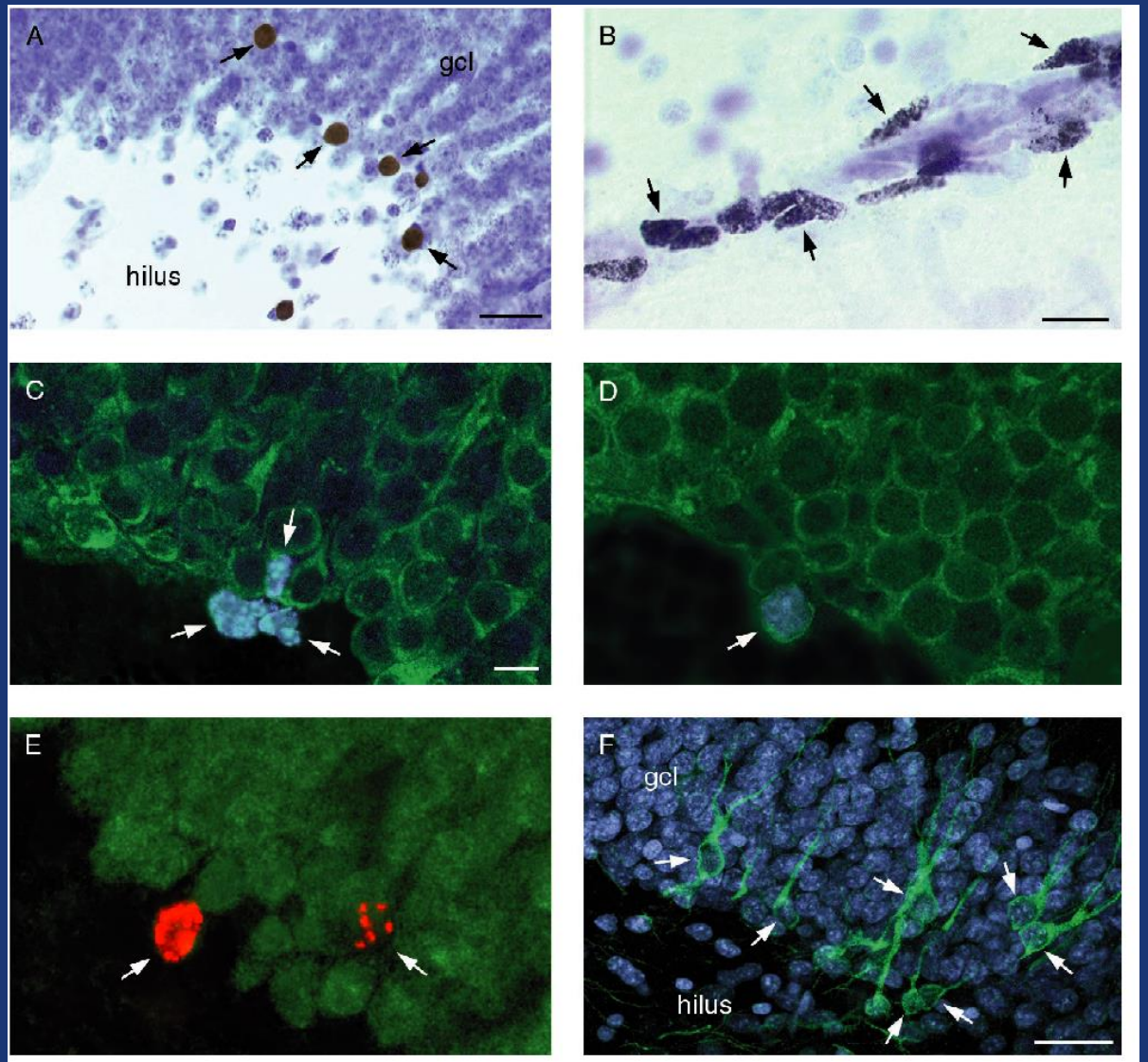


FIG. 1. Photomicrographs (*A* and *B*) and confocal laser scanning microscopic images (*C–F*) depicting new cells produced in the adult monkey brain. BrdUrd-labeled cells were observed in the granule cell layer of the dentate gyrus (*A*) (arrows) (animal 7) and in a region corresponding to the rostral migratory stream in rodents (*B*) (arrows) (animal 4). (*C*) Clusters of BrdUrd-labeled cells (blue nuclear stain) were observed in the subgranular zone of the dentate gyrus (arrows) (animal 2). Many of these clustered cells in animals injected with BrdUrd followed by short survival times (2 hr after BrdUrd injection) were not immunoreactive for NSE (green cytoplasmic stain). (*D*) In monkeys perfused 1–2 weeks after the last BrdUrd injection, BrdUrd-labeled cells expressing the neuronal marker NSE were observed (arrow is an example from animal 3). (*E*) BrdUrd-labeled cells in the granule cell layer of animals perfused 2 weeks after the last of five BrdUrd injections were immunoreactive for NeuN (arrows indicate double-labeled cells) (animal 1). (*F*) TOAD-64 stained cells with the morphology of granule cells were observed in the granule cell layer (arrows) (animal 1) (granule cells stained here with the DNA dye Hoechst 44323) gcl, granule cell layer. [Bars = 30 μm (*A*), = 15 μm (*B*), = 10 μm (*C*, *D*, and *E*), and = 40 μm (*F*).]

Gould, et al., PNAS 96, 5263-5267, 1999

Plasticity and Repair of the Damaged Brain

What We Can Learn About Brain Injury Can help Us to Understand Brain Plasticity

Injury-induced Plasticity In The Brain

- In brain imaging studies, during localization of sounds, blind humans activate large parts of the visual cortex as well as larger regions of posterior parietal cortex—areas involved in vision in seeing patients.

- Total left brain removal in children often spares much language function, suggesting a shift to the remaining intact hemisphere, but there may be subtle deficits later in life.

- PET and fMRI demonstrate that patients with left hemisphere epilepsy have much greater language representation in the contralateral hemisphere compared to controls.

- Using a variety of imaging studies, epileptic patients also show reorganization of language functions into healthy brain tissue surrounding the damaged area.

- How does other tissue "take over function" while maintaining its own function(s)?

Auditory Compensation For Early Blindness In Cat Cerebral Cortex

- Recorded single-cell activity in the visual cortex of cats deprived of vision for several years after birth and compared to normal controls.
- Normal cats responded to visual stimulation.
- Deprived cats responded vigorously only to auditory or tactile stimulation.
- **Conclusion: Cortical representation (function) changed as a result of experience from visual to auditory.**

Rauschecker JP, Corte M, J Neurosci

Re-wiring The "Connectome"?

- Early visual deprivation leads to an expansion of brain regions in the auditory or somatosensory domain and a corresponding improvement of function.
- This has been demonstrated in the superior colliculus and, most prominently, in the cerebral cortex.
- Similarly, blindness from birth in humans can cause reassignment of cortical regions from one sensory modality to another, as functional imaging studies have shown.
- The most exciting consequence of these recent studies is that sensory substitution in the blind may become a practical reality, allowing blind individuals to harness the power of crossmodal plasticity to perceive, localize and recognize objects with their auditory and tactile senses

Recovery From Subcortical Stroke: PET Activation Patterns In Patients Compared With Healthy Subjects

- Single, focalized lesions lead to depression of metabolism in the area surrounding the injury, but also to functional decreases in remote sites. One also finds changes in the hemisphere contralateral to the injury.

- In patients showing recovery of movement after stroke, rCBF changes are seen bilaterally distributed whereas in normals activation is only unilateral.

- These results demonstrate that the brain can show significant changes in multiple cortical (and subcortical) areas after local cerebral injury even if the injury is very restricted to the pyramidal tract.

Klaus-Martin Stephan and Richard Frackowiak

Can Changing Behavior Enhance Neural 'Plasticity'?

- "Behavioral treatment options can be used to restoring function and treating problematic symptoms. An example is mirror therapy, a technique used to treat phantom limb pain.

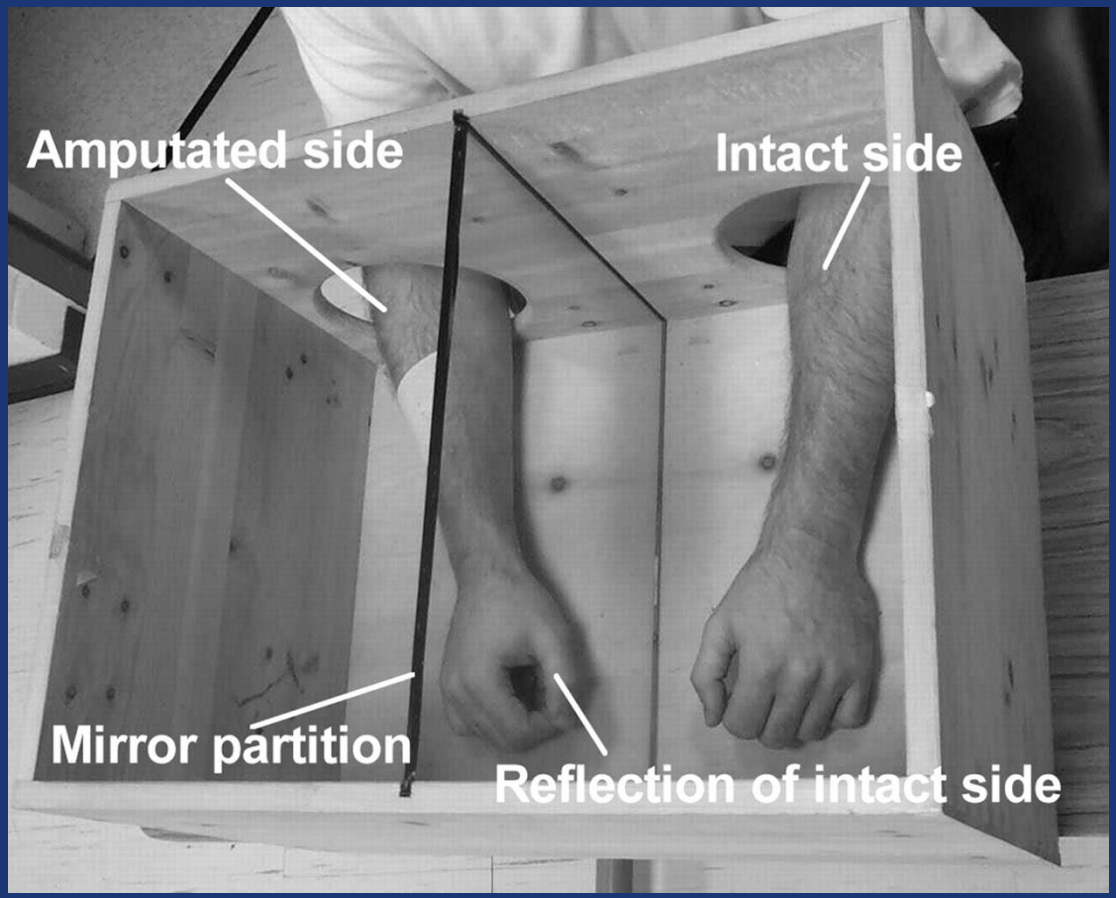
- In this situation, the patient uses a mirror to cover their amputation and focuses on watching their intact limb perform activities while imagining that both limbs are performing the same activity.

- One of the most studied rehabilitation techniques is constraint-induced movement therapy (CIMT).

- Used in patients with a stroke, the premise is that by constraining the functional limb, the affected limb is engaged in repetitive task practice and behavioral shaping".

- M. Puderbaugh; Prabhu D. Emmady. 2023

The Mirror-box Illusion: Immediate Reorganization Of Function



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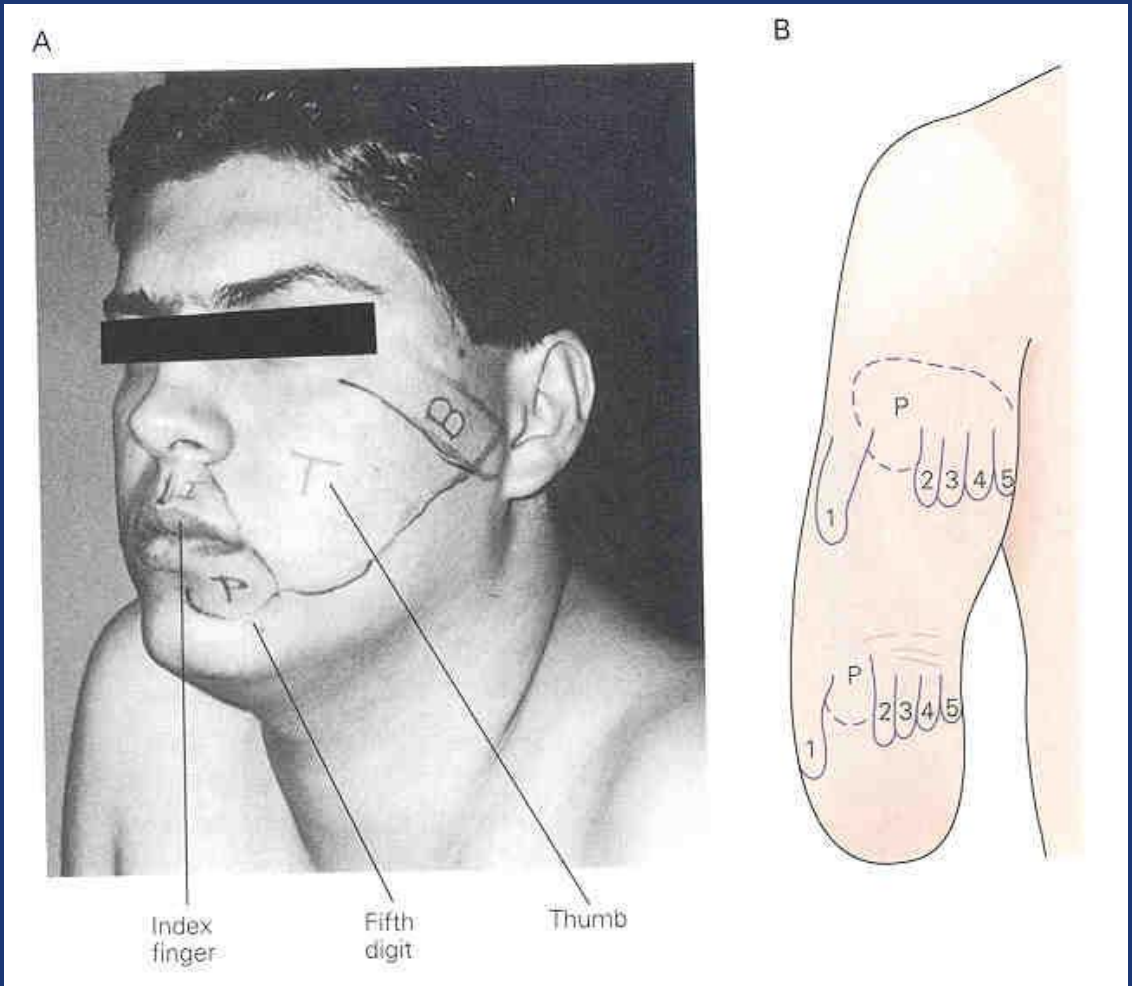
Hunter, J. P. et al. Brain 2003 126:579-589; doi:10.1093/brain/awg054

BRAIN
A journal of neurolo

Plasticity In Phantom Limbs Induced With Mirrors

- A mirror reflection of the patient's intact hand is superimposed on the felt position of the phantom.
- When the normal hand is moved so that the phantom is perceived to move in the mirror, kinesthetic sensations emerge in the phantom. The sensation of "clenching" spasms could also be removed when the mirror was used to facilitate "opening" of the phantom hand.
- The data "suggest that there is a considerable amount of latent plasticity even in the adult human brain. The strictly modular, hierarchical model of the brain that is currently in vogue needs to be replaced with a more dynamic, interactive model."

Phantom Limb Reorganization



Rapid Reorganization And Re-mapping The Brain - I

- Reorganization in response to injury can occur within minutes after the damage.
- Can loss of input into one cortical area lead to map expansion or to capture of that area by another modality?
- Is this change adaptive or an example of “negative plasticity”?

Rapid Reorganization And Re-mapping The Brain

- Rapid reorganization occurs in motor and sensory systems.
- Training and rehabilitation (therapy) *may* be needed to produce sustained reorganization.
- Inappropriate or ill-timed training can increase extent of injury and prevent recovery.
- Individual differences in cerebral organization are important and individual history plays a role.

Conclusions

- Cortical somatosensory maps are dynamic
- Cortical maps can change (or add new)
- representational matrices
- The self-organizing capacity of sensory fields does not end early in life.

The Marketing Of Brain Plasticity

Plasticity in a Bottle?

Top 10 Brain Supplements

1. Alpha Focus
2. Cerebral Charge
3. Neuro HD
4. MedixSelect Cresceo
5. MRM Neuro-Max II
6. FutureBiotics ThinkFast
7. ProSupps I-Focus
8. TheraBotanics Cebria
9. Vitazen CogniZen
10. Truetoniqs Brain Toniq

The Hard Sell

- Alpha focus has jumped to the top ranking in every category.
- It is specifically designed to boost memory focus, reduce mental focus and support healthy brain function.
- Alpha focus helps your brain naturally increase its potential and immediately improves function.
- Alpha focus jump-starts your mental focus.
- The natural ingredients smooth enural pathway to give razor-sharp focus without negative side effects.

Another Form of Plasticity
Microplastics



Be Careful! There's a lot of 'Hoaxes' Out There

Brain Plasticity Exercises **Neuroplasticity** Exercises - Proven **brain** training exercises to help you think faster, focus better, and remember more. Proven memory, attention, and speed exercises - train your **brain** in just minutes a day. **Brain** Health Classes. **Sponsored** Study.com
https://www.study.com/

What is **Neuroplasticity**? - Lesson | Study.com Discover Video Lessons. Worksheets. Practice Questions and More. All in One Place. Used by Over 30 Million Students & Teachers. Join Today To Find Out Why! 70,000+ effective lessons. Easy to

Scientists Agree: Meditation Is The #1 Brain Changer. So, what's the best way to build a better brain? Backed by 1000's of studies, meditation is the neuroscientific community's most proven way to upgrade the human brain.
Here we dive into **9 key brain regions** enhanced through meditation, with a focus on the massive life-transforming implication

Brain Plasticity: Understanding the **Brain's** Ability to Heal and Adapt

The Magic of NeuroPlasticity: Scientists Agree: Meditation Is The #1 Brain Changer. So, what's the best way to build a better brain? Backed by 1000's of studies, meditation is the neuroscientific community's most proven way to upgrade the human brain. Here we dive into **9 key brain regions** enhanced through meditation, with a focus on the massive life-transforming psiHand helps overcome stroke recovery plateaus. Explore **brain**-activated therapy—supporting arm...

Neuroplasticity: How our brains are wired for change: The MindBody Food Institute. 100% online. Flexible and soft-paced. Affordable payments. Holistic Life Coach, Mind-body practicioner, somatic pain practicioner.n

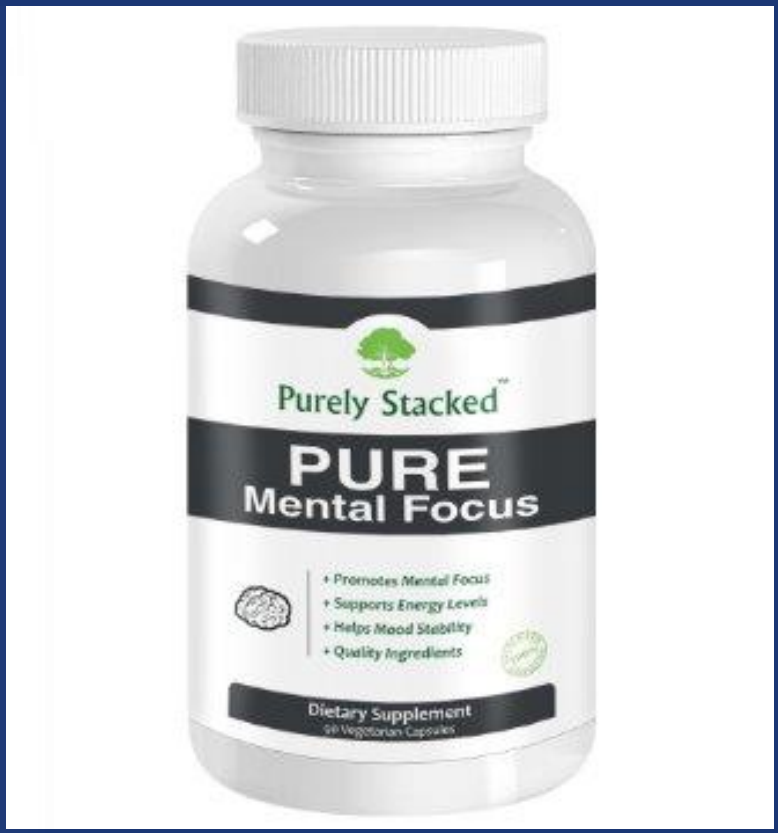
“While Results May Vary, Over 95% Of Clinical Study Participants Experienced Improved Short-term Memory After Taking Redimind For 30 Days, And Our Customers Agree! ”

A Total of 56 volunteers participated in this “clinical” study –paid for by the maker of the supplement.



Neuroplasticity In A Bottle





The 5 Must-Have Ingredients for a Good Memory Supplement

- Alpha GPC naturally occurs in the body as a precursor to acetylcholine, one of the key neurotransmitters in the brain's neural network.
- Huperzine A has been shown to increase bioavailable levels of acetylcholine by inhibiting the enzyme that breaks it down, acetylcholinesterase.
- **Lion's Mane**Used for thousands of years by Buddhist monks to increase focus during meditation, lion's mane mushroom helps improve cognition by enhancing activity of choline acetyltransferase.
- Bacopa monnieri is an herb commonly used in traditional Ayurvedic medicine for its positive influence on memory and focus.
- Ginkgo biloba, one of the world's oldest tree species, has been used for thousands of years in traditional Chinese medicine for its neuroprotective effects.

An Objective Evaluation Of The Supplement?

- The physicians and nutrition experts of our staff have *developed an intuitive sense of what works and what does not after* decades of extensive, hands-on experience with patients and clients.

- *When a user purchases one of these products through any of these links, we receive a portion of the proceeds. In addition, the company that owns and operates this website also has ownership interest in the companies that manufacture or sell some of the products that we review.*

Remaining Issues in Plasticity and Recovery Research and Theory

- Glial and stem cells: what are their roles in the repair process?
- Genes and receptors: what are their roles in inducing factors that enhance repair and recovery?
- To what extent is the whole brain reorganized after injury and during repair?
- What age and gender factors contribute to recovery?

Conclusions

- There are now multiple opportunities for brain repair and functional rehabilitation, including:
  - pharmacological, genomic and proteomic manipulations
  - transplants of stem cells and glia
  - neurogenesis
  - direct stimulation
  - behavioral training
  - enriched environment
  - robotics
  - and others to be discovered
- *Functional* recovery is likely to be dependent on the context of the injury and involve multiple physiological processes.
- History, gender, training and experience of the patient can influence the extent and type of cerebral reorganization.

When The Street Name Outlives The Street

"Like disused train stations glinting in the murky light of subway tunnels, or the faded lettering of past businesses on aged brick, the streets have become ghosts, spectral flashes of lives once lived here. Although the city's grid, hewn as it is from concrete and steel, asphalt and shist, can seem permanent, it is actually fluid, a flux driven by ever-changing traffic patterns, populations and development imperatives. The streets, like people, fatten and thin over time, change course or direction and one day simply vanish. But sometimes they leave a trace."

Diane Cardwell, New York Times, May, 10th, 2004

End