BUILDING AND REPAIRING ORGANS THROUGH BIOTECHNOLOGY:
A NEW WORLD FOR INQUISITIVE MINDS

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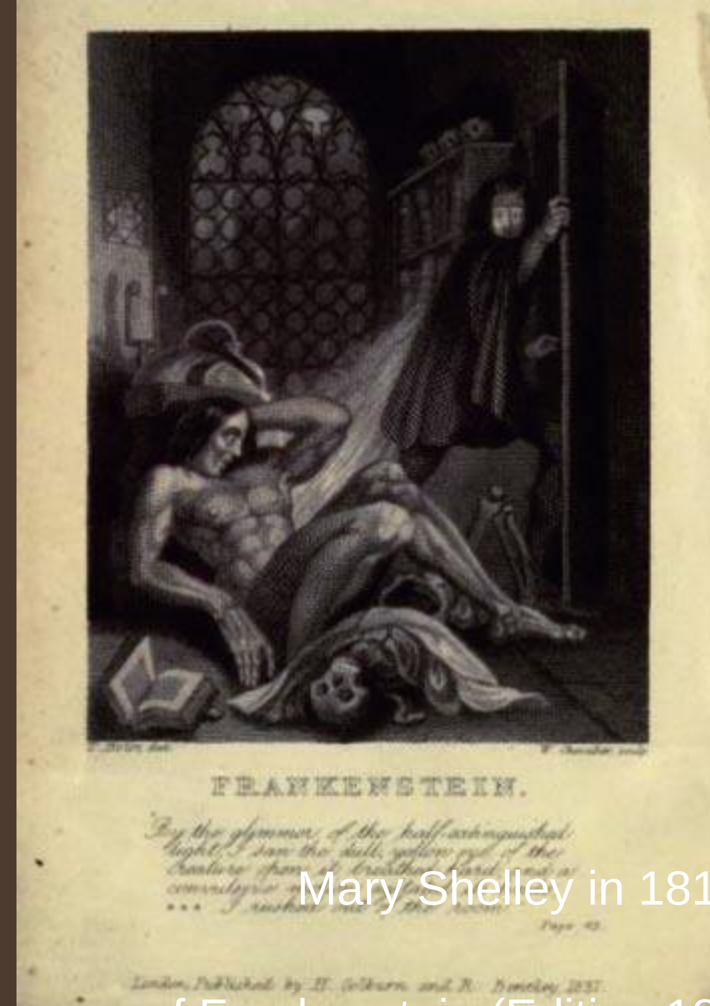
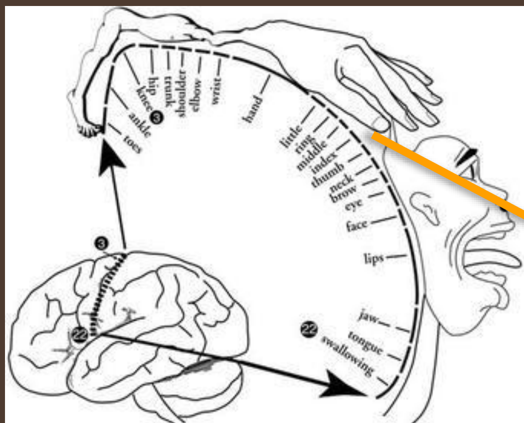


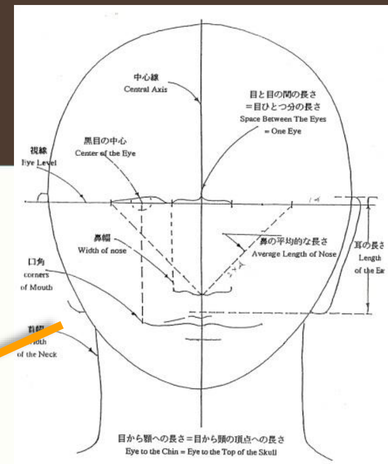
Mary Shelley in 1818

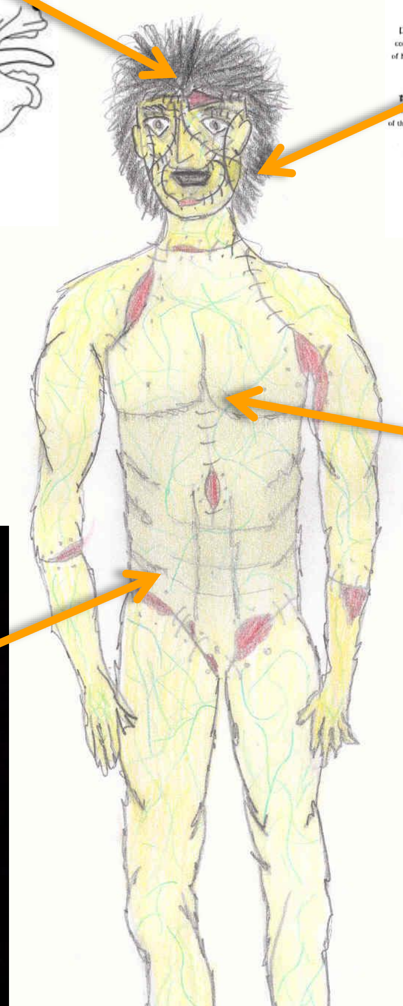
Book cover of Frankenstein (Edition 1831

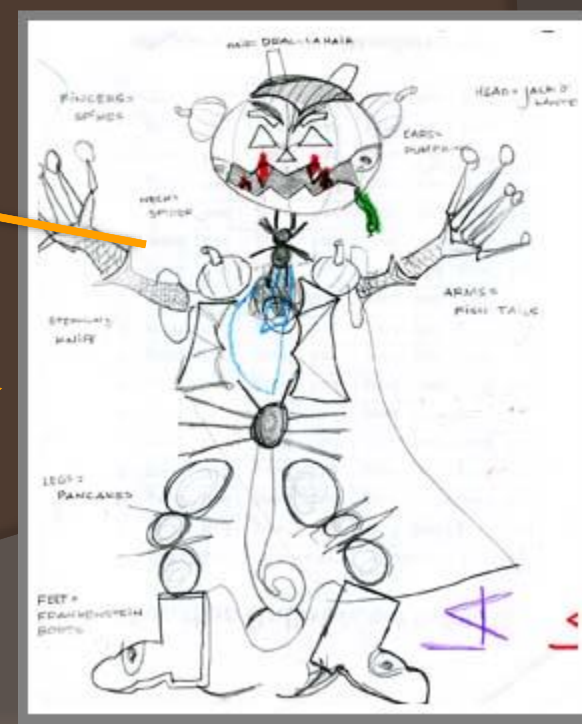
Frankenstein trailer

How to make a Frankenstein

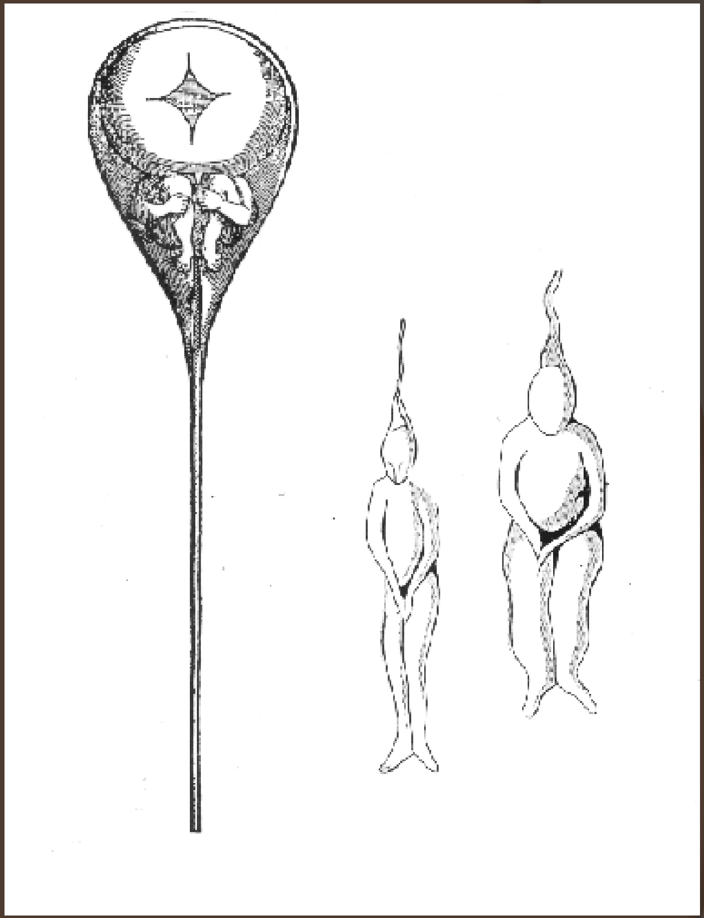








Depiction of Dr. **Faustus** and his **Homunculus.** The creation of the artificial being Homunculus in Goethe's Faust is a central part of the drama, by which Goethe reveals various transformational processes working in the human soul. In other words regeneration of a human for its parts.



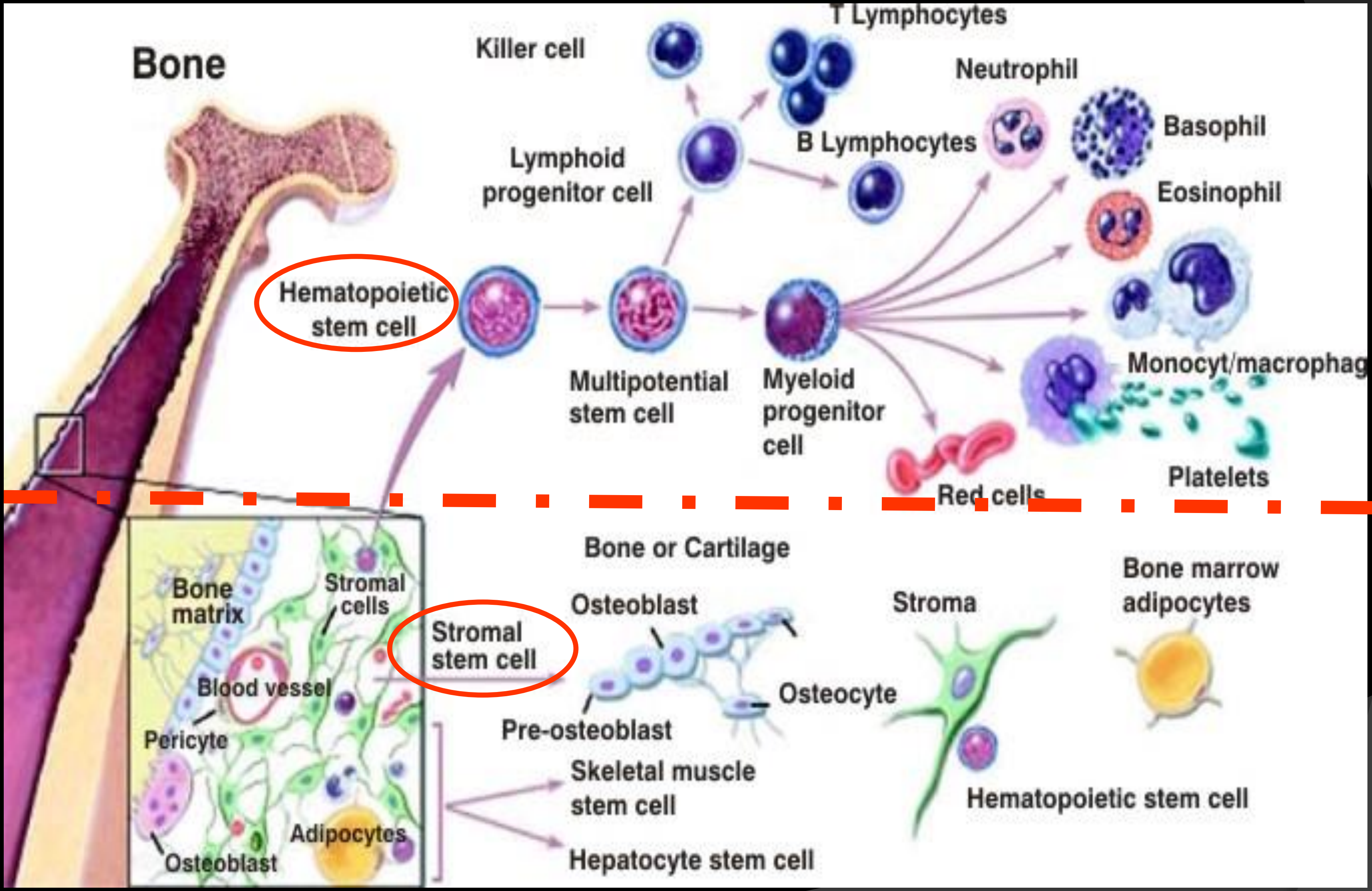
Homunculi in sperm as drawn by N. Hartsoecker in 1695. Philosophical theory of heredity, claimed that either the egg or the sperm (exactly which was a contentious issue) contained a complete preformed individual called a homunculus. It was held the belief that the sperm was in fact a "little man" (homunculus) that was placed inside a woman for growth into a child

Salamander limb regeneration

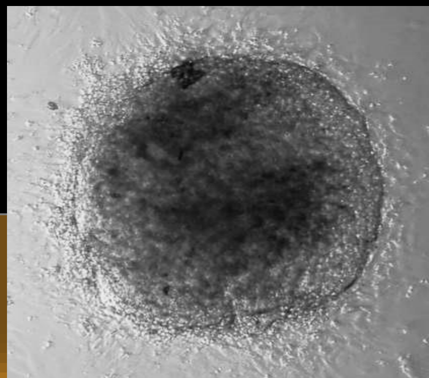
Salamander limb regeneration

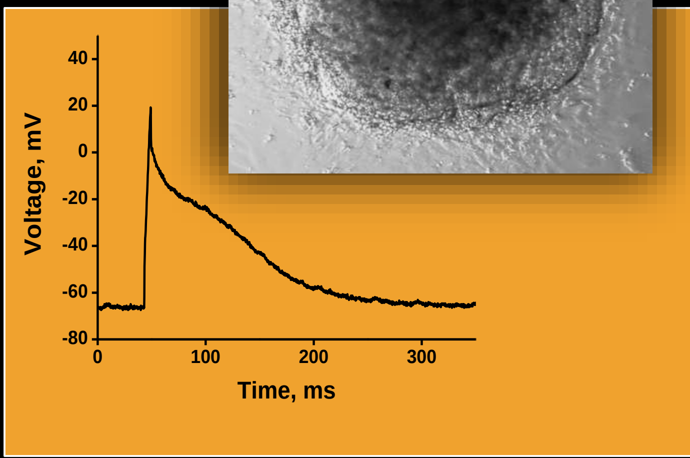
http://www.youtube.com/results?search_query=salamander+regeneration&aq=f

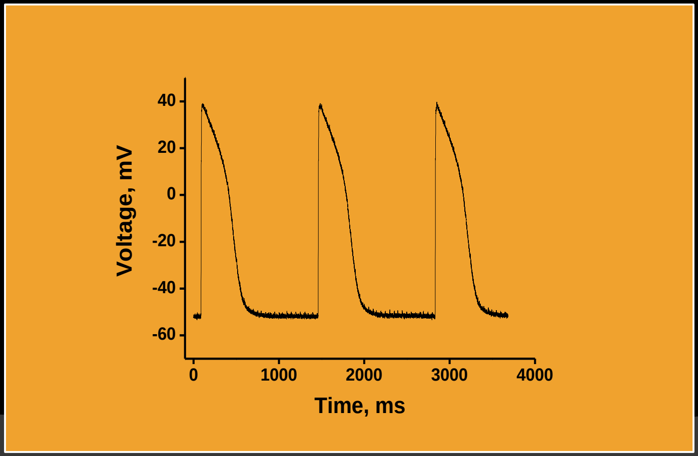
Bone Marrow Stem Cells (BMSC)



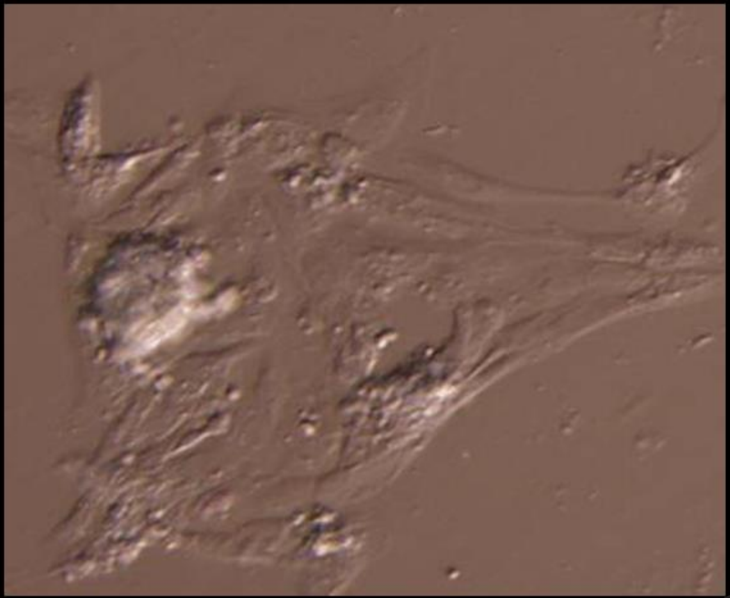
Live Stem Cardiomyocytes





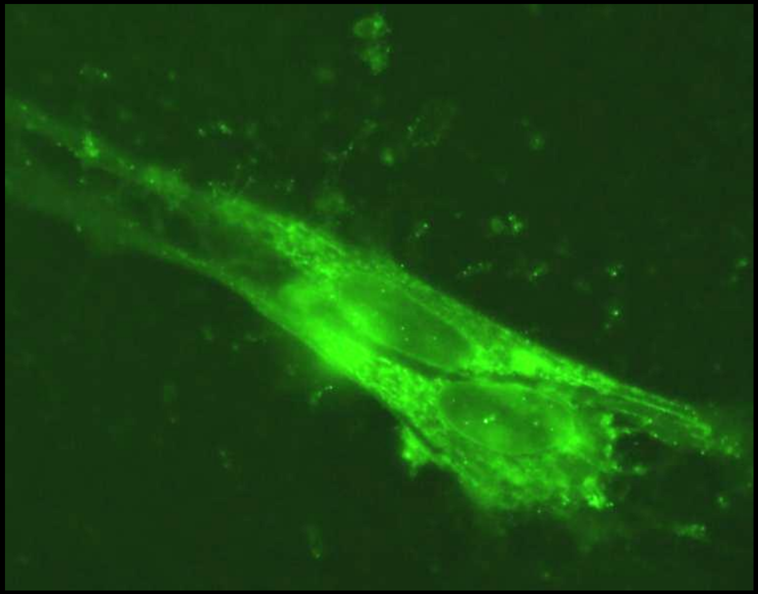


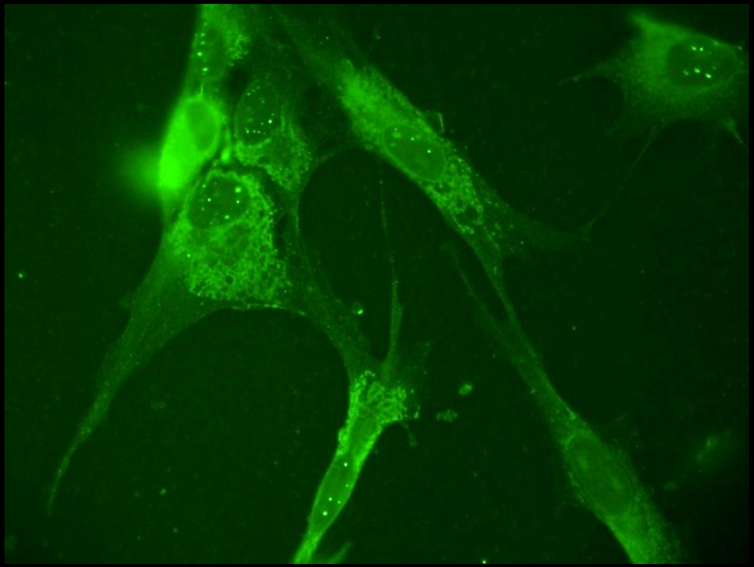
- Heart stem



Examples of colonies of isolated right atrial (RA) cardiomyocytes, all of which exhibited spontaneous contraction

Stro1- Fetal BM Stromal Cells



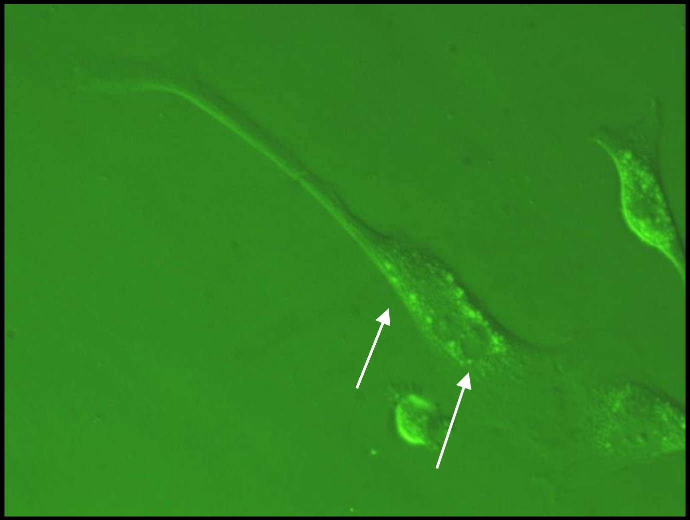


Immortalized with Retroviral backbone with pLXSN-HPV-16 E6/E7. Co-infected with hTERT and GFP (Halbert 1992).

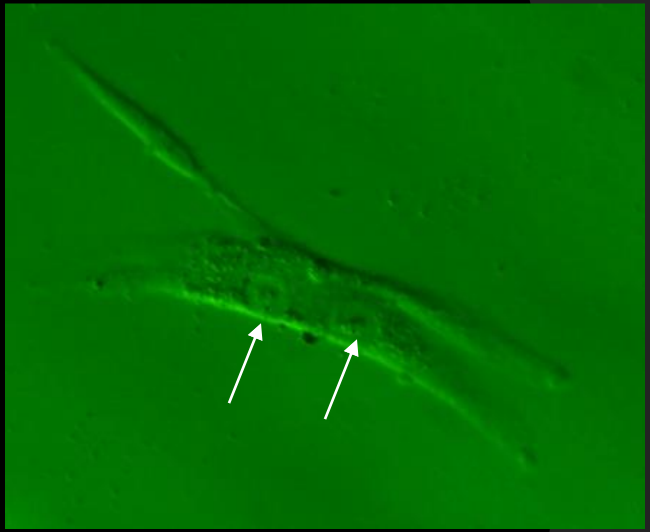
Stem cells phenotypes

>Dividing

>Labeled

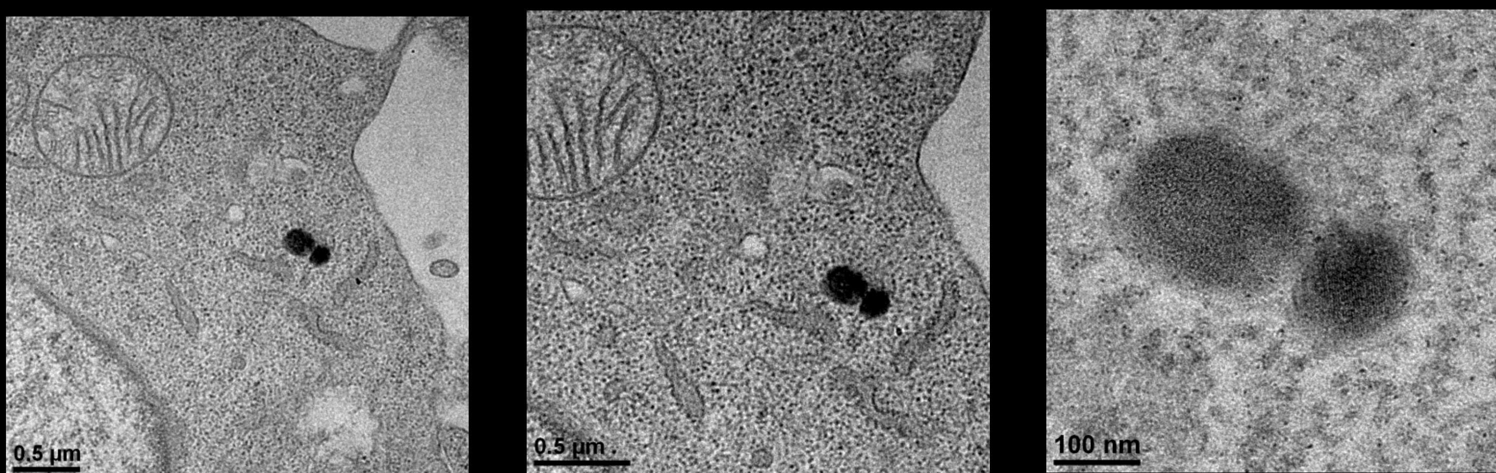


FITC-MSN 96hr



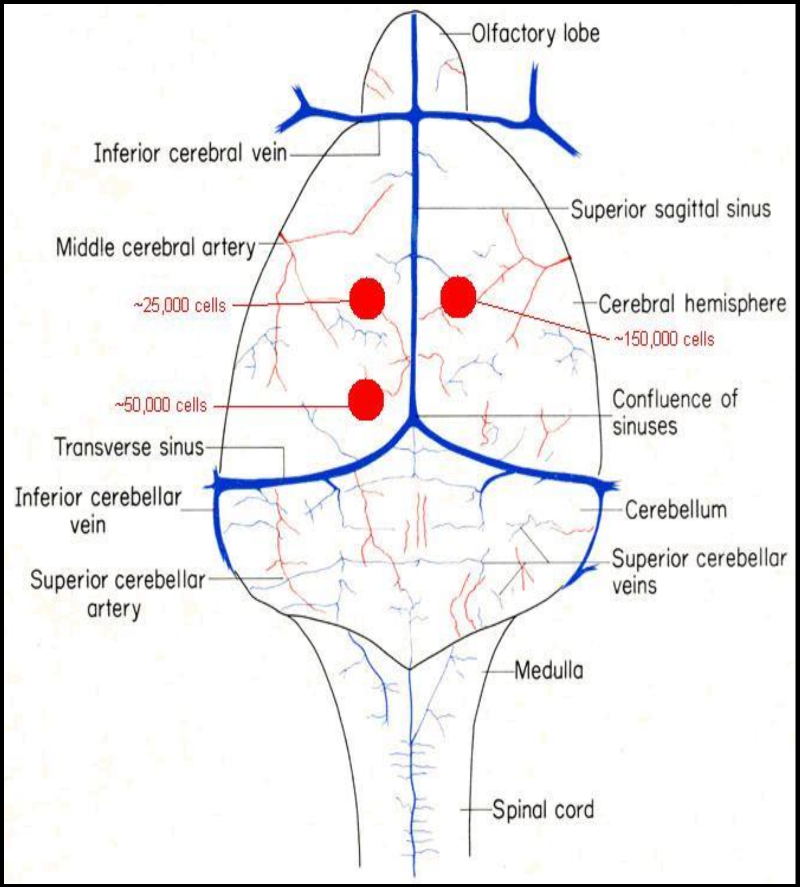
Fe -MSN 96hr

Electron Microscopic Evaluation of Msn nanoparticles



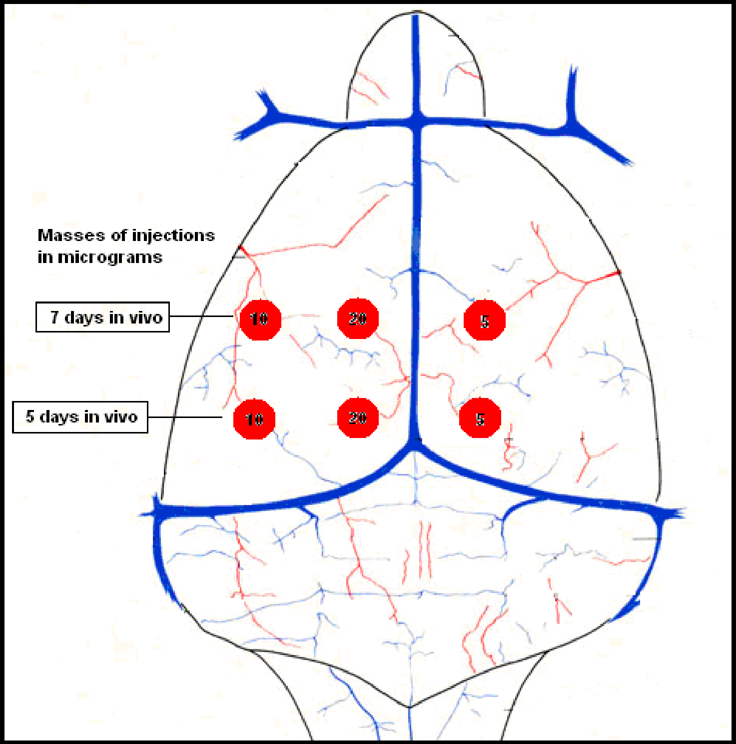
VIABILITY, intracellular interaction with subcellular organelles

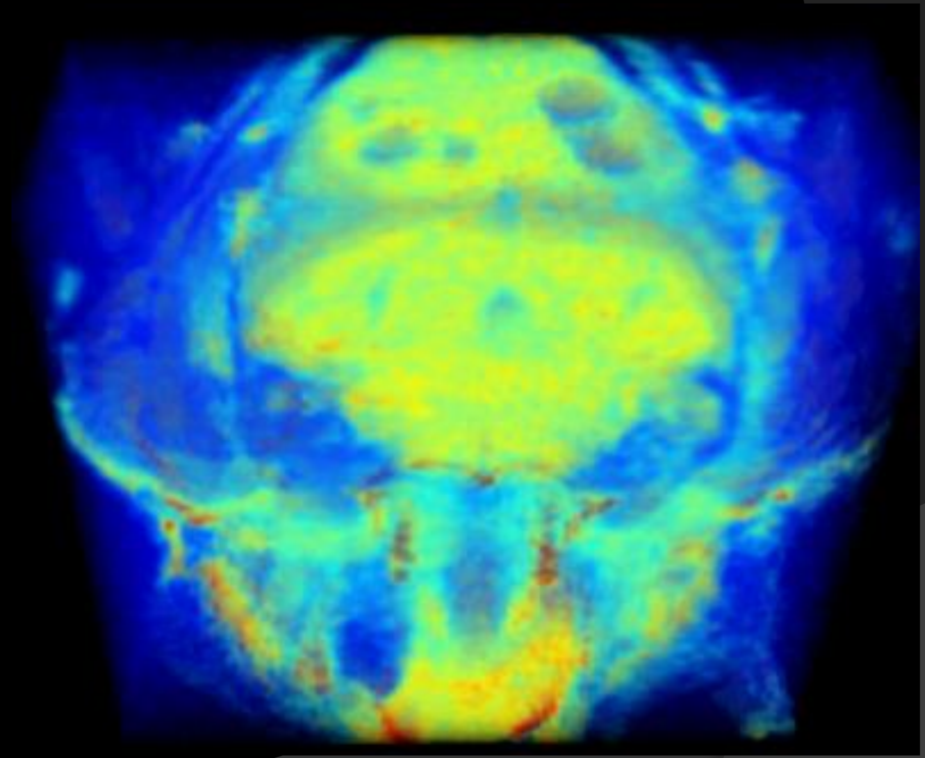
MRI experiments HSC MSN-FITC and MSN-FE



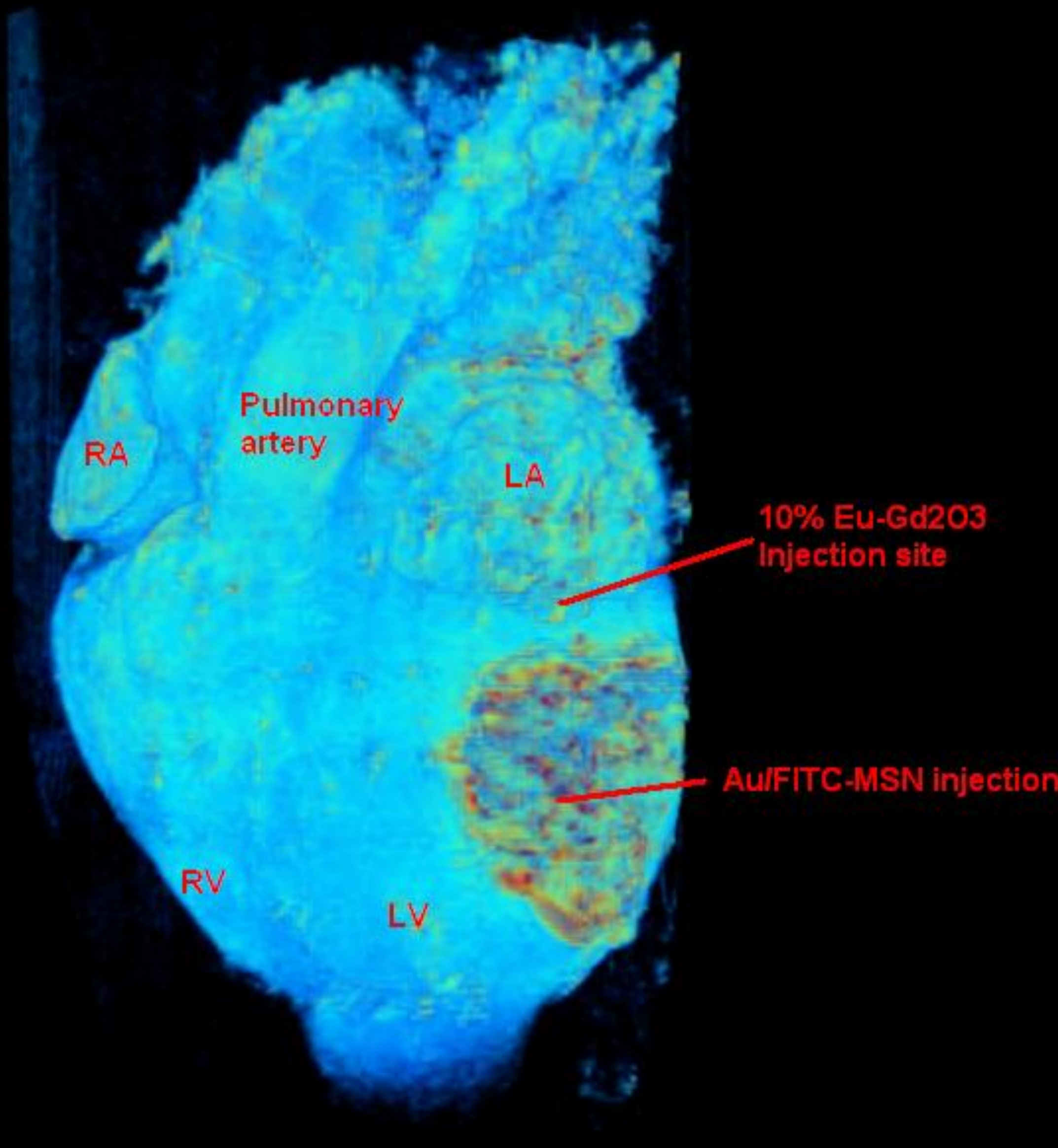
In vivo tracking (MRI)

- Evidence for contralateral migration of particles
  - Murine cerebral microinjections of 10% Eu-doped Gd_2O_3 (RD-147)

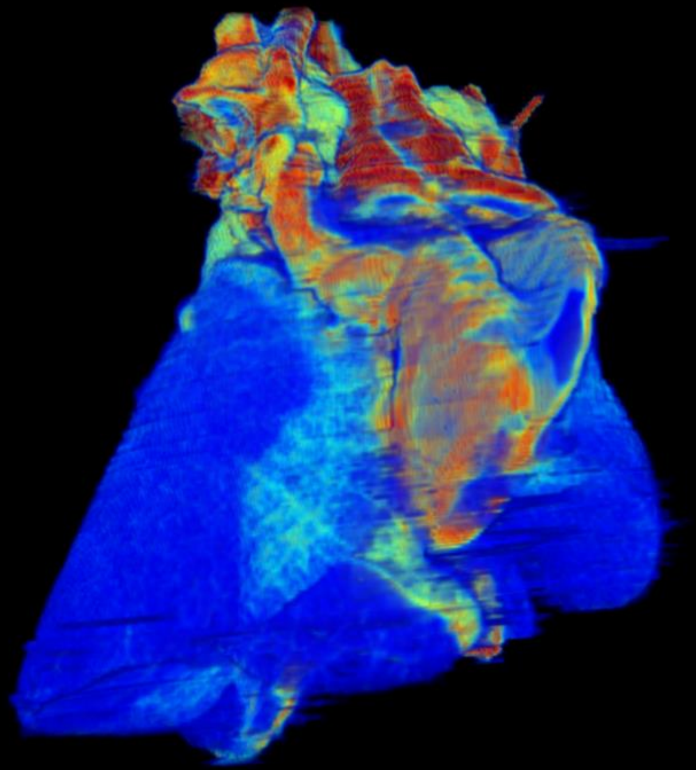




Additional ex vivo heart MRI



Lung evaluations



Comparison of CT scan parameters:
Ferrite: Perfusion Fixed 01: 60.0 kVp, 200.0 mA
Perfusion Fixed 02 (this is the specimen analyzed below): 50.0 kVp, 400.0 mA
Perfusion Fixed 03: 60.0 kVp, 500.0 mA
Gold: 50.0 kVp, 400.0 mA
Bismuth: 50.0 kVp, 400.0 mA

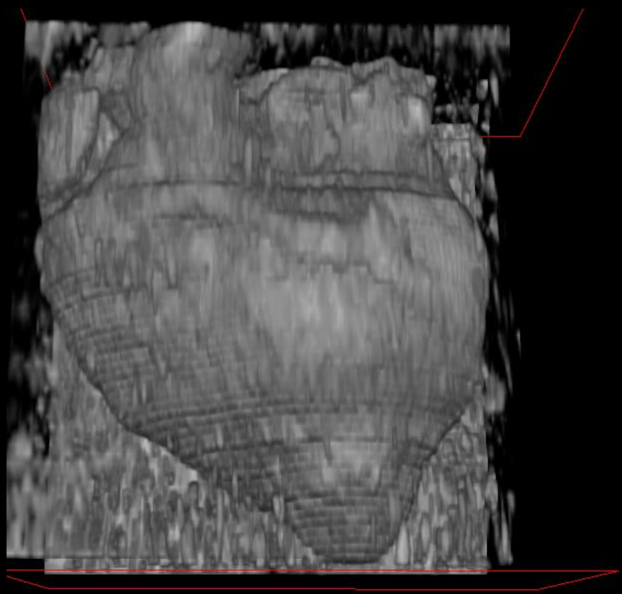
CT lung

http://www.engineering.uiowa.edu/~assoulin/LungCTgold1/LungCTgold1.html

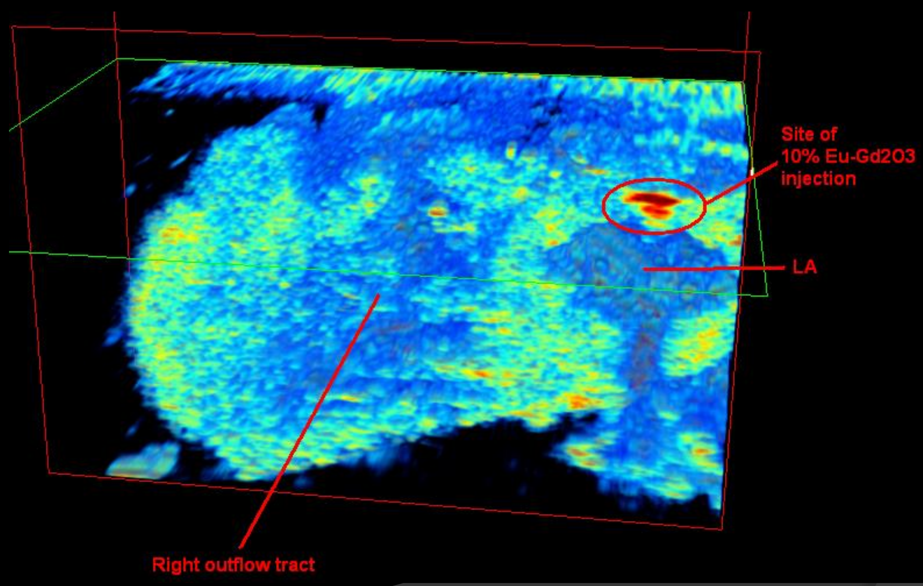
Ex-vivo cardiac ultrasound

- Heart injected with 20 μL 10% Eu-Gd_2O_3 @ 10 μg/μL in left atrial wall
- Mounted in 1% agarose gel and scanned at 30 MHz

3d rendered ultrasound



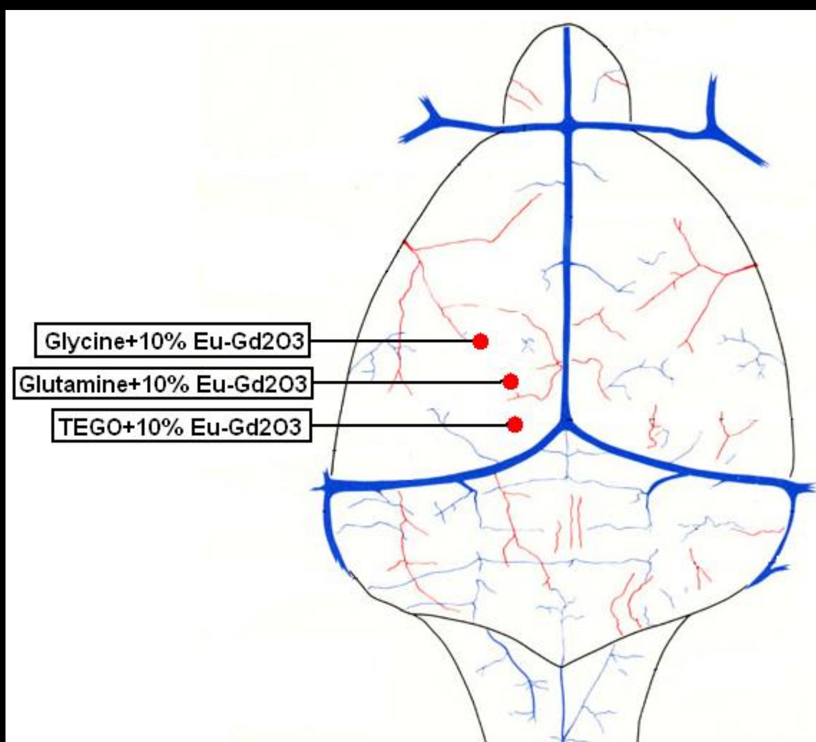
Pseudocolor highlighting injection site

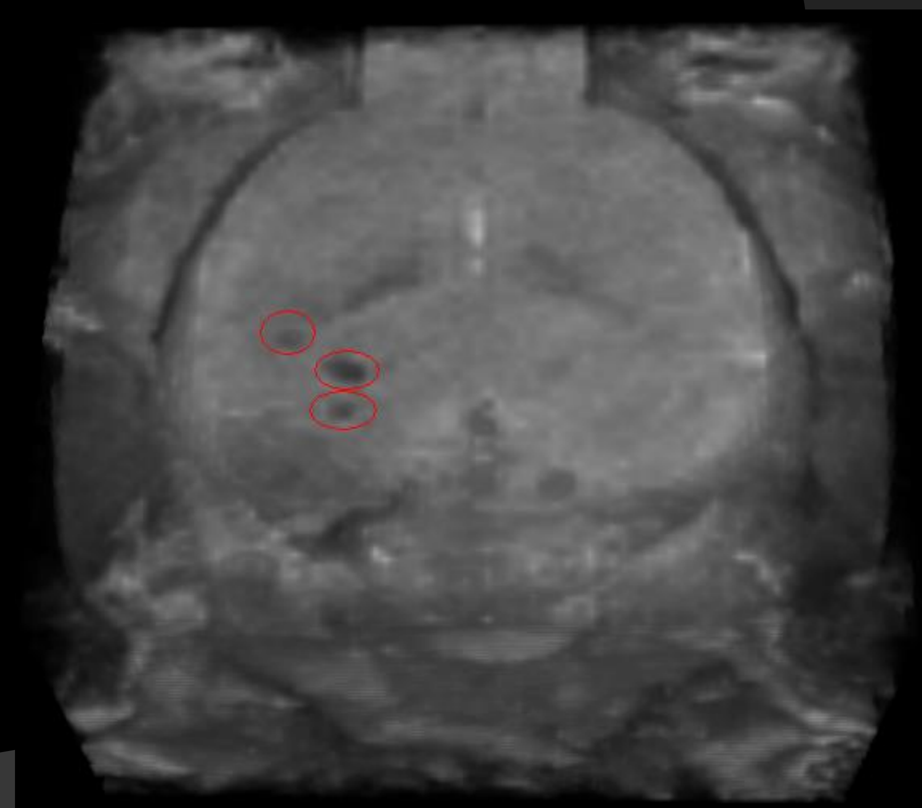


In vivo mouse studies are forthcoming

MRI of In vivo transport, functionalized particles

- Glycine- and glutamine-functionalized particles in parietal lobe
- TEGO-functionalized particles in hippocampus
- MRI imaging 1, 24 and 48 hours after injection



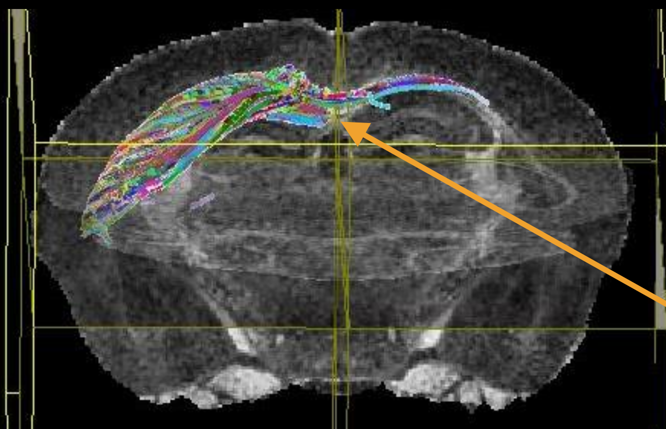


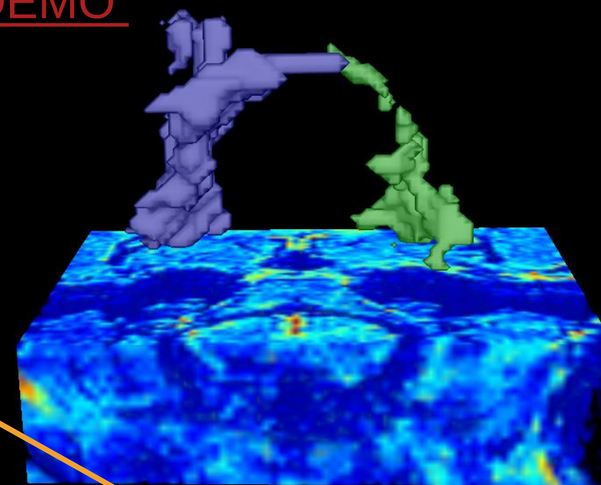
Predictive DTI tractography compared with actual image, VOI surface shown

Parietal injection, predicted tractography via corpus callosum

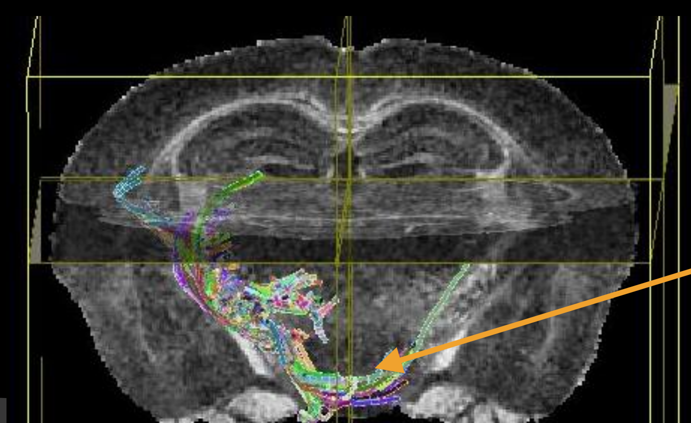
1 hour post injection

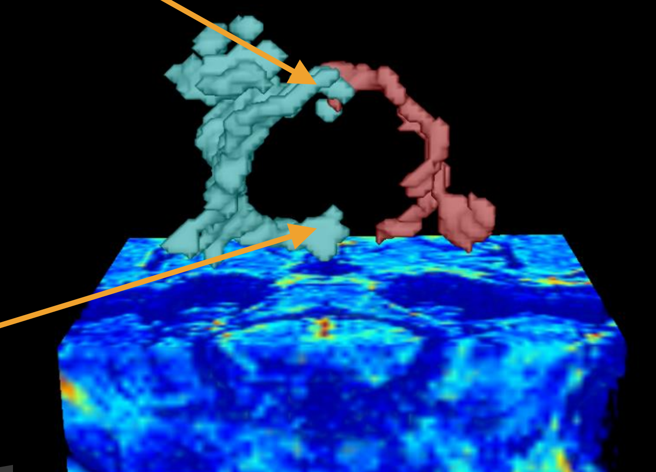
Videos DEMO





Hippocampal injection, predicted tractography:





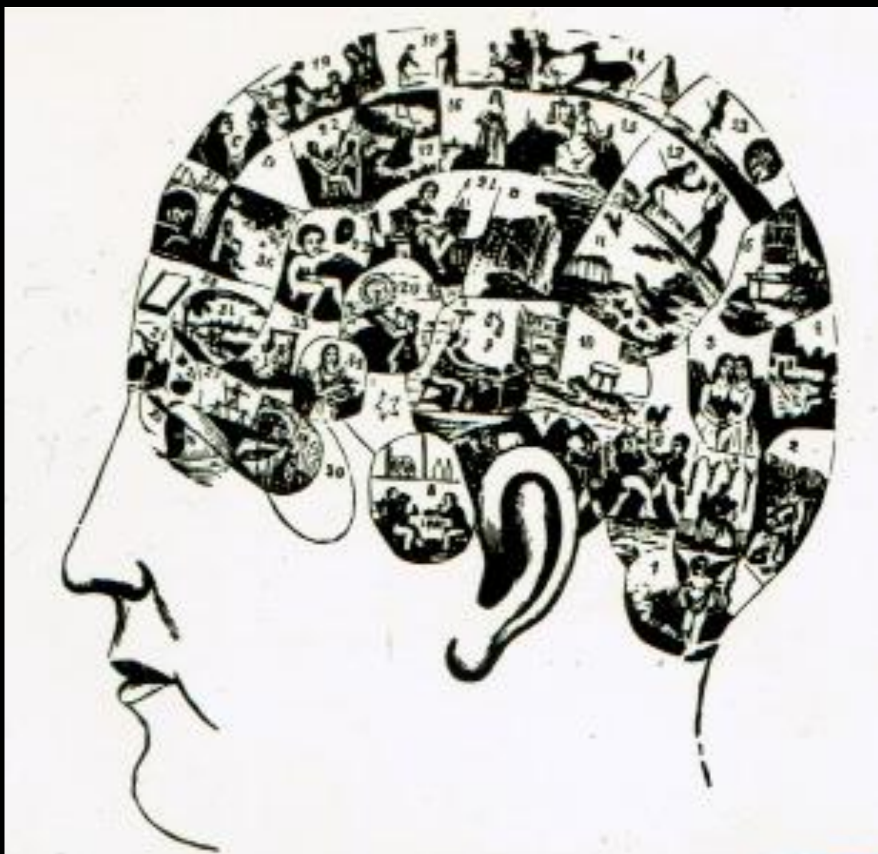
48 hours post injection

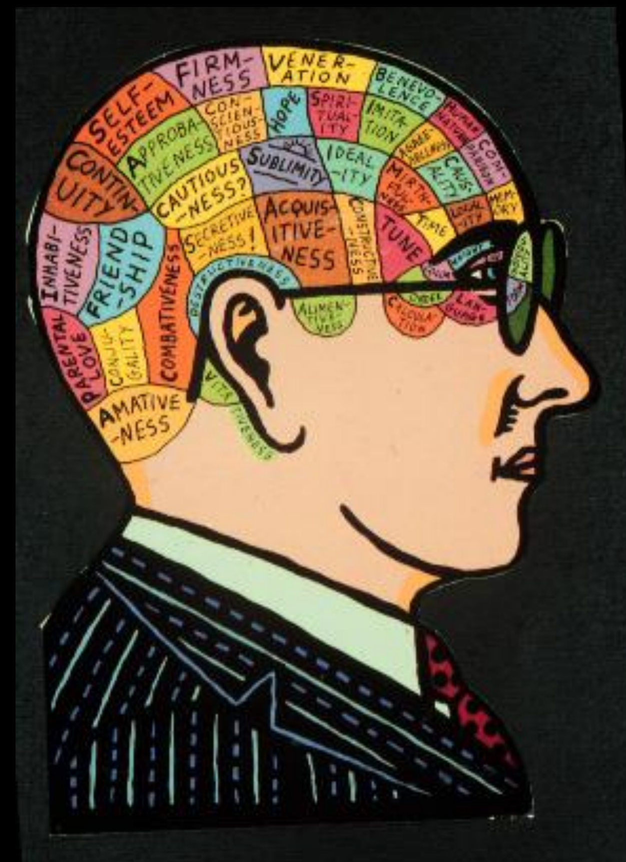
Rationale:
Stem cell regenerative medicine

- Potential uses
  - Heart (myocardial infarction)
  - Lungs (asthma, COPD, cystic fibrosis)
  - Brain (Parkinson’s, Alzheimer's, stroke)
- Fate of stem cell transplants
  - Immune rejection/clearance
  - Teratoma/errors in differentiation
- **Therefore, there exists a need to trace stem cell transplants *in vivo* and non-invasively**

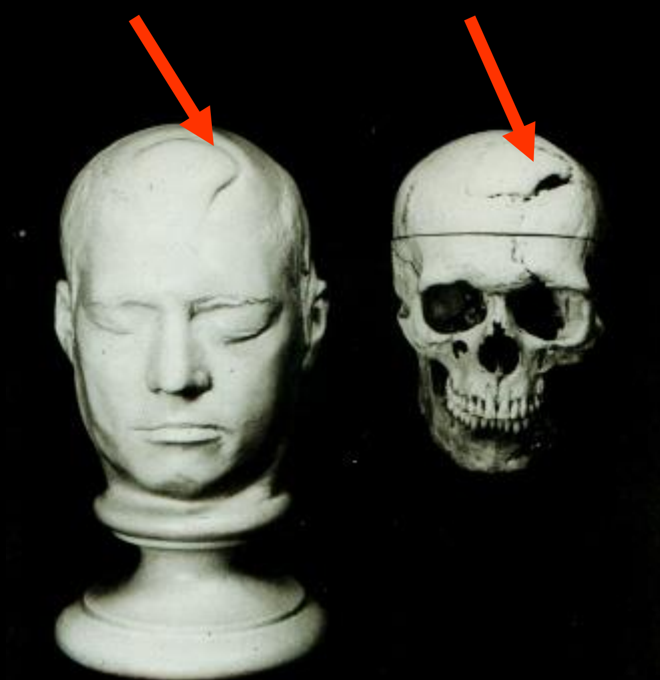
Lees, J. G. et al. *Regen. Med.* **2007**, *2*, 289-300.
Fong, C. Y. et al. *J. Cell. Biochem.* **2010**, *111*, 769-781.

Earlier hypotheses on the brain functions

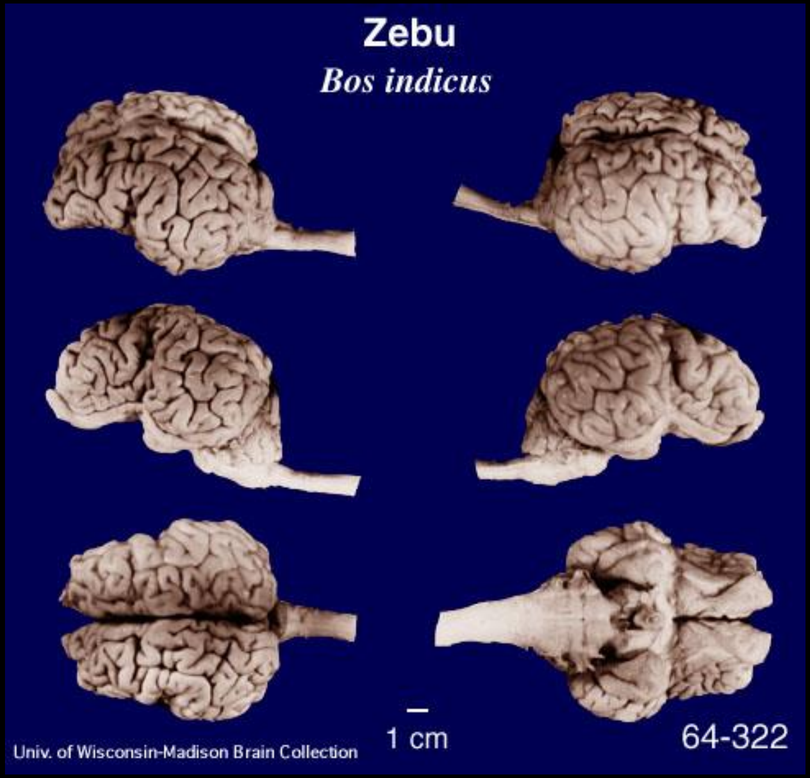


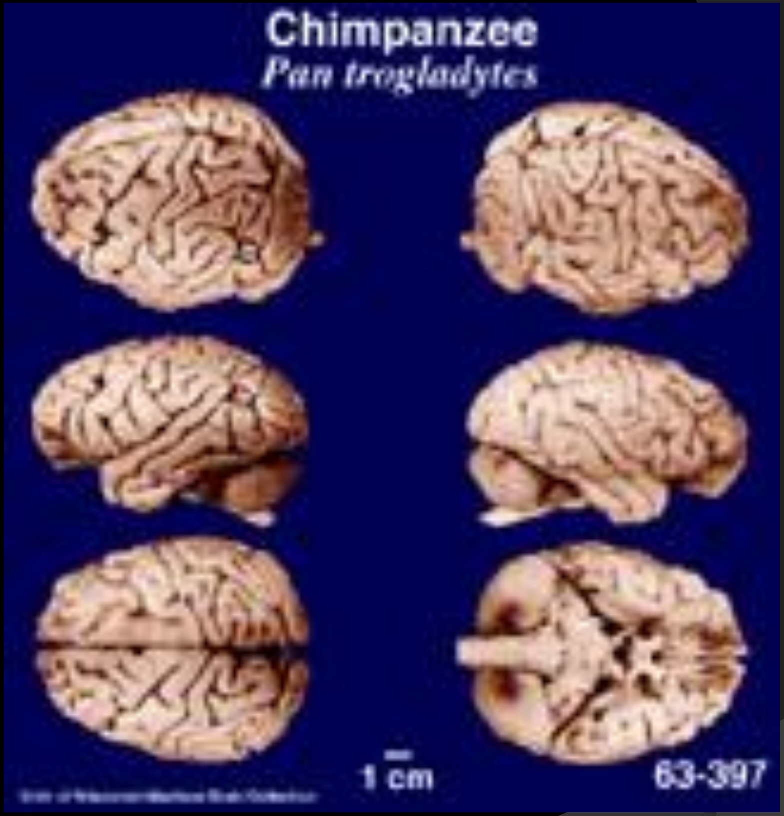


The Phineas Cage's case:
an example of personality disorder
a great step in brain mapping of emotion

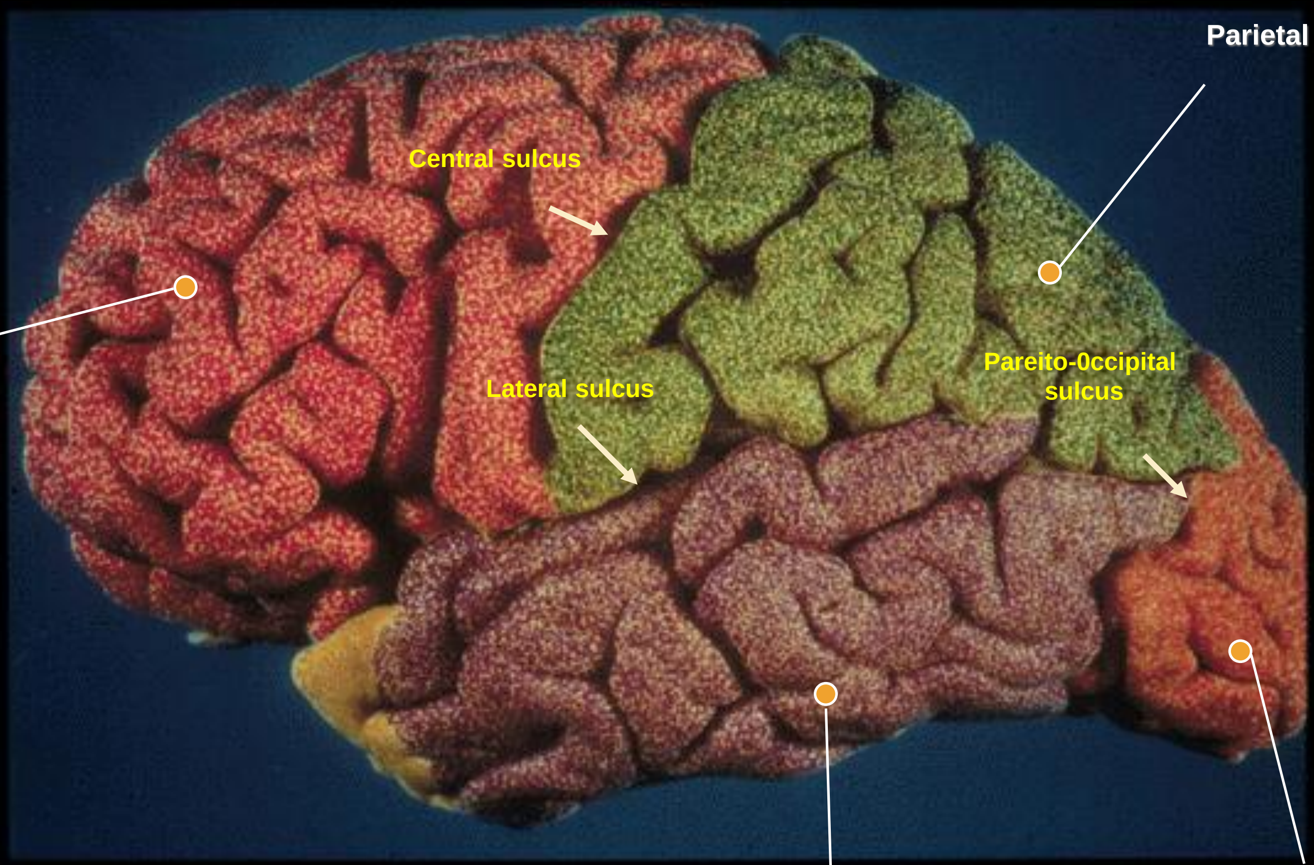


Evolution of Brains and Behaviors (part 1)

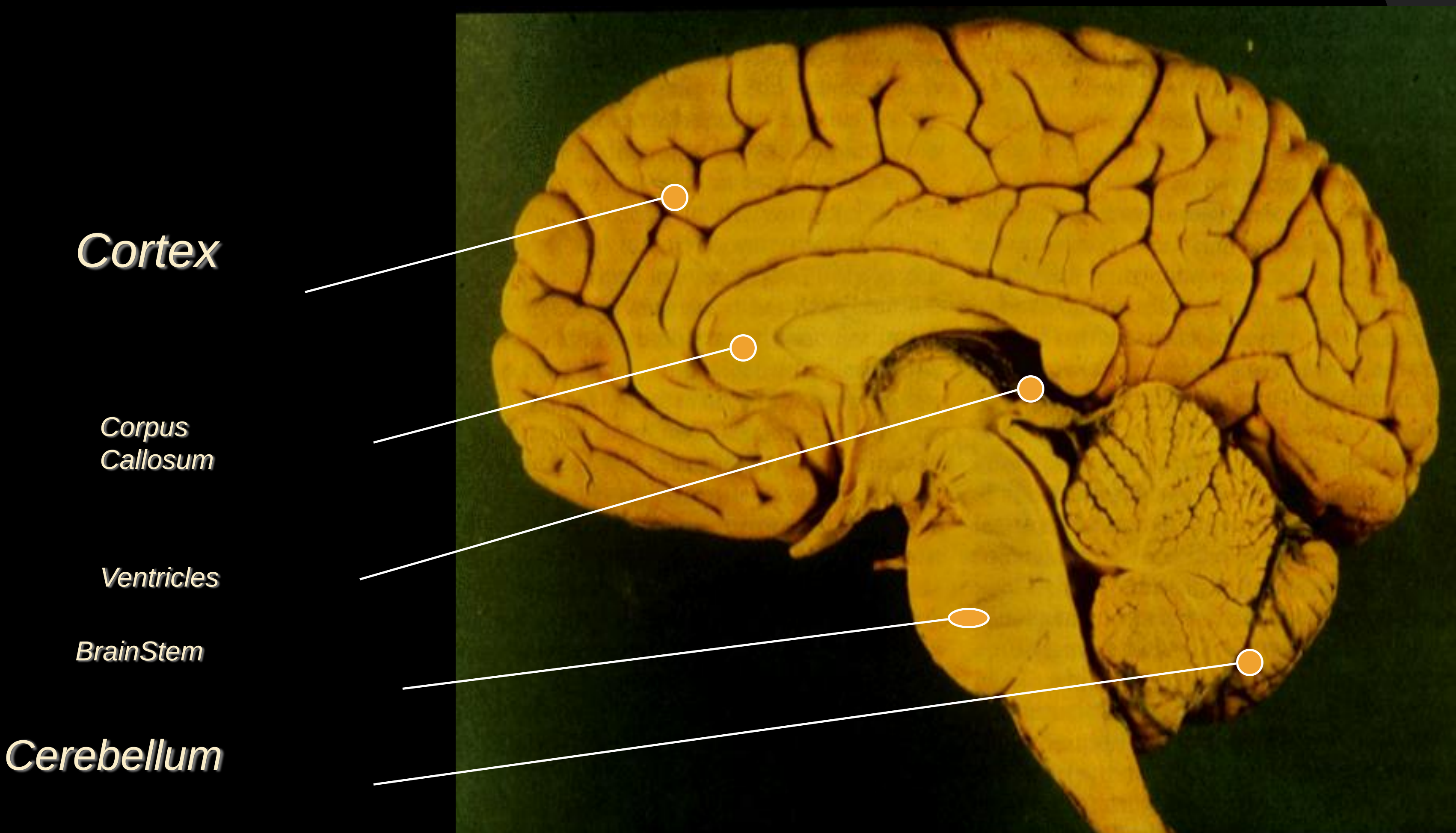




Brain anatomical/functional regions



Hemisection of the Brain (inside view)



AREA OF THE BRAIN ESSENTIAL FOR HIGHER COGNITIVE FUNCTIONING

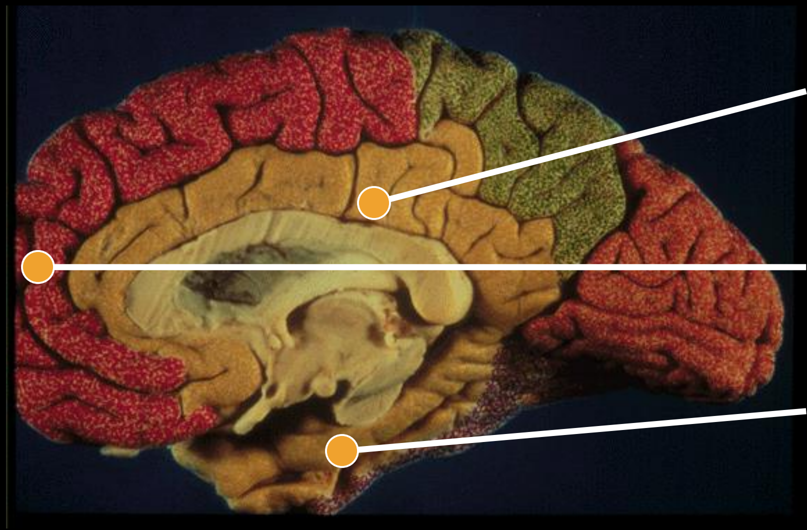
- **Hippocampus** *(recent memory ; no retention of new facts)*
- **Temporal and parietal lobes** *(Language and emotions)*
- **Wernecke's and Broca's areas**

  (Language comprehension and speech)
- **Thalamus**

  (Relay for sensory and motor functions)
- **Amygdala**

  (Emotion , stress, storage of memory)
- **Prefrontal , cingulate, occipital cortices**
- **Vermis of cerebellum**
- **Diffuse inherent memory storage capacity for all neurons**

Important centers for emotion and memory part 1



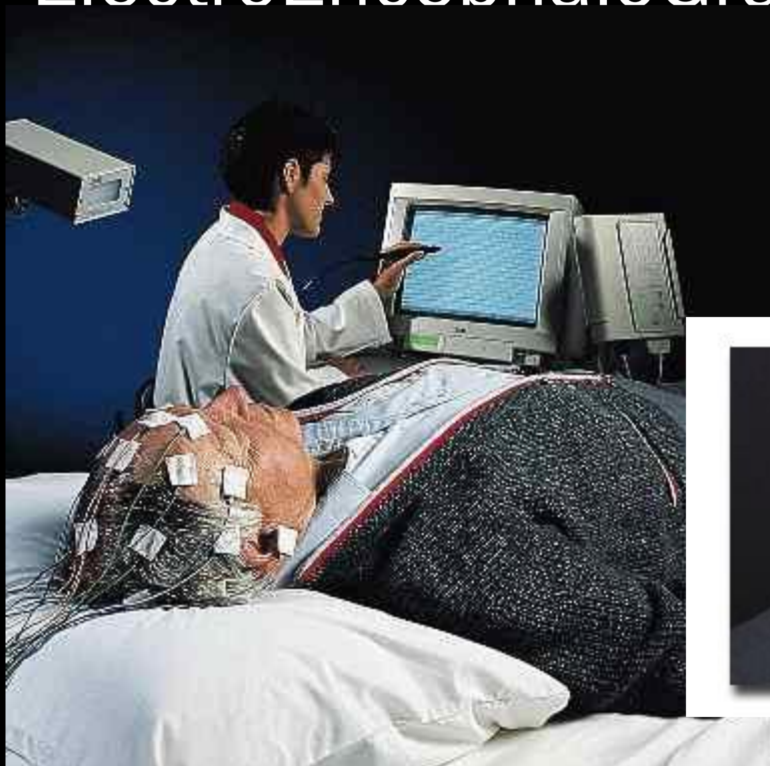
- **Amygdala** – limbic structure involved in many brain functions, including emotion, learning and memory. It is part of a system that processes "reflexive" emotions like fear and anxiety.
- **Cerebellum** – governs movement.
- **Cingulate gyrus** – plays a role in processing conscious emotional experience.
- **Fornix** – an arch-like structure that connects the hippocampus to other parts of the limbic system.
- **Frontal lobe** – helps control skilled muscle movements, mood, planning for the future, setting goals and judging priorities.
- **Hippocampus** – plays a significant role in the formation of long-term memories.
- **Limbic system** – a group of interconnected structures that mediate emotions, learning and memory.

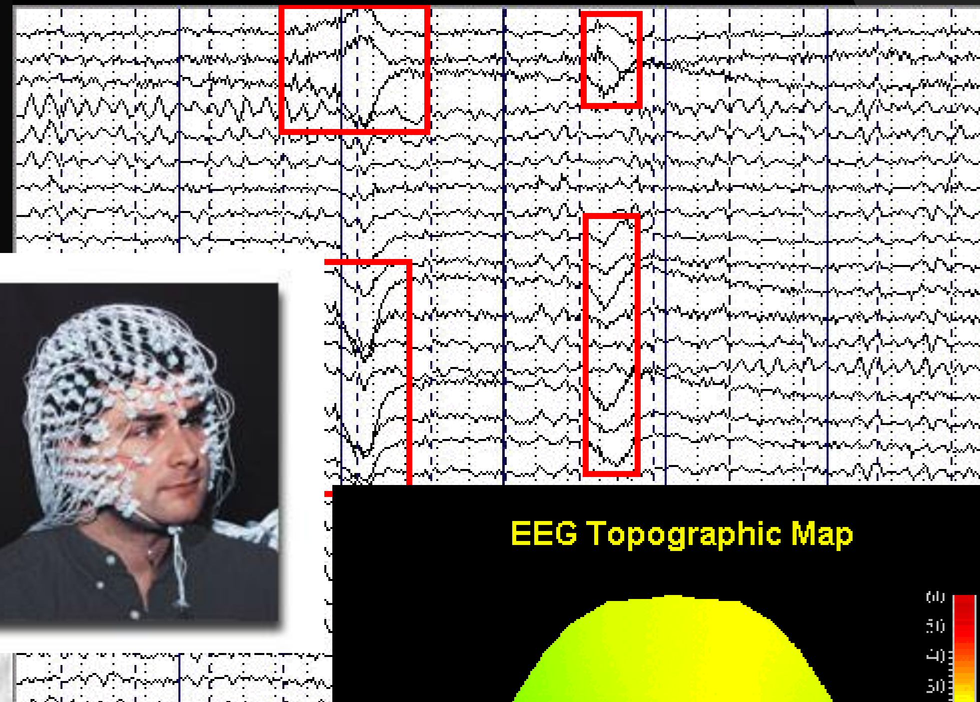
Methods and tools to study the brain

- ElectroEncephaloGraphy (EEG) Technology
- Angiography and Nuclear Magnetic Resonance (MRI)
- PET/SPEC functional Imaging
- Functional Magnetic Resonance Imaging (fMRI)
- Microscopic techniques to visualize cells
- Genetic and Informatics techniques

ElectroEncephaloGraphy (EEG) Technology

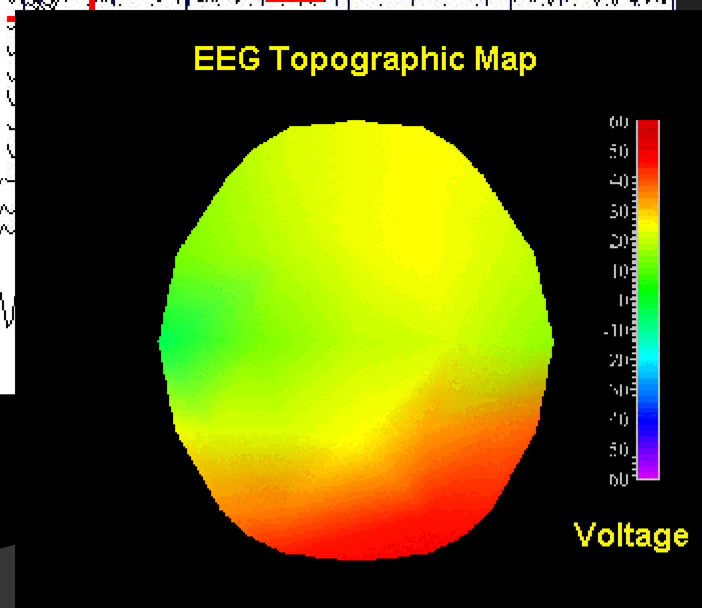
Multi-channel (32) EEG record





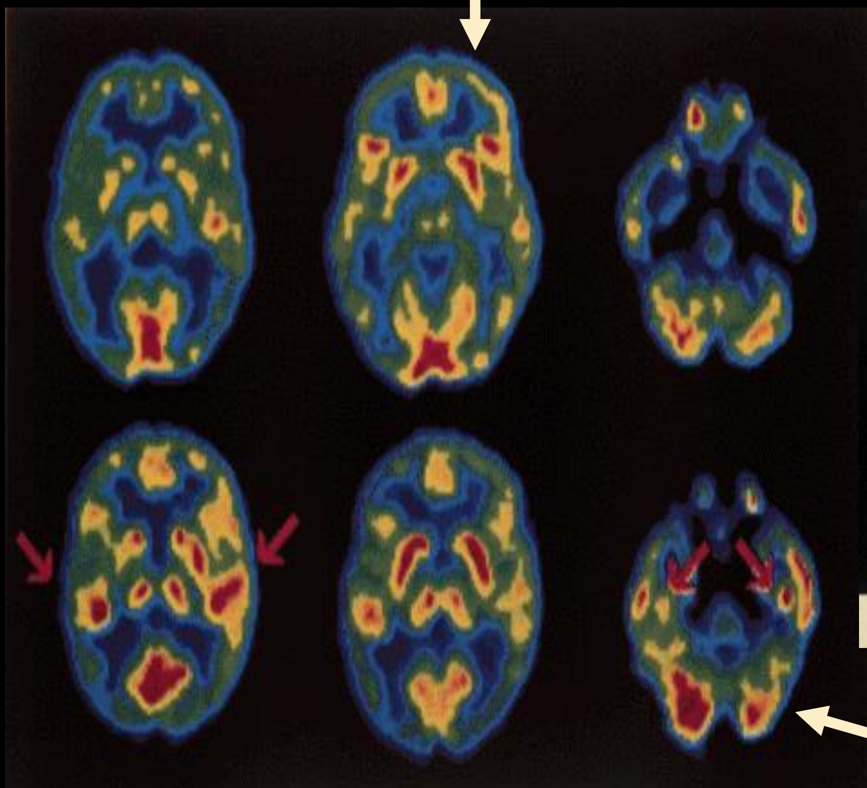
Single EEG record

New methods up to 256 channels

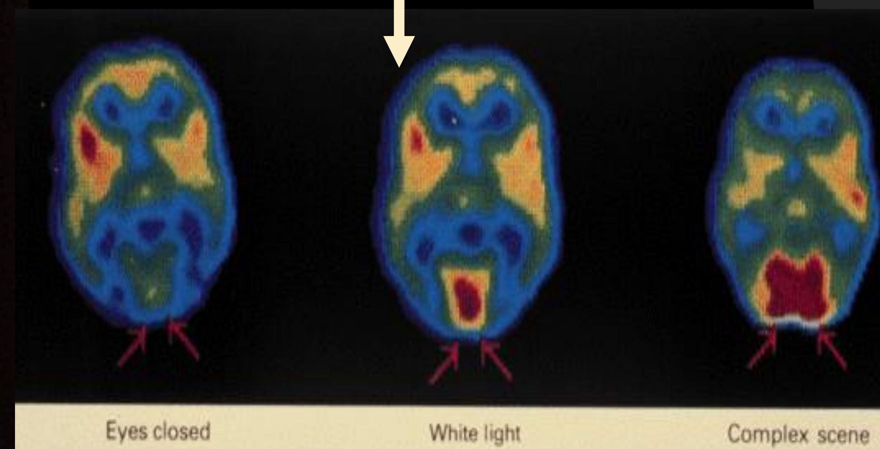


PET/SPEC functional Imaging

Normal (at rest)



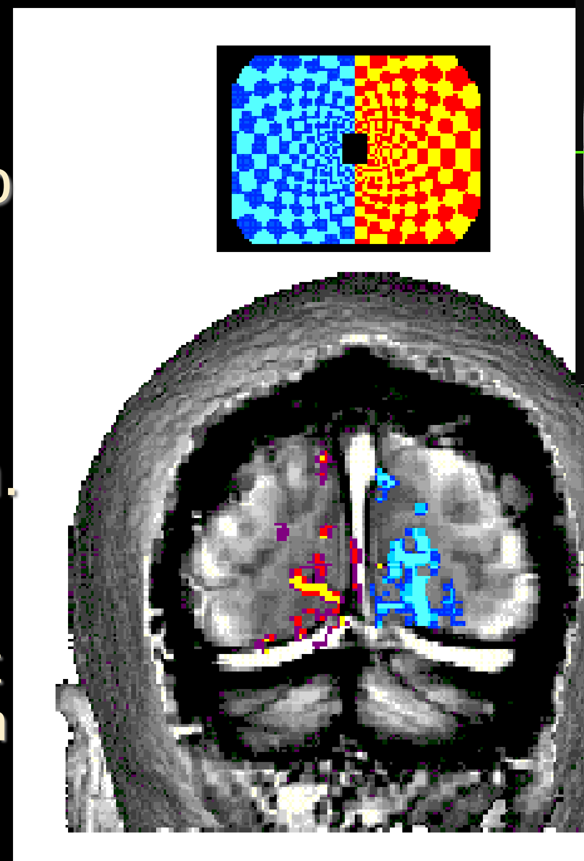
Visual Stimuli

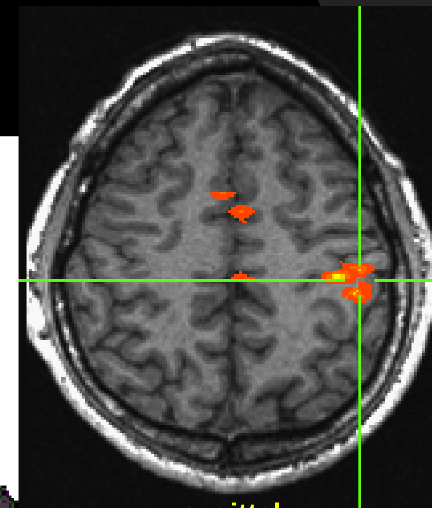


Auditory stimuli

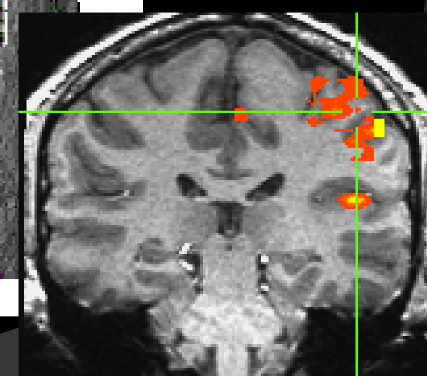
Example:

Images result of a <u>complex visuo-motor task</u>, subject asked to press a button according to a target randomly appearing before him.





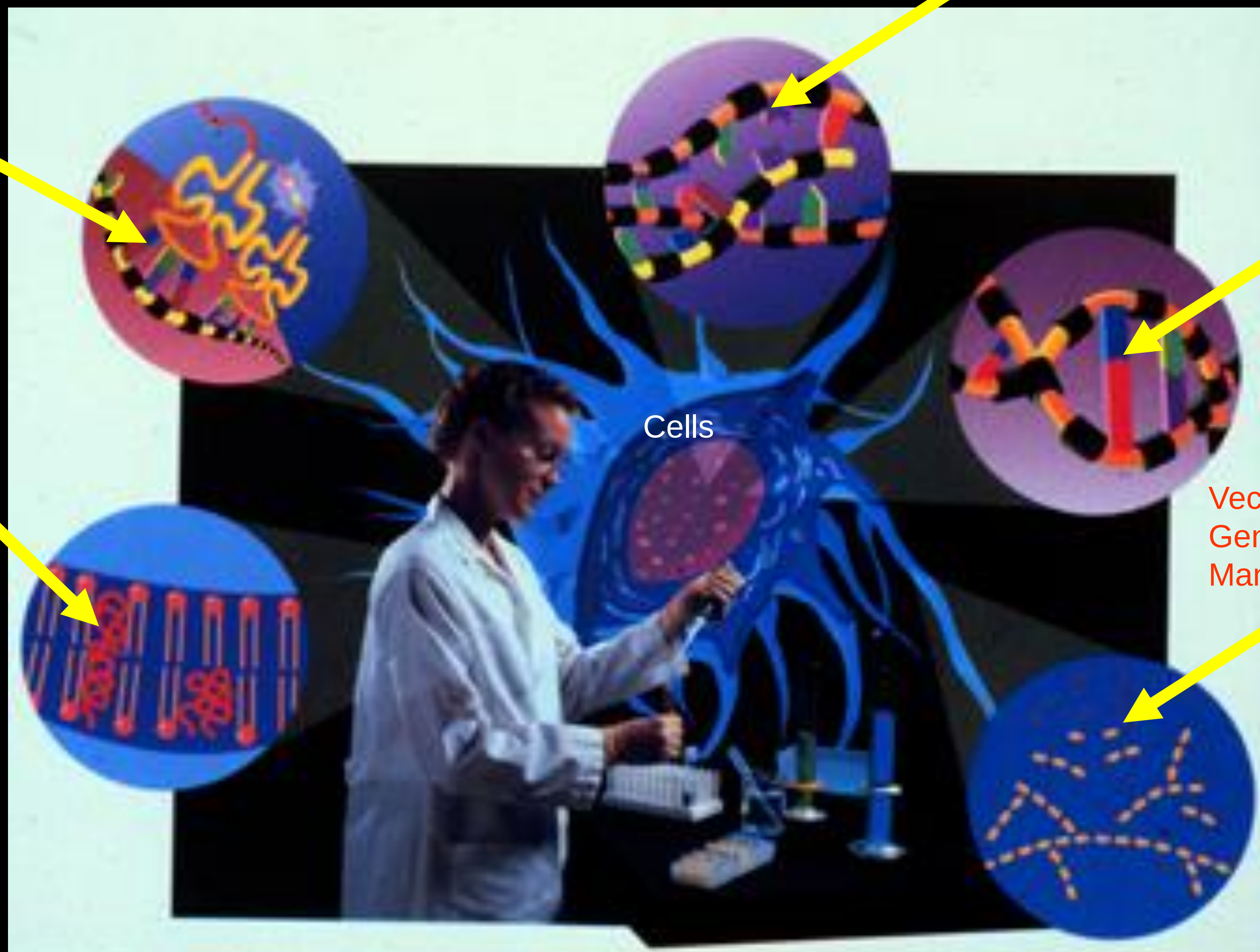
sagittal



coronal

- 1 mm thick axial, sagittal and coronal slices of the same 3D volume data set (functional data resolution 4 mm, anatomic data *resolution 1 mm)*

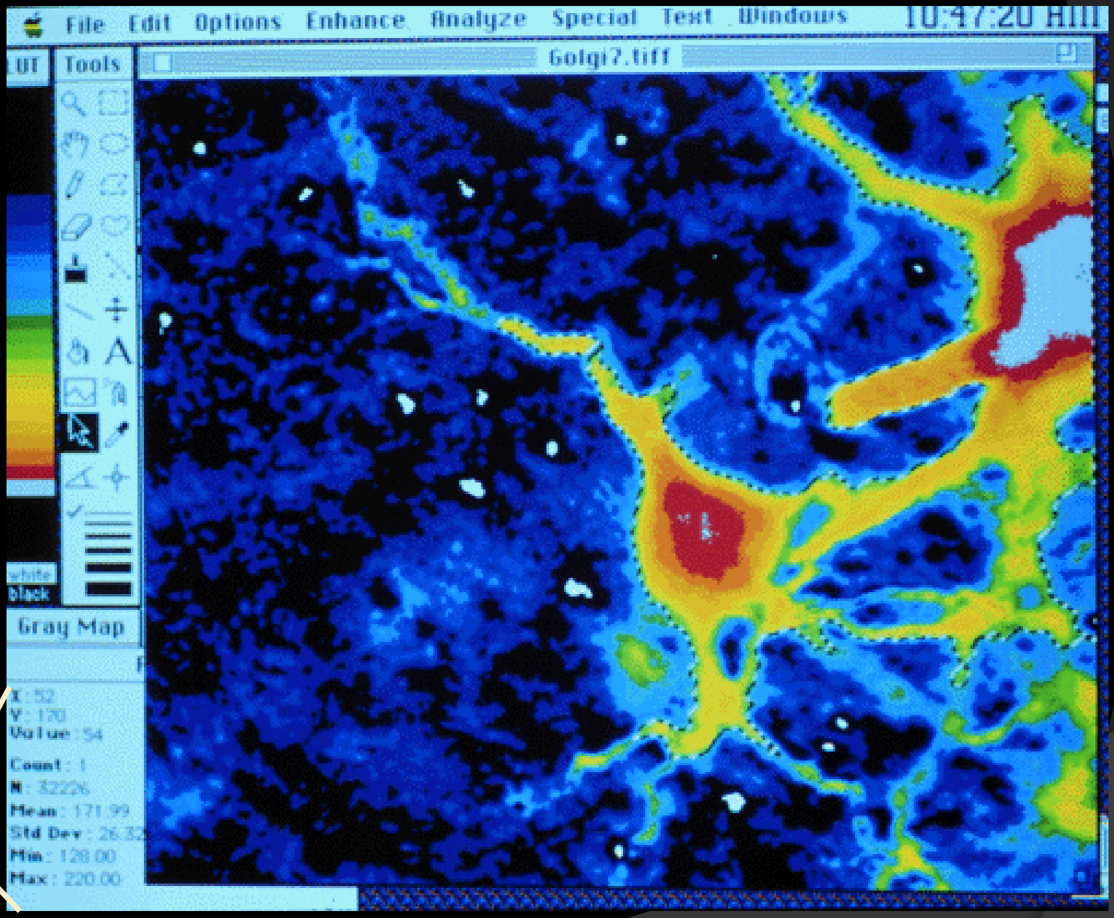
A New World of Science and Technology



Morphometric Analyses of Neurons

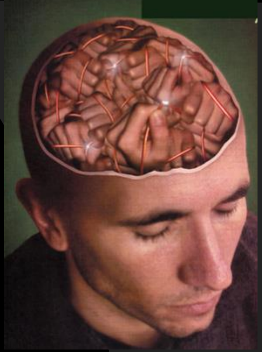
Computer processed imaging

Silver staining



Measurements

Synapses:
Units of neuronal communication



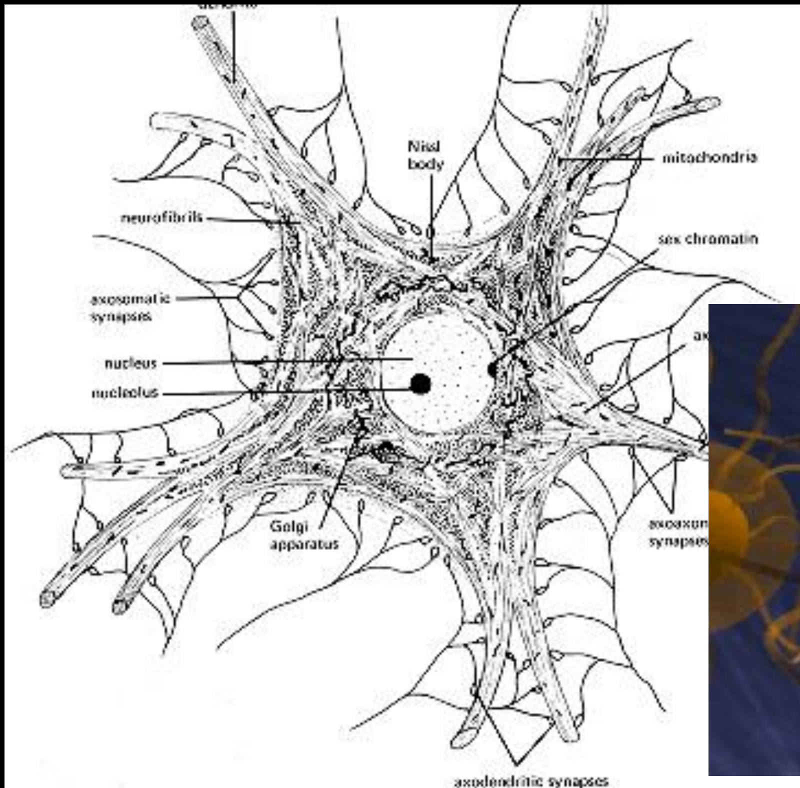


FIG. 2-2. Semidiagrammatic representation of the constituents of a nerve cell.

duced by about 10–15 mV to

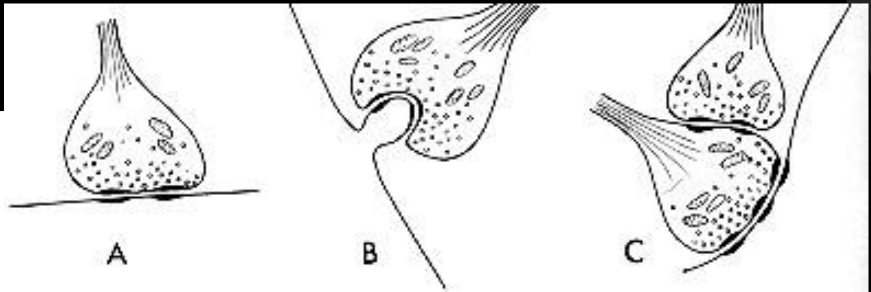
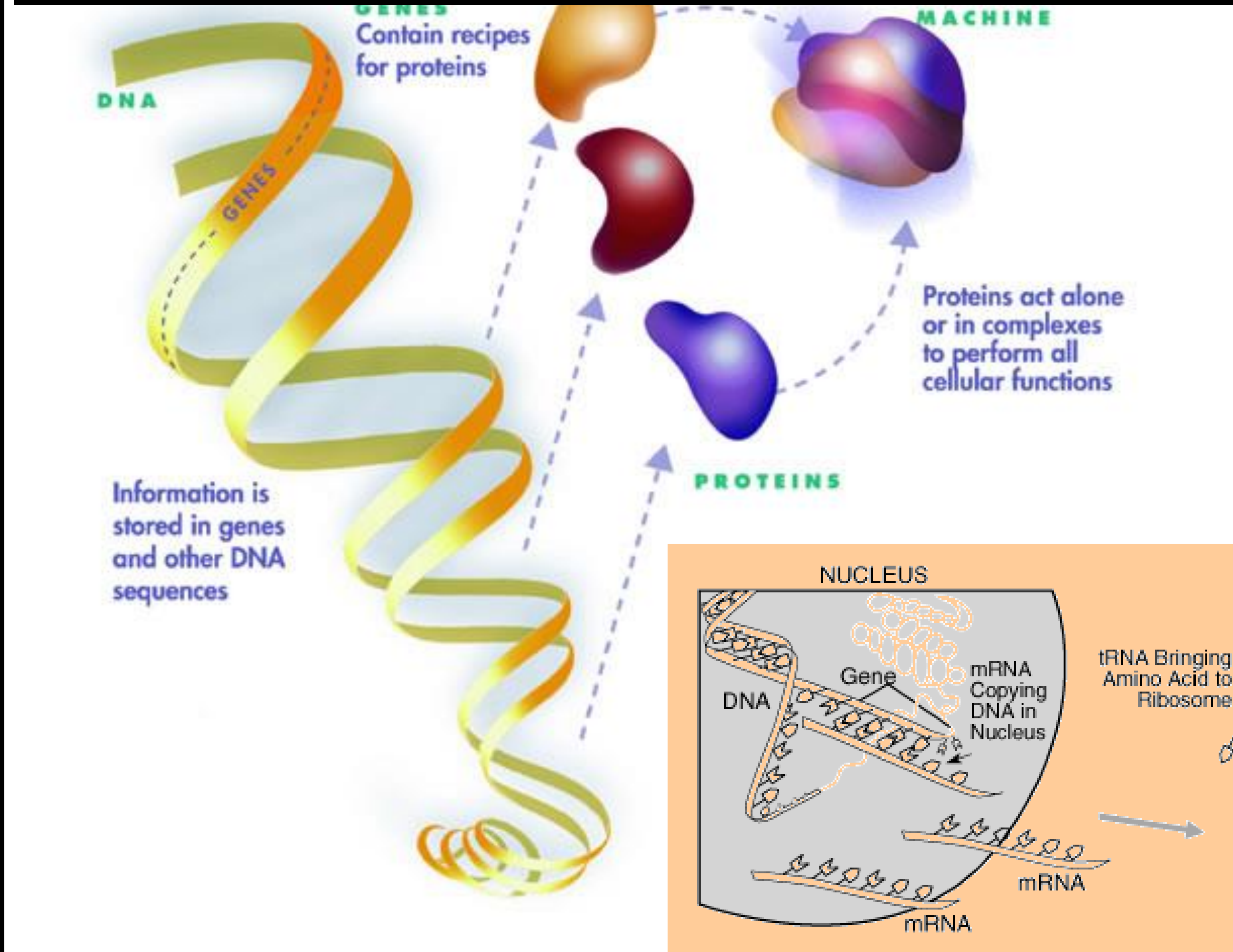
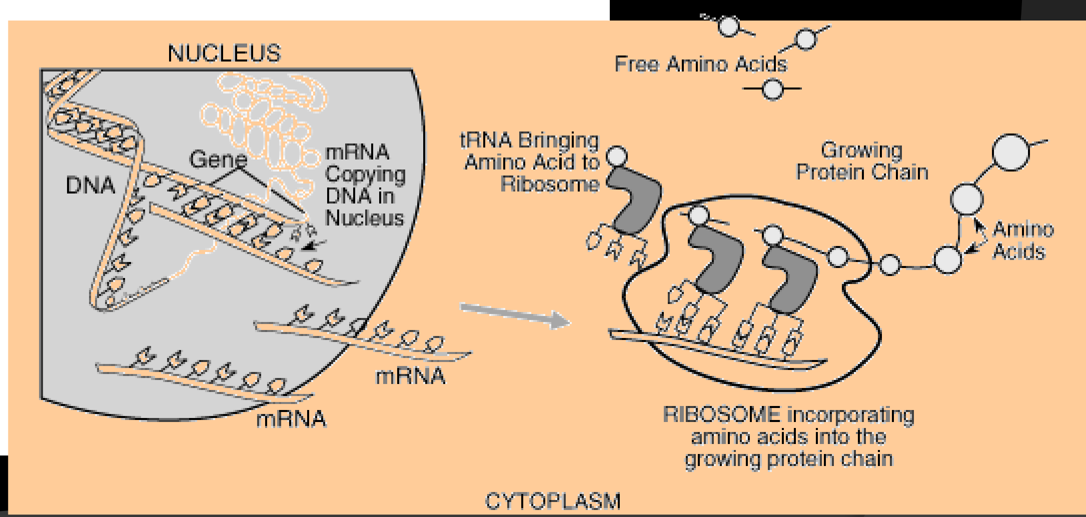


FIG. 2-6. Ultrastructure of synapses. A. Axodendritic or axosomatic synapse. B. Axodendritic synapse, in which an end bulb is in synaptic relation with a dendritic spine. C. Axoaxonic synapse of the end bulb to end bulb type. See text for details.

How does neuro-transmission works?

Genes-Proteins Machinery



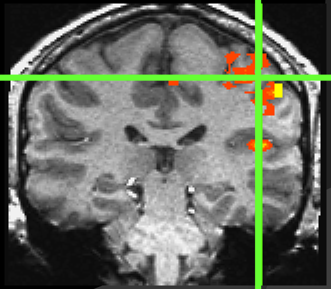


NeuroInformatics

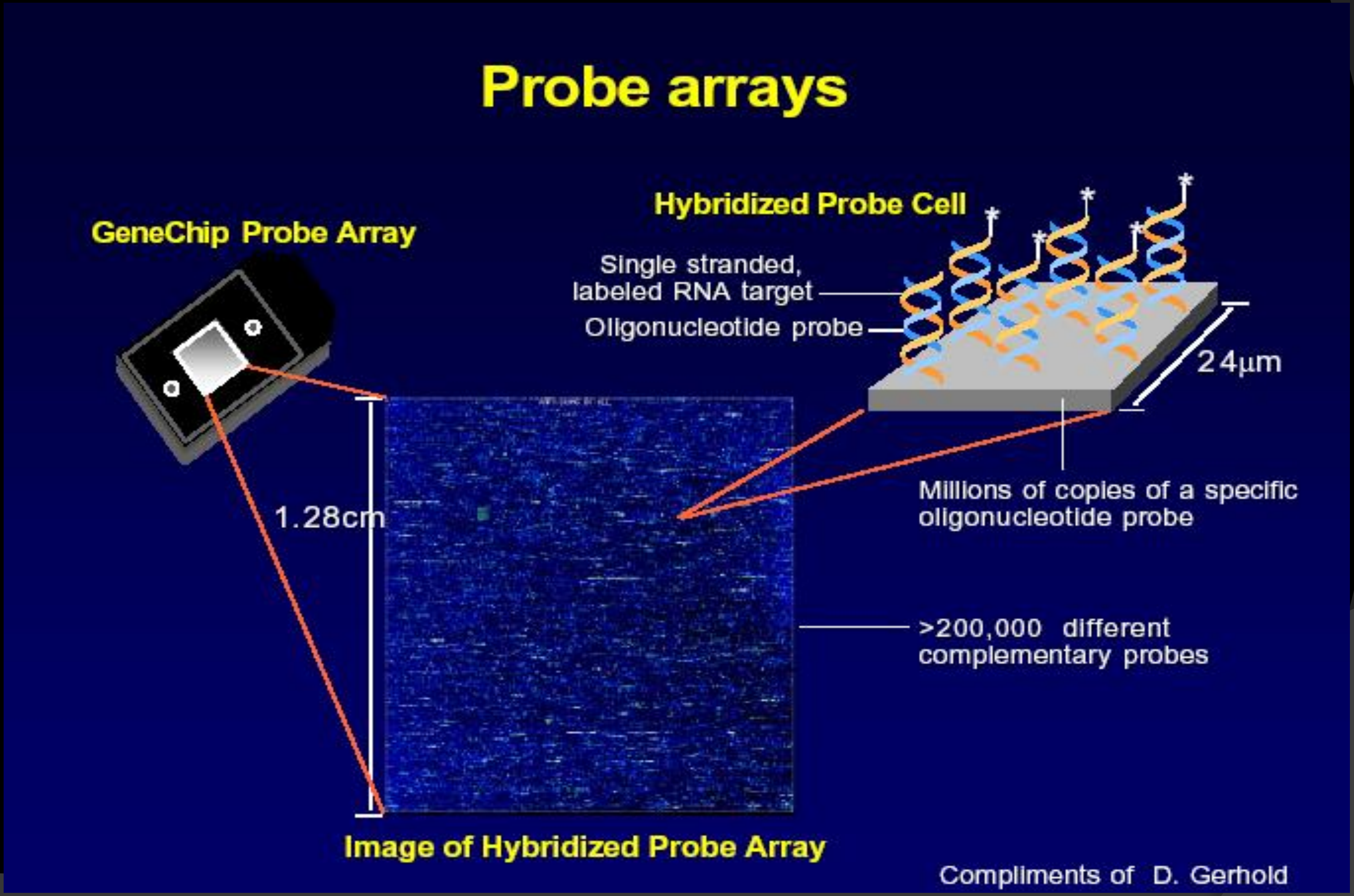
Combines various subdisciplines neuroscience and expertise informatics research to develop and apply advanced tools and approaches essential for a major advancement in understanding the structure and function of the brain.

- Hope is

Neuroinformatics research will lead to new digital and electronic tools for all domains of neuroscience research reflecting normal and diseased states across the life span.

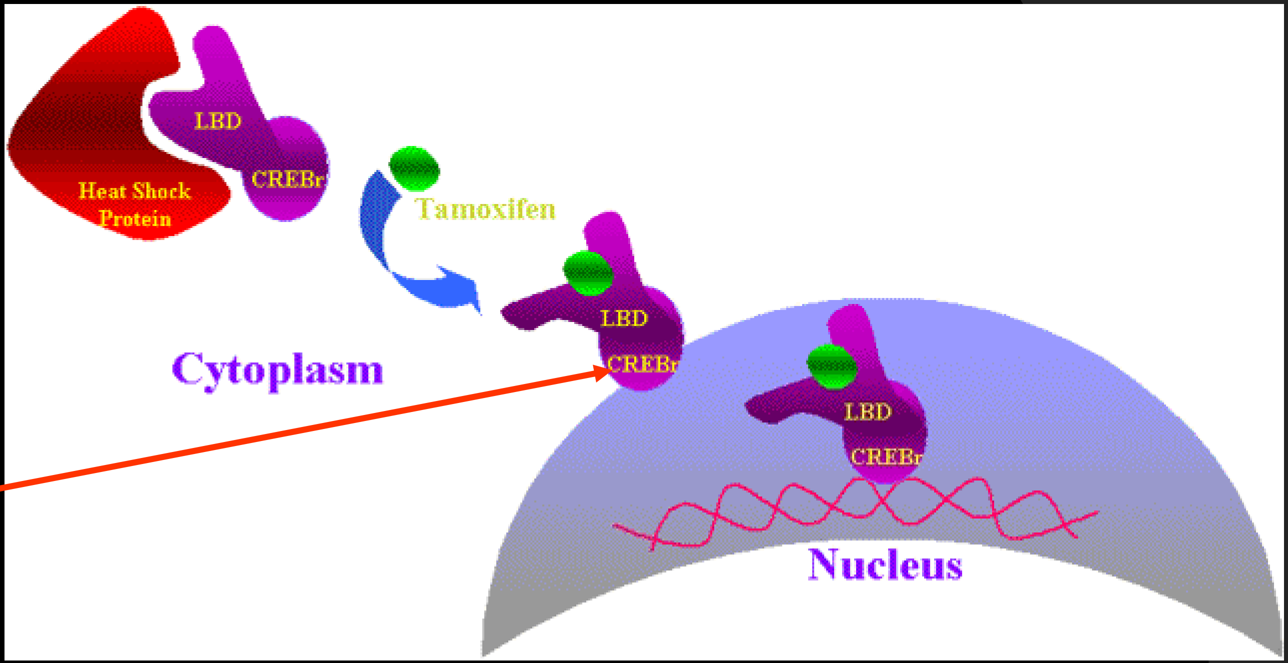


Affymetrix GeneChip Arrays
Whole genome evaluation: Differential gene expression



Intelligence at the Molecular level

cAMP responsive element binding protein (CREB)



Studies in a variety of species, indicate that CREB) family of transcription factors is critical for both the **long term stability** of changes in synaptic function, and for **long term memory**

- Mutation of the CREB gene showed normal short-term memory, but abnormal long-term memory for a variety of tasks
- CREB is one of the determinants of the training schedules required for long term memory formation

Rational for Stem cell technology in Regenerative Medicine

- Maintain and replace parts of organs
- Correct functional deficits (diseased area)
- Develop new technologies to assess diseases remotely (non-invasively)
- Great potentials for new investigators with a cleaver minds