Fetal stem cell transplants: Surgical realities and hopes

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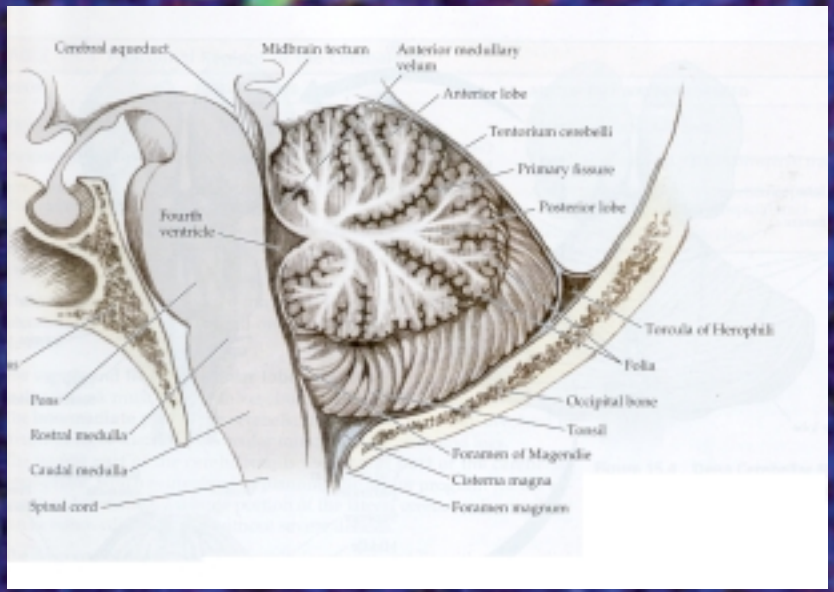
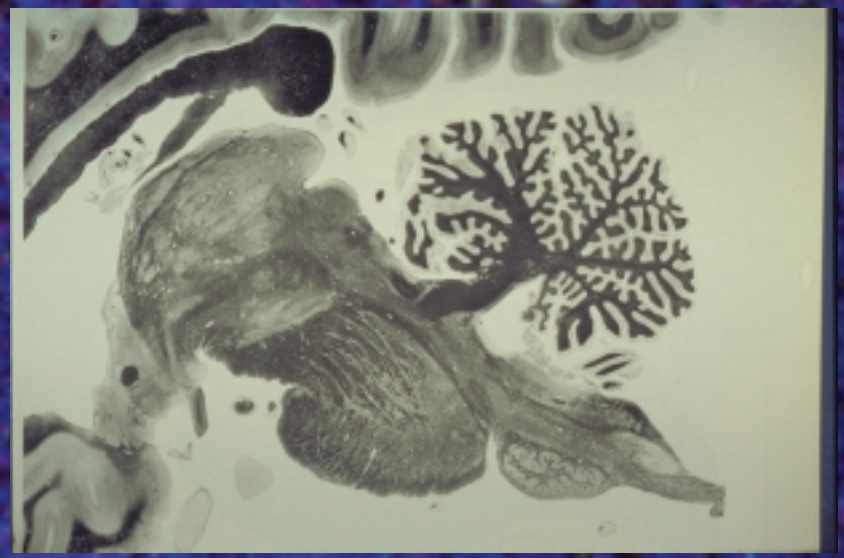
Outline

- Anatomy of cerebellum
- Discuss symptoms of ataxia
- Introduction to fetal cells/stem cells
- Review human studies in PD
- Fetal/stem cell studies in ataxia
- Deep brain stimulation for tremor

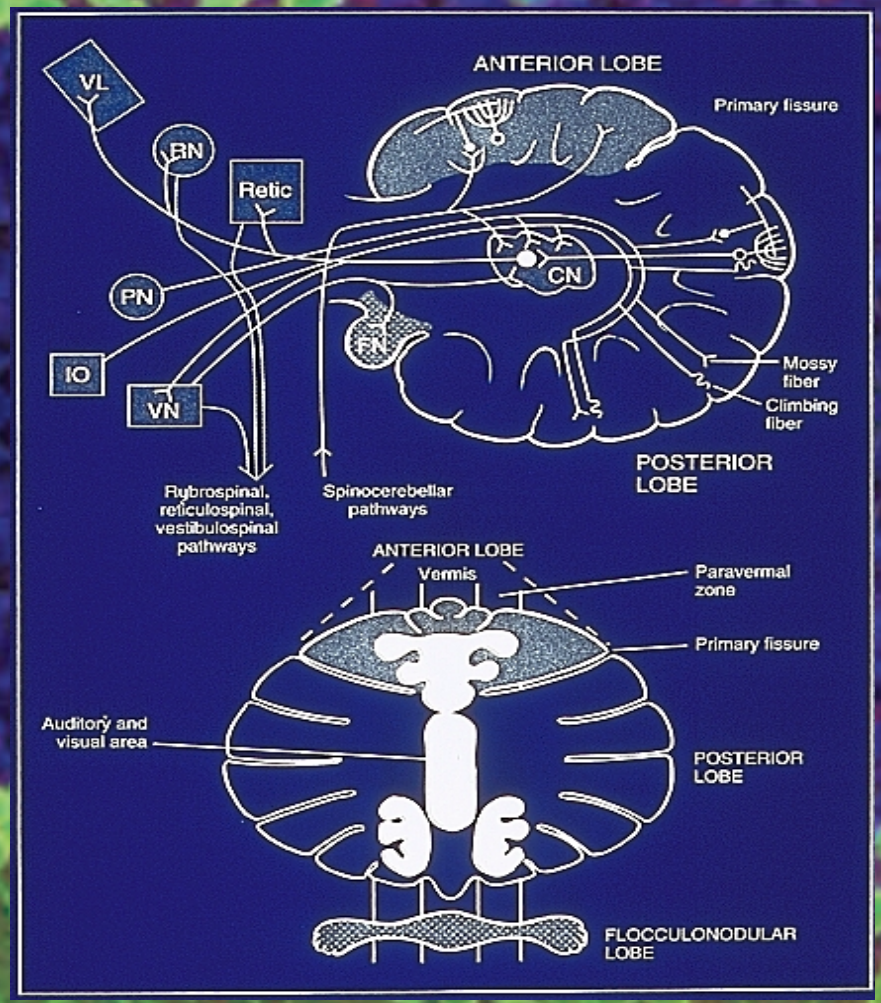
The cerebellum





- Diagram: Blumfeneld, Neuroanatomy through clinical cases, Sinauer, MA. 2002
- Photomicrograph: Dr. Conrad Pappas

Parts of the cerebellum

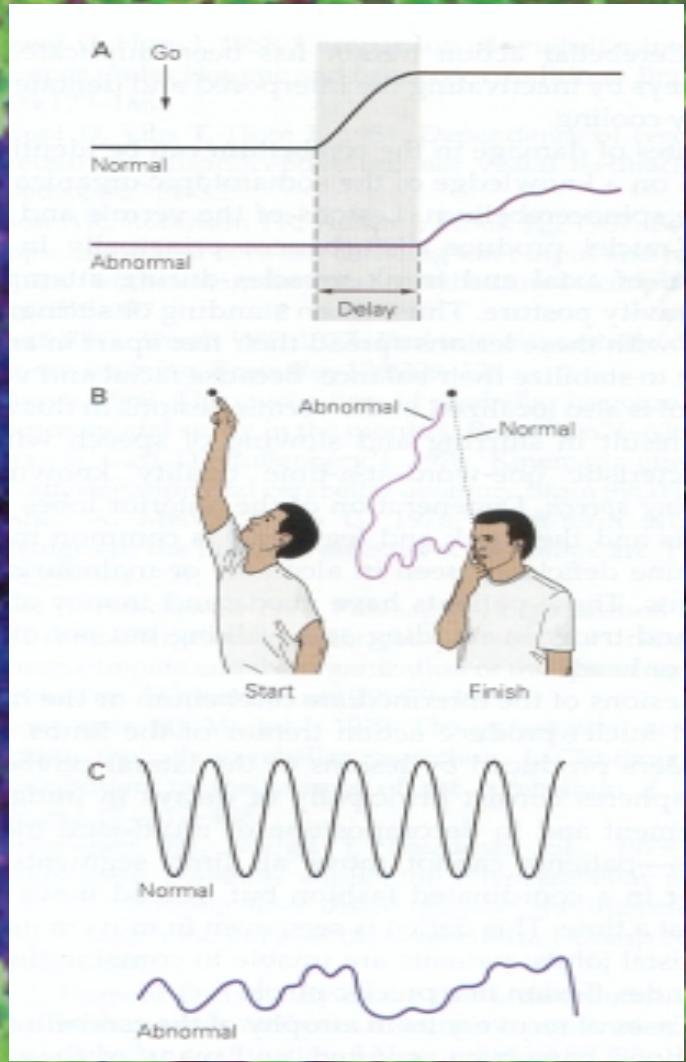


- Flocculonodular lobe: receives balance information
- Anterior lobe: receives spinal cord input
- Posterior lobe: receives input from frontal lobes
- Diagram: Patton, Neurological Differential Diagnosis, Springer 1977

Cerebellar location	Symptoms
Flocculonodular ,	Eye movement problems, postural and gait problems
Anterior	Truncal and gait ataxia
Posterior	Arm and leg ataxia, intention tremor, speech problems, cognitive changes

Ataxia

- Uncoordinated or inaccurate movement not due to paresis, alteration in tone, loss of postural sense or the intrusion of voluntary movements
- Diagram: Kandel, Schwartz, Jessel. Principles of Neural Science, MaGraw-Hill, 2000.



Clinical signs

- ***Gait ataxia***: Wide-based gait; fear of falling
- ***Truncal ataxia***: Unstable trunk; may wobble or have tremor; may need support to sit up
- ***Limb ataxia***: Inaccurate coordination of arms and legs

Clinical signs

- ***Nystagmus***: Brief, rapid involuntary eye movements which occur during visual tracking.
- Difficulty with fixing eyes steadily on a target.

Clinical signs, cont.

- ***Dysarthria***: Slurring of speech; difficulty coordinating breathing and speaking
- ***Tremor***: In arms outstretched; interferes with eating, writing, drinking, buttoning, fine movements
  - May also be present in legs, trunk, voice, head

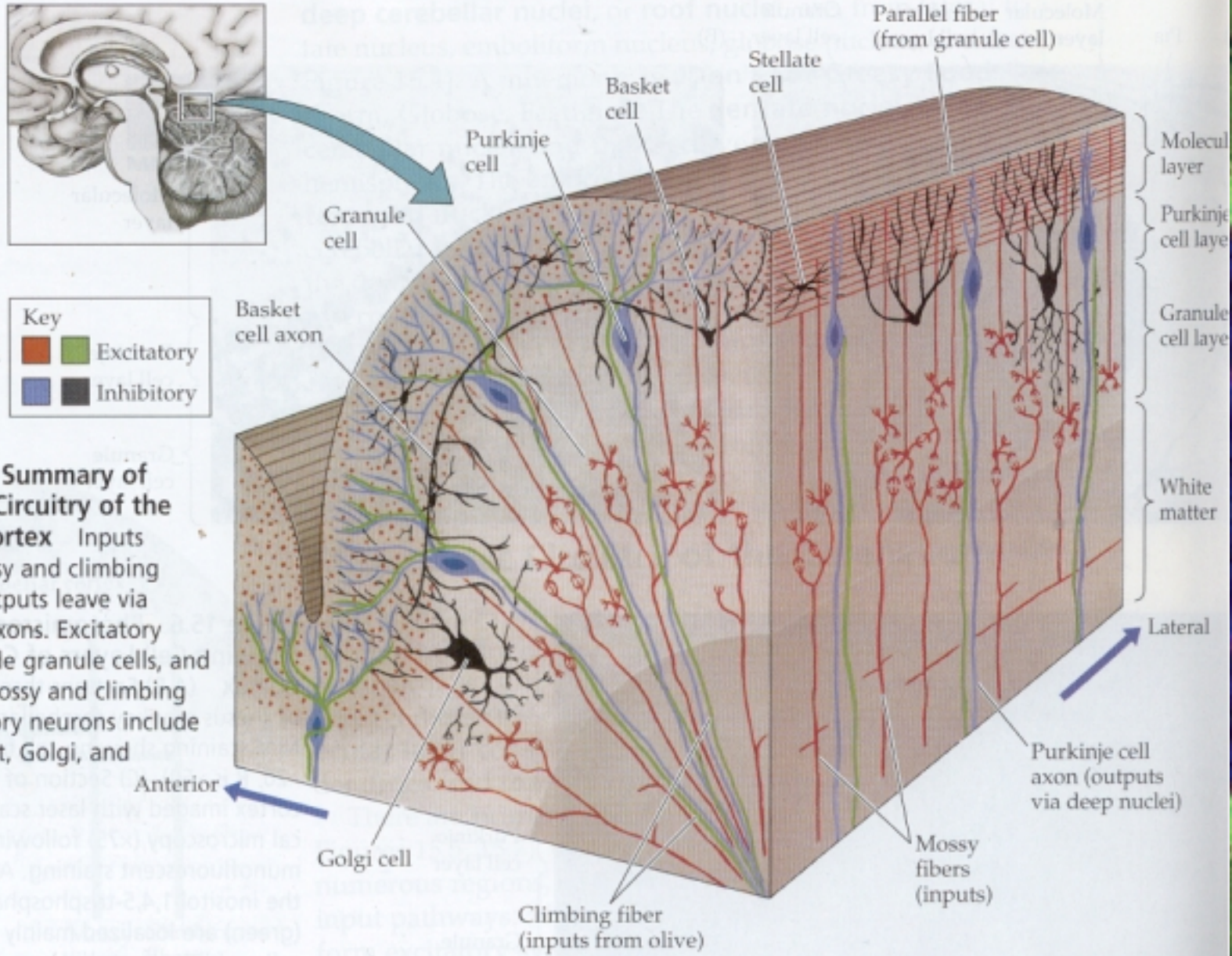


Figure 15.7 Summary of Microscopic Circuitry of the Cerebellar Cortex Inputs arrive via mossy and climbing fibers, and outputs leave via Purkinje cell axons. Excitatory neurons include granule cells, and inputs from mossy and climbing fibers. Inhibitory neurons include stellate, basket, Golgi, and Purkinje cells.

Diagram: Blumfeneld, Neuroanatomy through clinical cases, Sinauer, MA. 2002

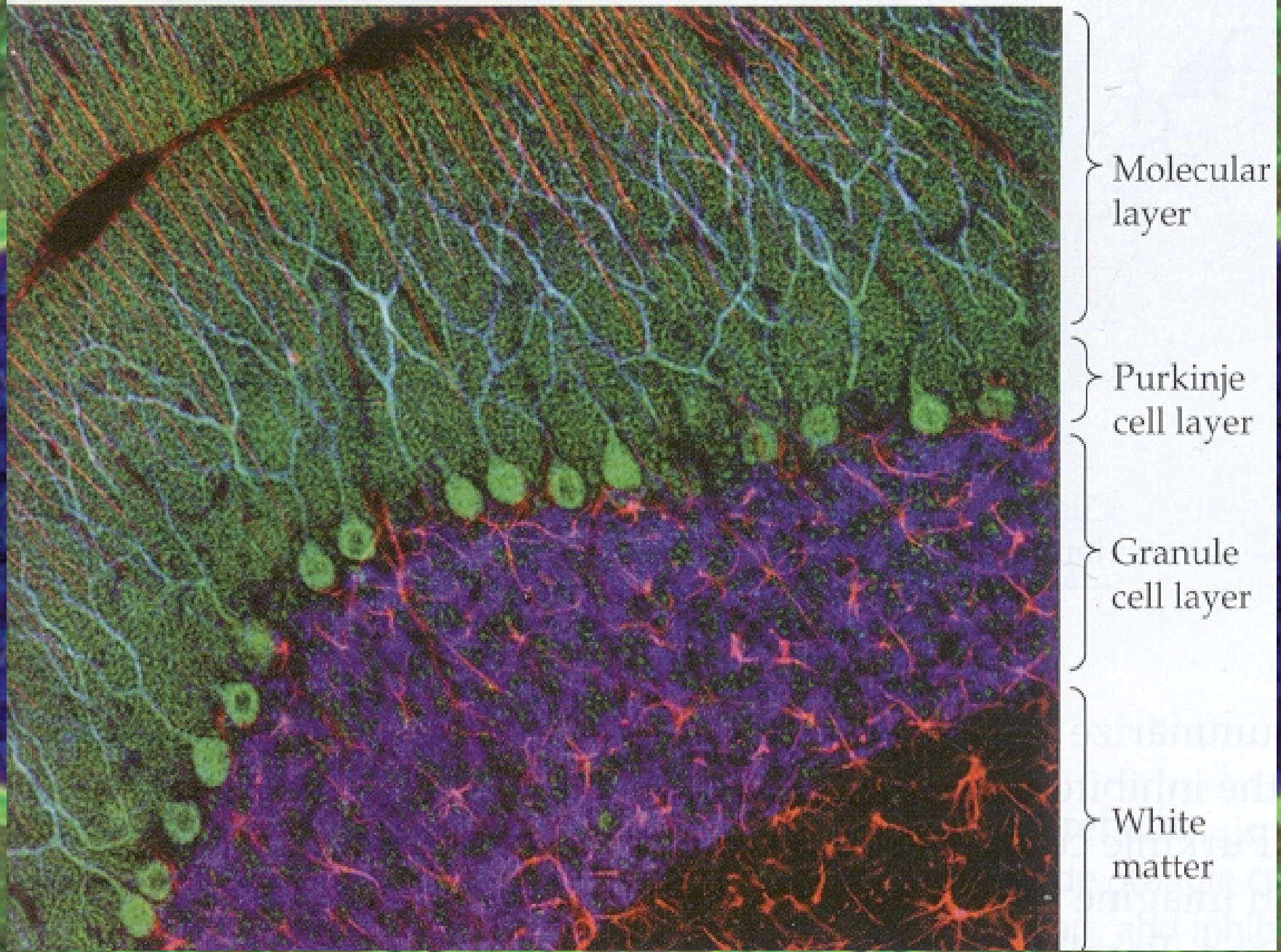


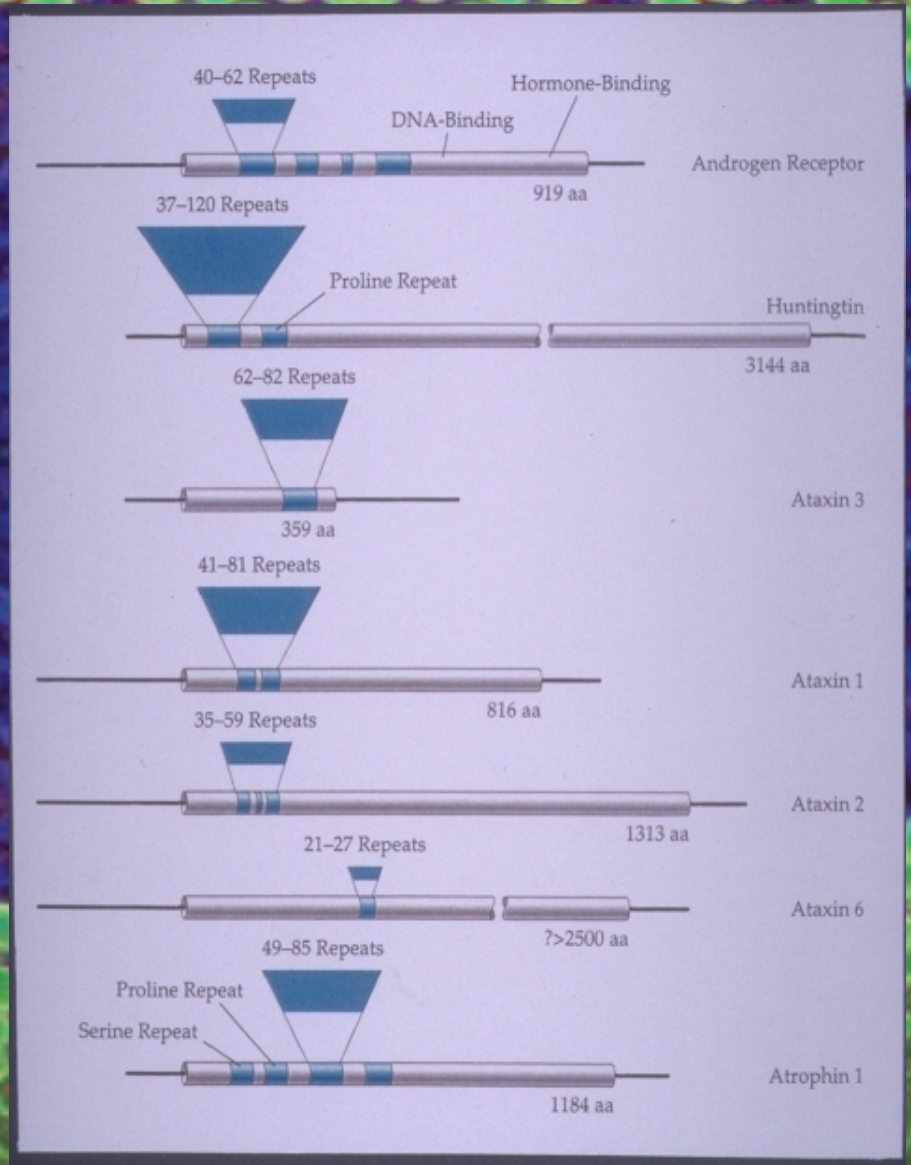
Diagram: Blumfeneld, Neuroanatomy through clinical cases, Sinauer, MA. 2002

What causes ataxia?

- Inherited ataxias
- Non-genetic neurodegenerative
- Multiple sclerosis
- Tumors
- Strokes
- Infections and immune problems
- Medications

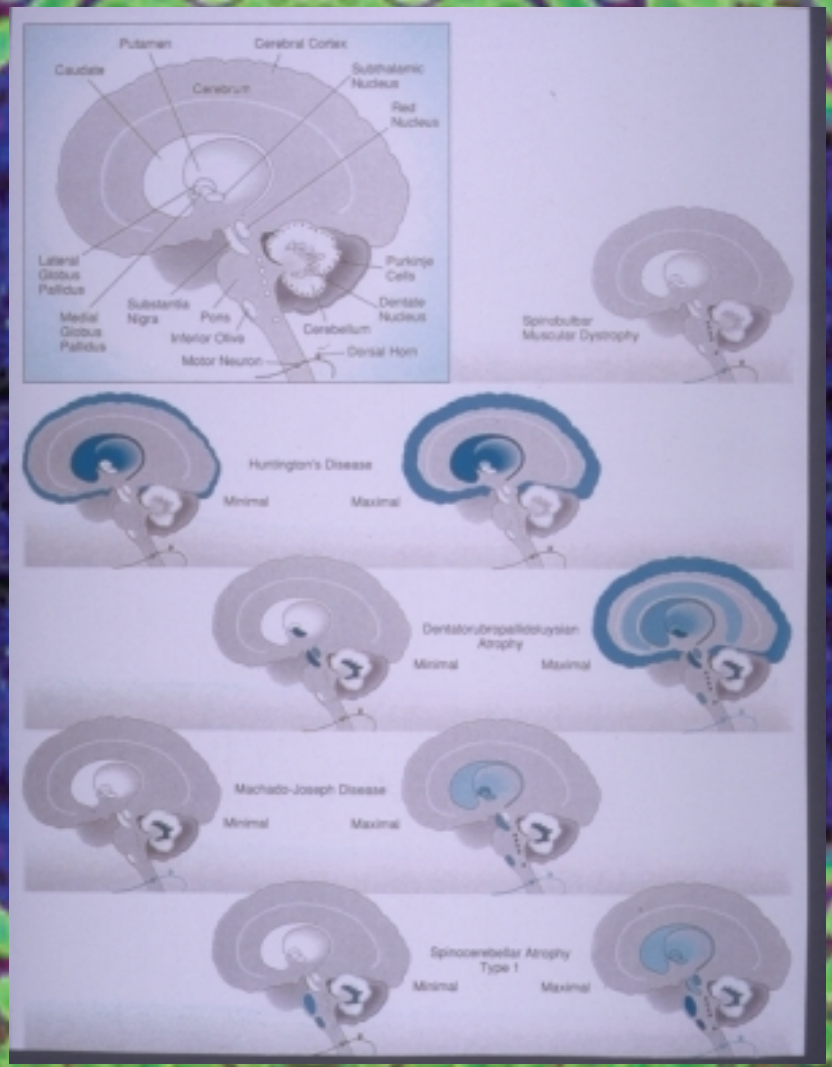
Genes that cause neurological diseases

Diagram: Young, HD and other trinucleotide Repeat Disorders in Molecular Neurology, Martin, ed. Scientific American, 1998

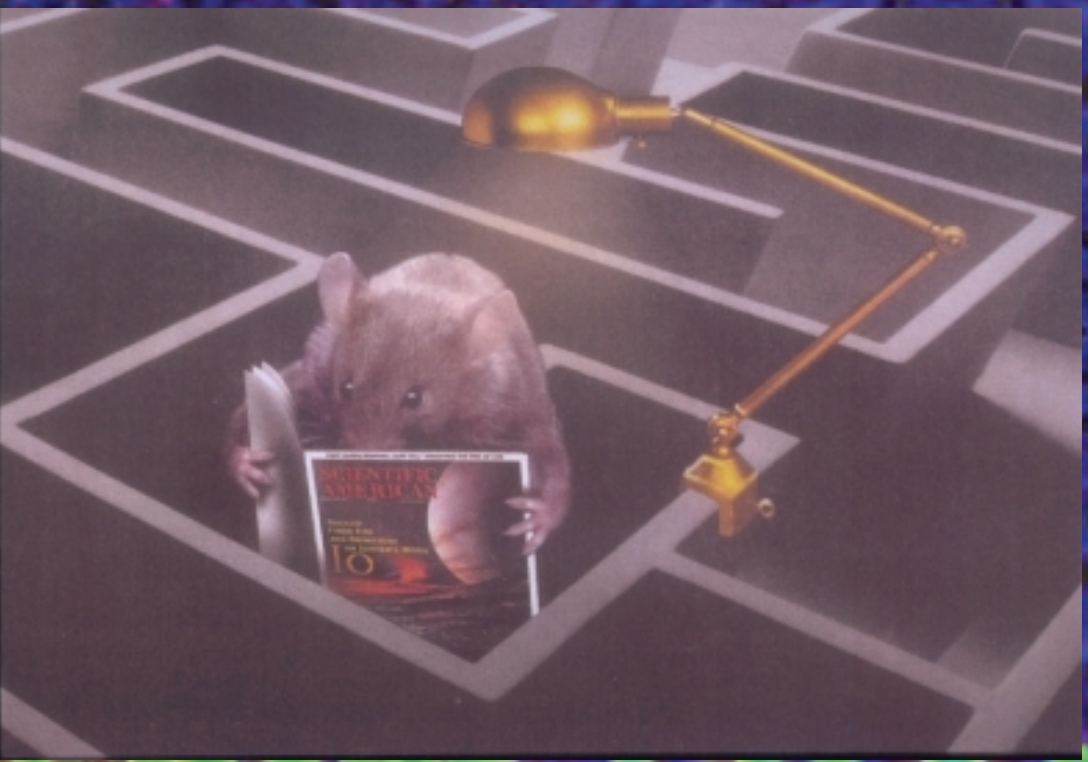


Polyglutamine diseases

Diagram: Young, HD and other trinucleotide Repeat Disorders in Molecular Neurology, Martin, ed. Scientific American, 1998



Ataxia mouse models



- *pcd* mouse
- *Shaker* rat
- Transgenic mouse

The challenges in treating ataxia

- Many different causes
- No specific brain chemical loss
- The cerebellum is so richly interconnected with visual, hearing, touch, movement and thinking areas
- In hereditary ataxias, other brain and spinal cord areas may also be affected

Potential surgical treatments

- Fetal cells
- Stem cells
- Deep brain stimulation

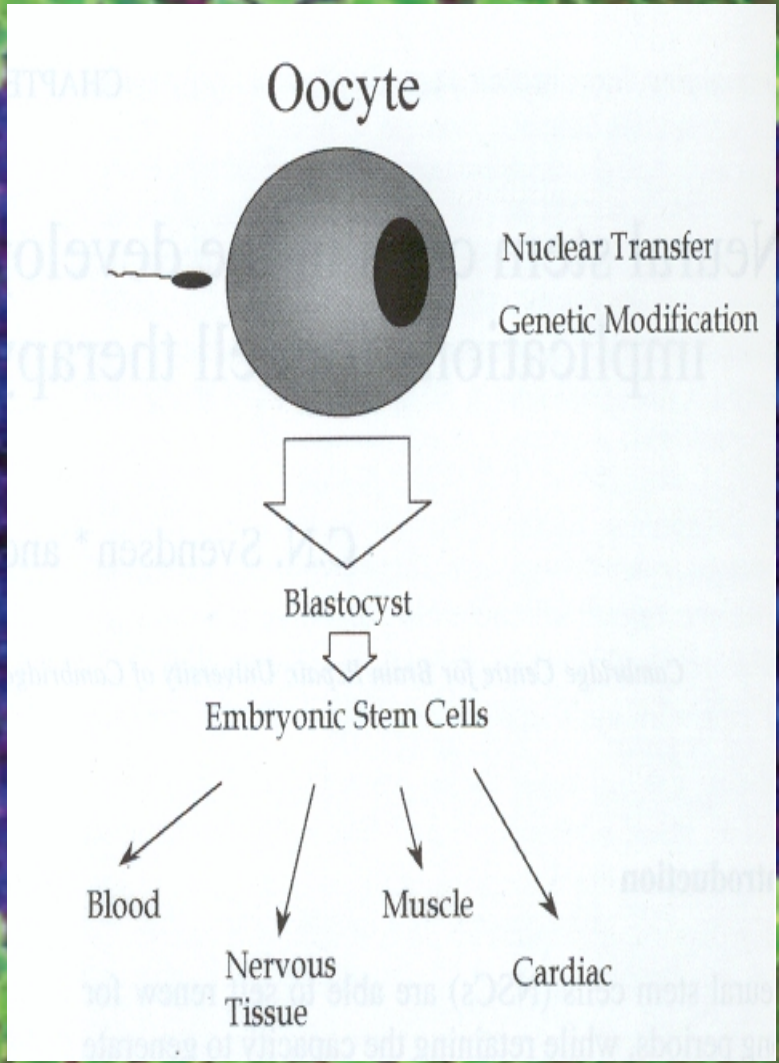
Fetal cells

- Fetal cells can form specific connections to the proper target areas
- Derived from brain region already undergoing growth and specialization
- Source is limited: Taken from donated embryos age 7-8 weeks

Stem cells

Diagram: Svendsen, in Functional Neural Transplantation II. Novel Cell Therapies for CNS disorders. Elsevier 2000.

- Formed from fertilized egg, human brain regions, tumor cells, other species
- Can be grown in the laboratory



Stem cells

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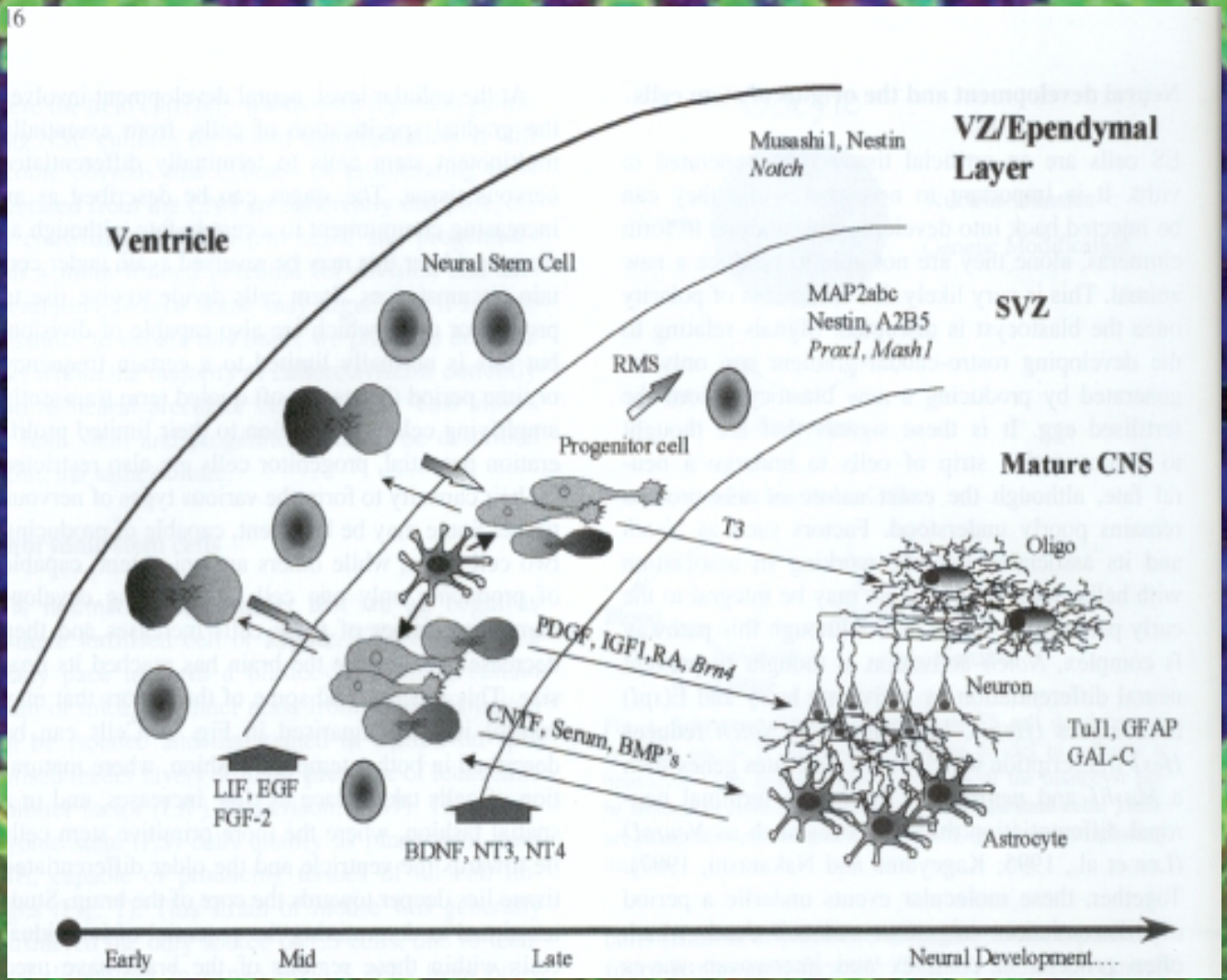


Stem cell questions

- Can they be grown in sufficient numbers in the laboratory
- Do they remain stable over time in the lab?
- Can they restore damaged areas of the brain?
- How is their migration and behavior regulated in the host brain?

Can other neurological diseases gives us clues for treating ataxia?

- Alzheimer's disease
- Parkinson's disease
- Huntington's disease

Fetal cell transplantation in PD

- Initial report of “curing” PD in 1987 by Madrazzo in Mexico City
- Because fetal tissue was not available in US in 1980s, adrenal gland cells from PD patients were removed and transplanted to brain late 1980’s
- ***It didn’t work!***

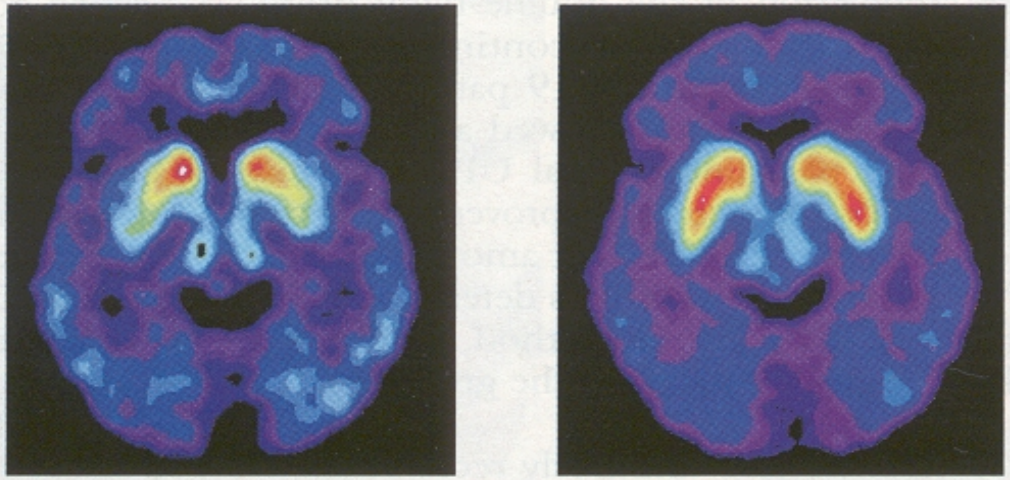
Fetal cells in PD

Freed C et al. NEJM 2001;344:710-9

- "Gold Standard" study: Used a control group of 20 patients who had "sham" surgery
- Outcome measures: patients' rating of their symptoms
- Brain scans showed that the fetal cells did survive in 17/20 patients

Freed C et al. NEJM 2001;344:710-9

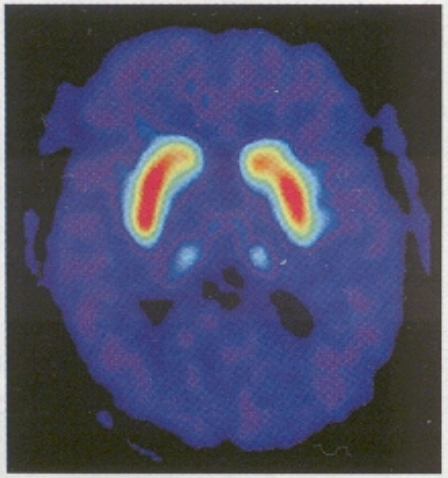
Transplantation of Embryonic Dopamine Neurons



Before surgery

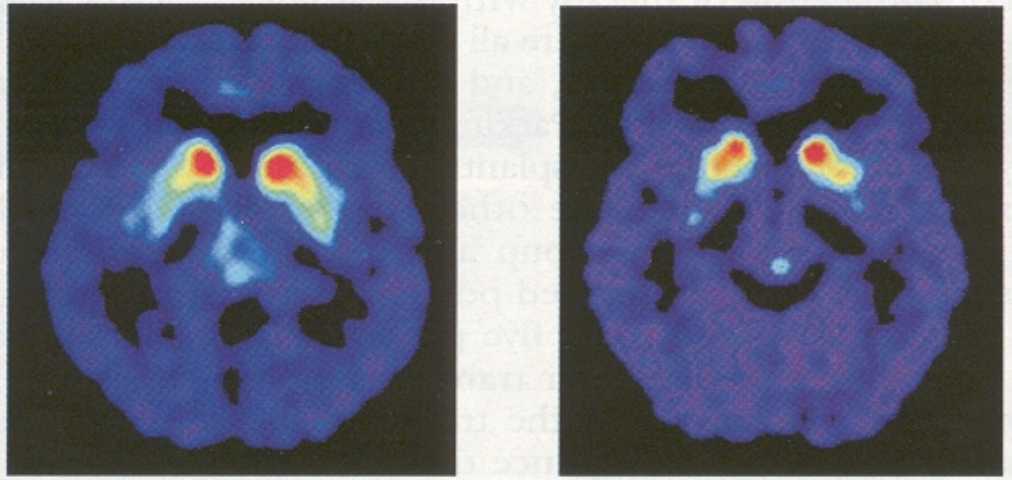
After surgery

Fluorodopa PET Scans



Normal

Sham Surgery



Before surgery

After surgery

Fetal cells in PD

Freed C et al. NEJM 2001;344:710-9

- Results: disappointing
- There was no significant difference between the grafted and the control patients' symptoms.
  - There was a small improvement in the neurological exam in some patients under 60 yrs
- 4 patients developed severe side effects: uncontrollable, disabling involuntary movements

Important

- Do fetal cells and stem cells do the right thing when transplanted into the human brain?
- Do scientists know enough yet about the growth and behavior of these cells?
- Some have called for holding off on human trials of transplants in PD and HD until these questions are answered.

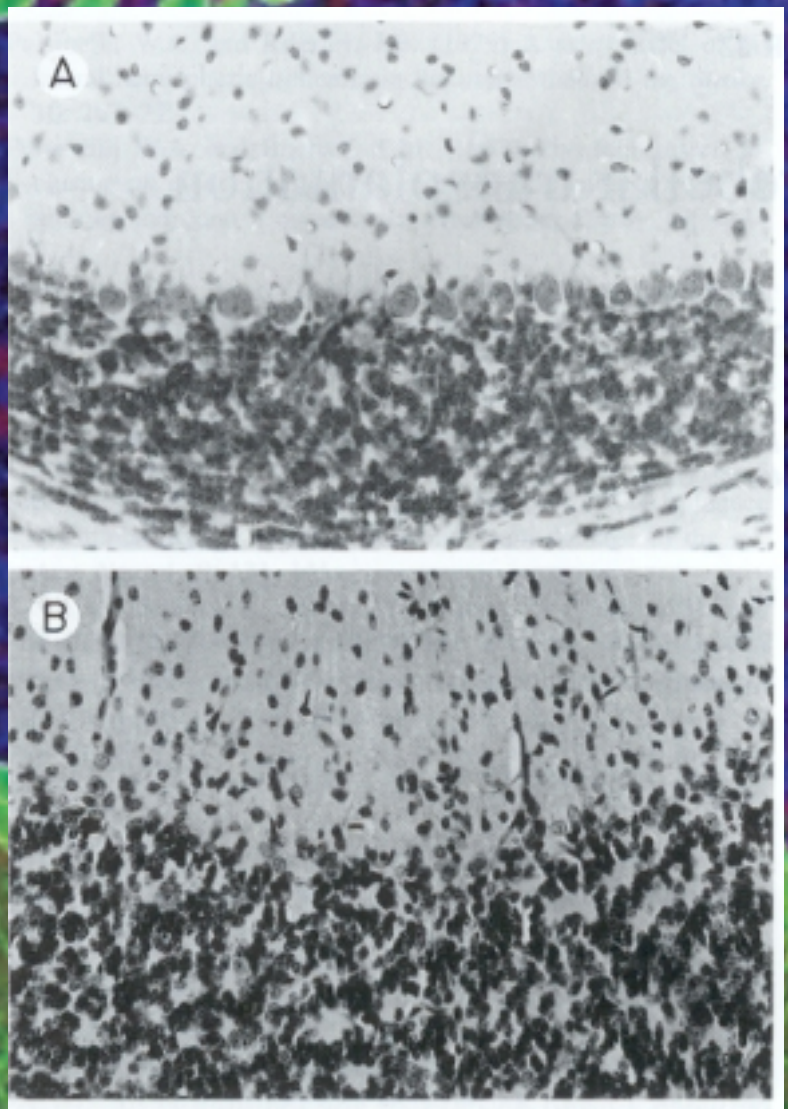
Fetal tissue grafts for cerebellar atrophy in humans

Wu CY. Chinese Medical Journal 1991; 104:198-203

- 6 patients, ages 12-60 years, ataxia on average 6.5 years
- Results: 3 “moderately” better, 2 “markedly” better.
- CT brain scans – no difference after surgery
- Problems with this study:
  - Exact diagnosis of cause of ataxia unclear
  - Little data about symptoms
  - Unblinded assessment
  - No evidence about survival of grafts

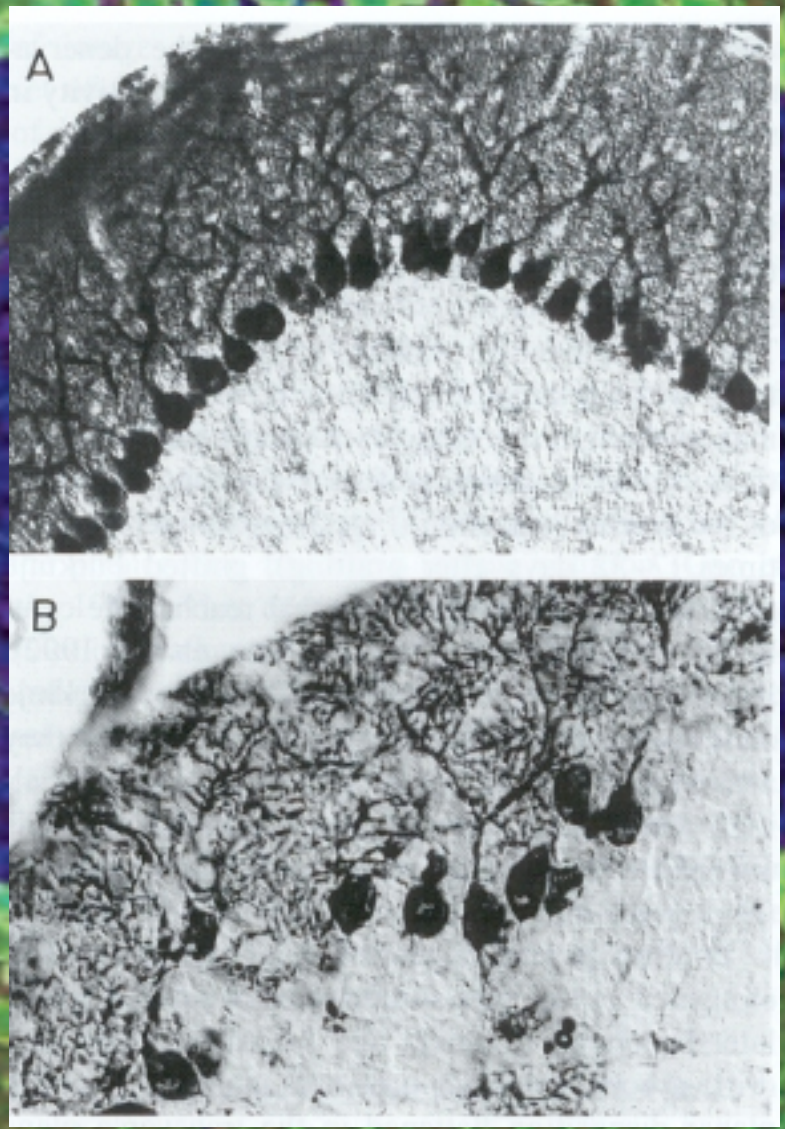
Fetal cell grafts in *pcd* mouse model

Triarhou LC, Cell Transplantation 1996; 5: 269-277.

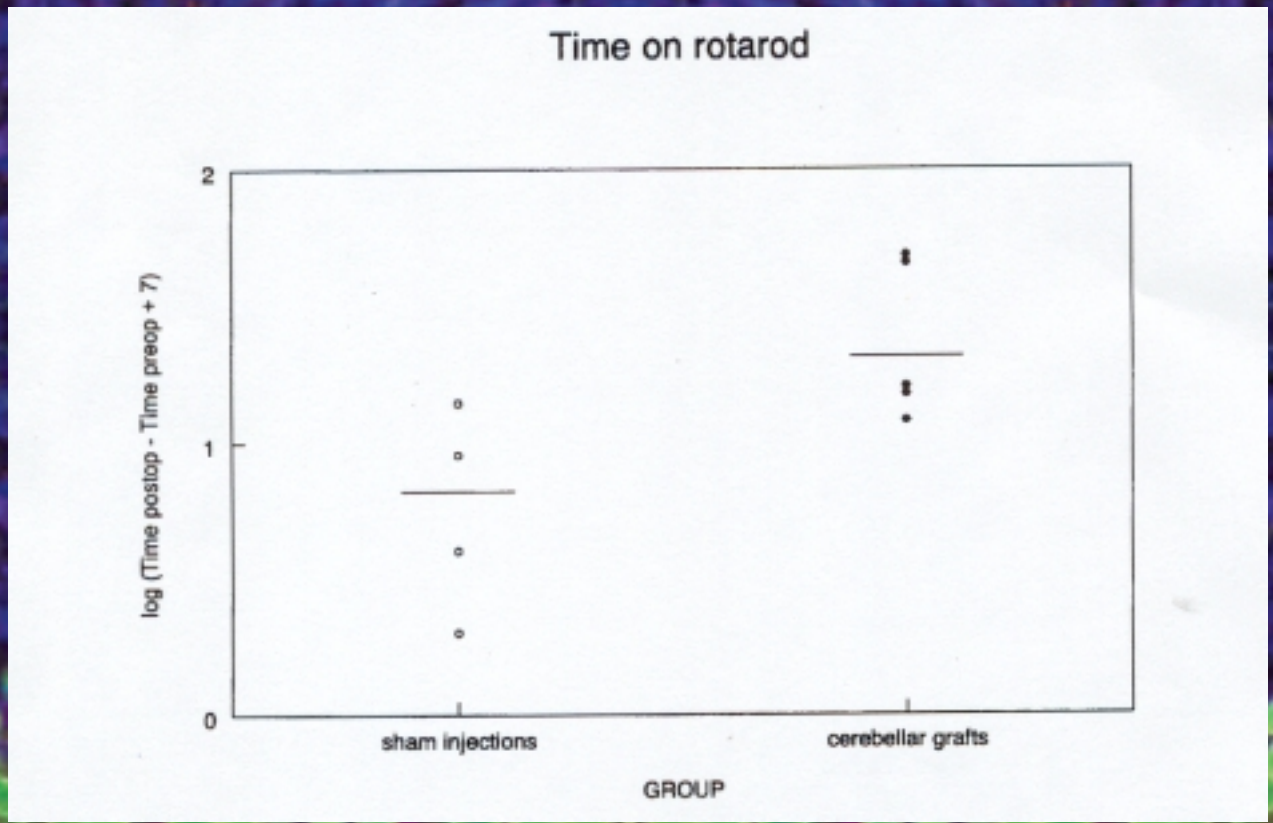


- Model: *pcd* mice become ataxic at about 3-4 weeks age. Purkinje cells die.
- 6 mice had grafts, 6 had sham surgery
- Outcomes: balance tests, mobility, brain exam

Results: 6/6 grafts survived



Results: transplanted mice had better motor function



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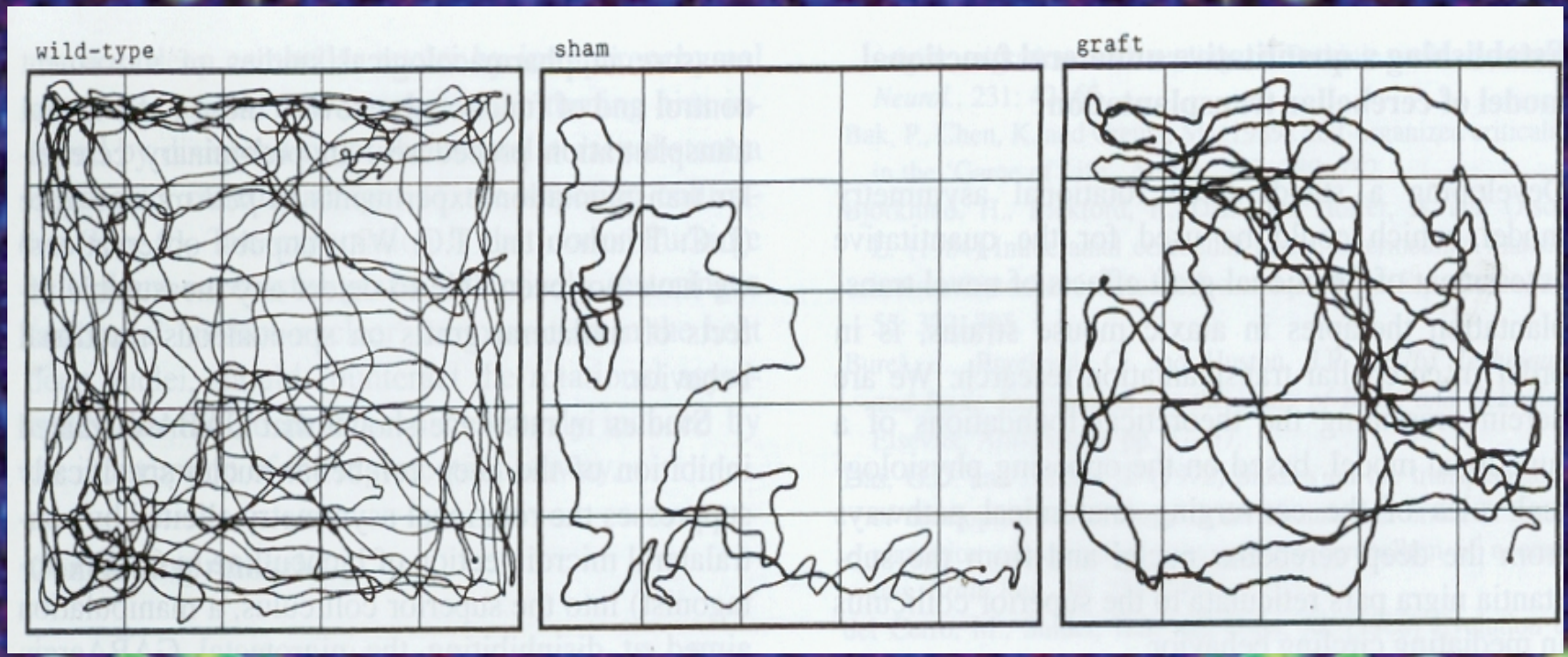


Purkinje cell transplants in *Shaker* rats

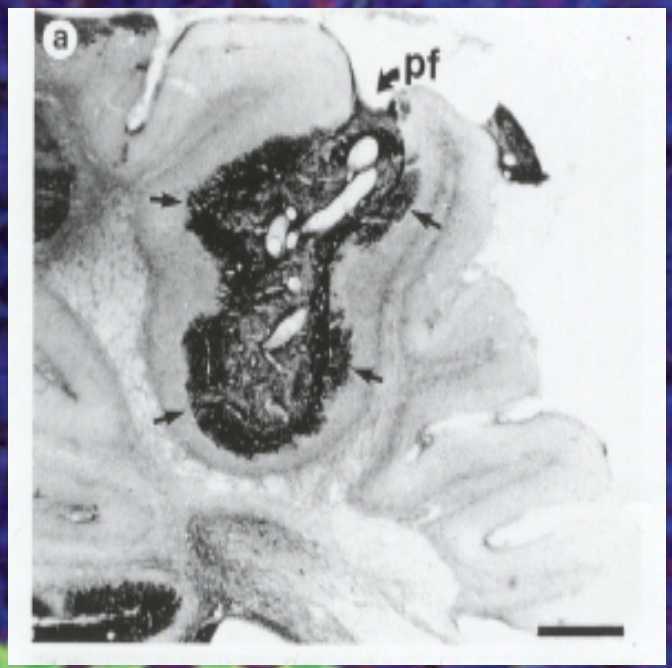
Tolbert DL Experimental Neurology 1998; 153: 255-267

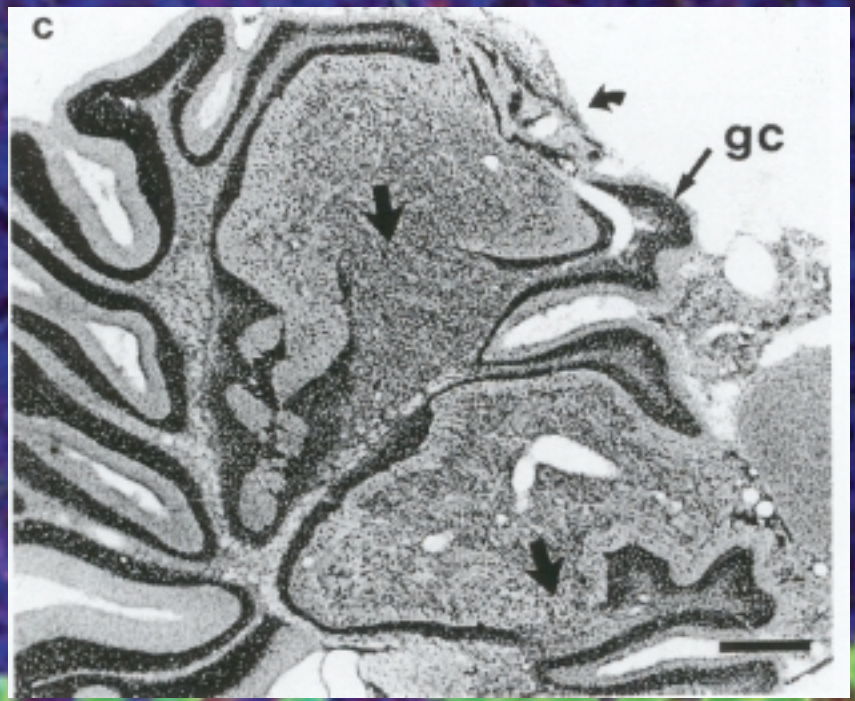
- Shaker rats have adult-onset ataxia with Purkinje cell loss
- 6 rats were used; no control group
- Outcome: brain exam

Results

- Donor Purkinje cells survived, but most ended up outside the cerebellum
- A few donor cells did migrate into the right place, but they weren't able to connect with other cells.

Results





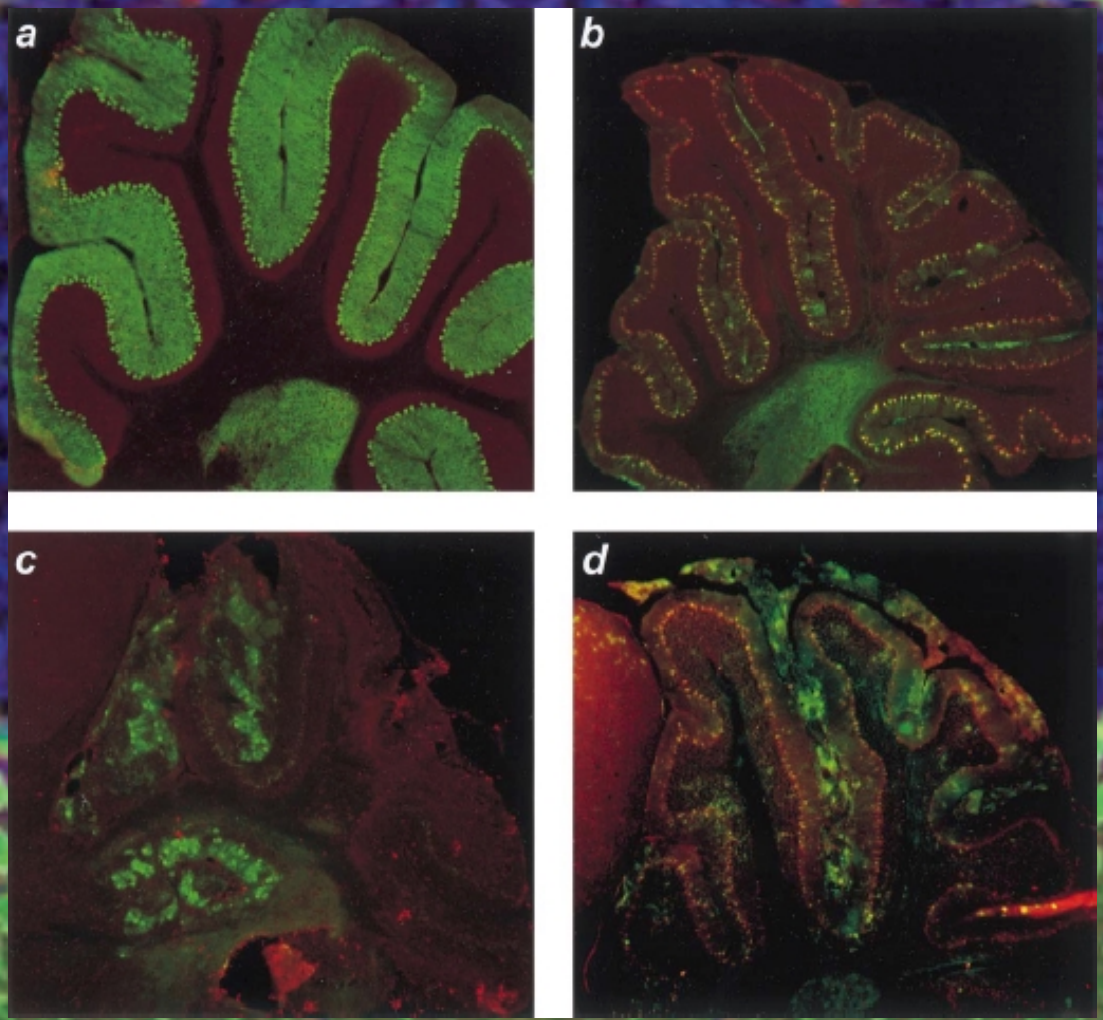
Fetal cerebellar transplantation in SCA-1 mouse model

Kaemmerer WF Exper Neurol 1999; 158:301-311

- Transgenic mouse model with human SCA-1 gene
- Ataxic mice were given fetal mouse cerebellar implants or sham surgery (control group).
- Outcomes: tests of balance, gait width and movement, brain exam for graft survival

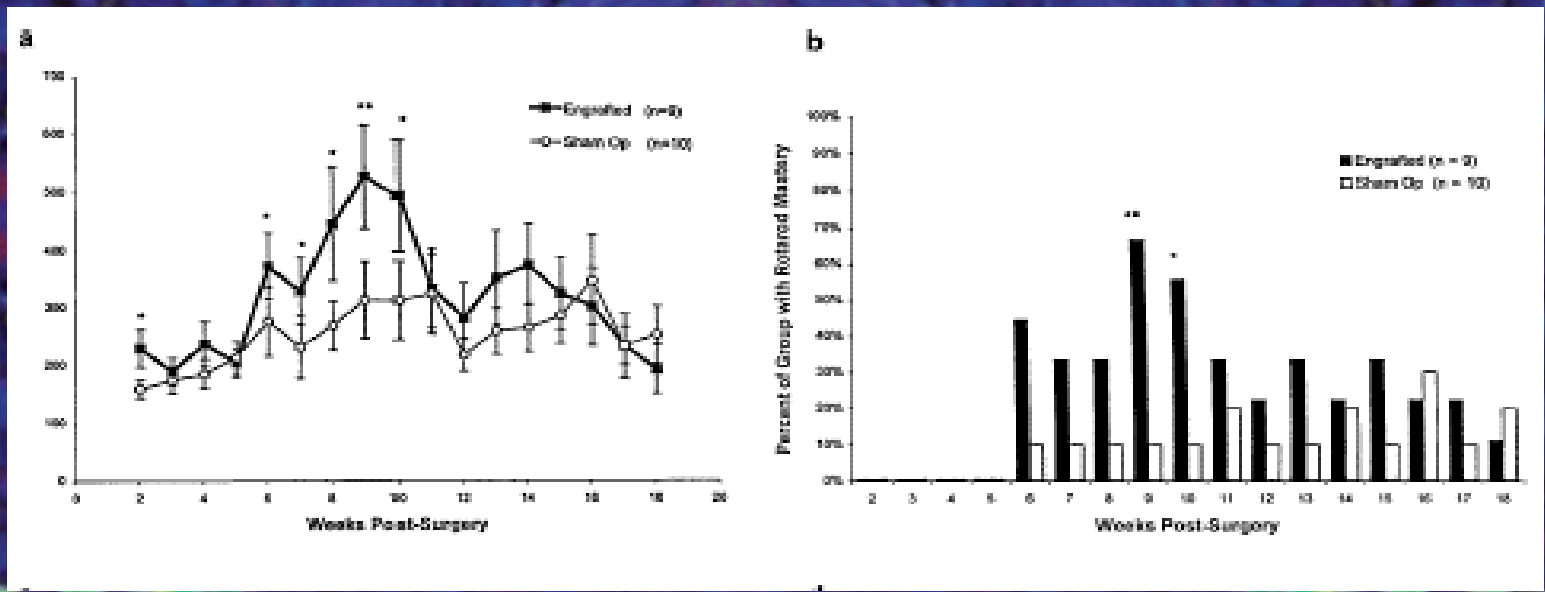
Results: grafts survived in 9/12 mice

Kaemmerer WF Exper Neurol 1999; 158:301-311

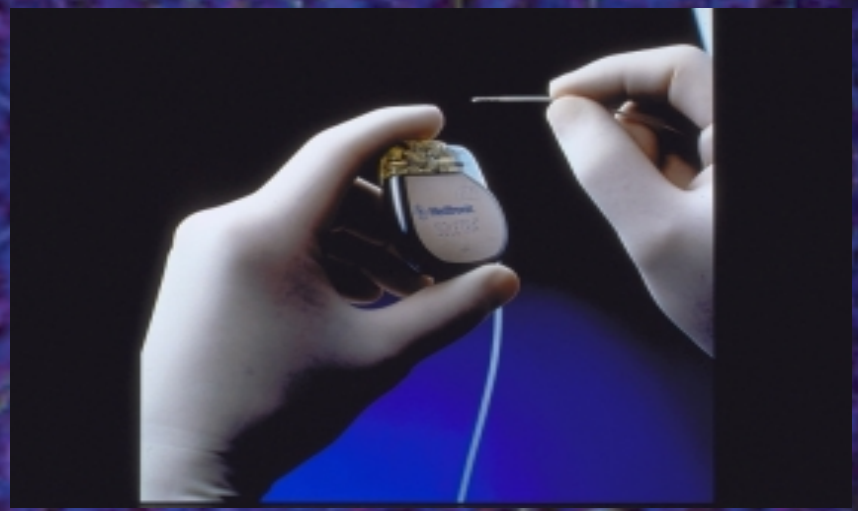


Results: Mice with grafts had improved balance, narrower gait, improved mobility for several weeks

Kaemmerer WF Exper Neurol 1999; 158:301-311



Deep Brain Stimulation for Ataxia



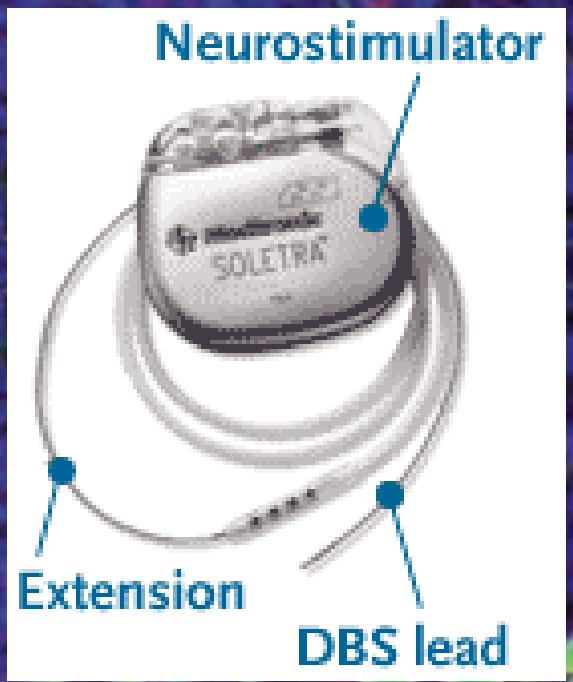
Historical roots of DBS

- *Observation that tremor stopped during electrical stimulation of certain brain regions in 1950s-1960s*
- *Various early DBS systems tried in 1970s-1980s with little success*
- *Failure of medicines to help PD, advances in knowledge and techniques led to return to neurosurgical treatment in early 1990s*
- *Clinical trials early 1990's*

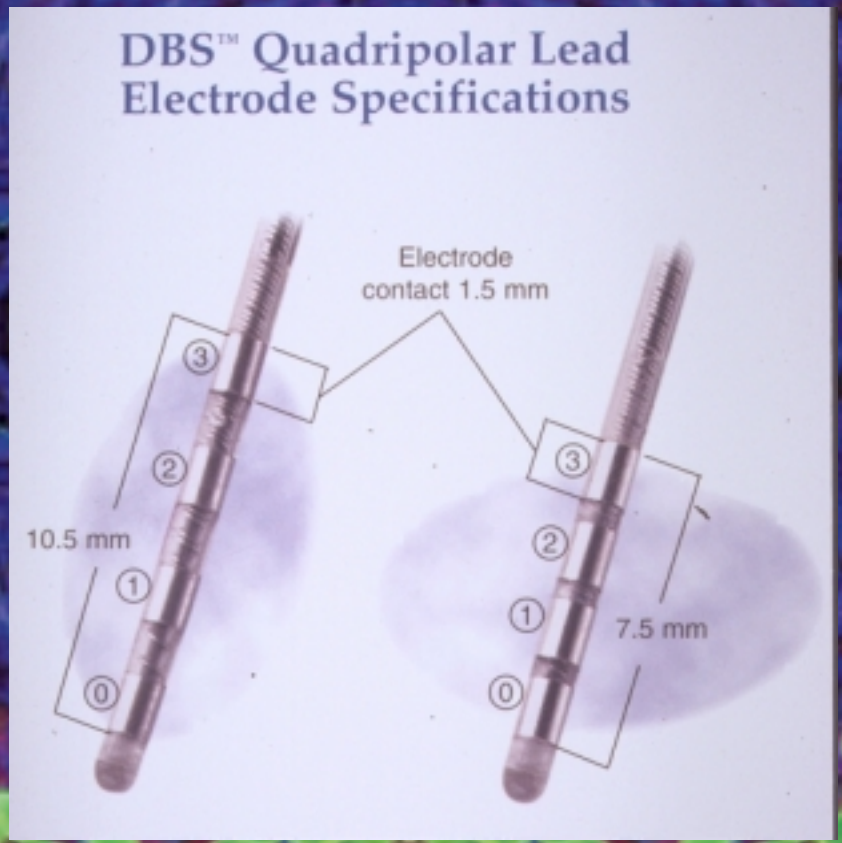
Current era of DBS

- *FDA approval of Medtronic DBS system 1997 for thalamic DBS for PD and Essential tremor (ET)*
- *DBS of other brain targets for PD approved 2002*
- *DBS for dystonia approved 2003*
- *Other indications: MS-related tremor, pain*

DBS system



DBS electrode



Screening for DBS candidates

- Neurological examination
- PD, ET or Dystonia rating scale (videotaped examination)
- MRI of brain
- Neuropsychological testing

A word about essential tremor…

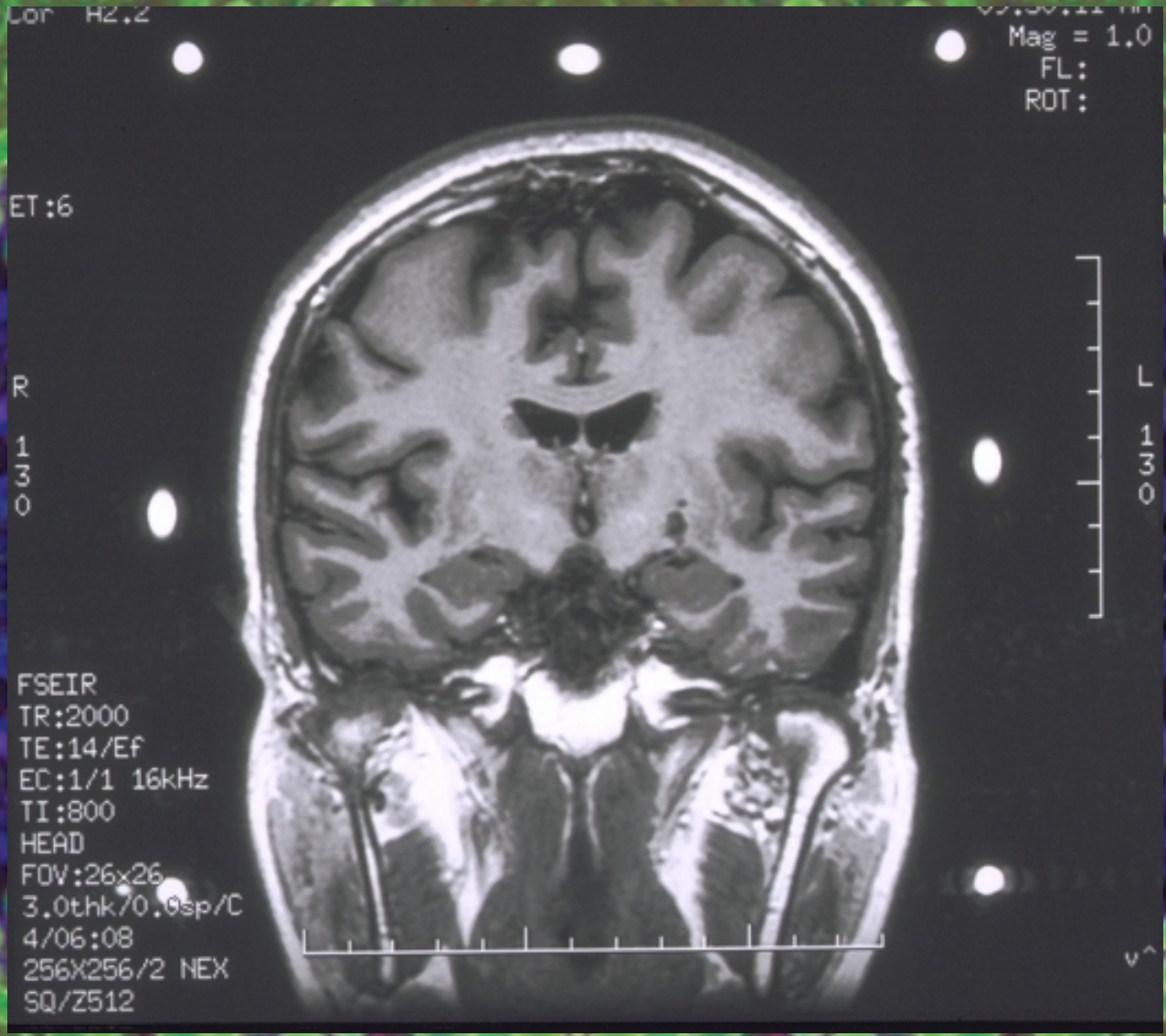
- Symptoms: tremor of the hands/arms while doing activities
  - Can also affect voice, head, trunk, legs
- Cause not known; no known brain changes
- Recent research shows that people with ET have subtle signs of ataxia (cognitive changes, gait problems)

Inclusion criteria for DBS

- Symptoms of PD, ET, dystonia which significantly interfere with daily life and cannot be controlled with best medical therapy
- Good general health
- No dementia

On the day of surgery….

- Head frame is attached to skull
- MRI of brain with head frame for targeting
- In OR, small opening made in skull with drill
- “Brain mapping” procedure to locate and confirm target using microelectrodes
- DBS lead inserted and tested
- Lead extension and IPG implanted under general anaesthesia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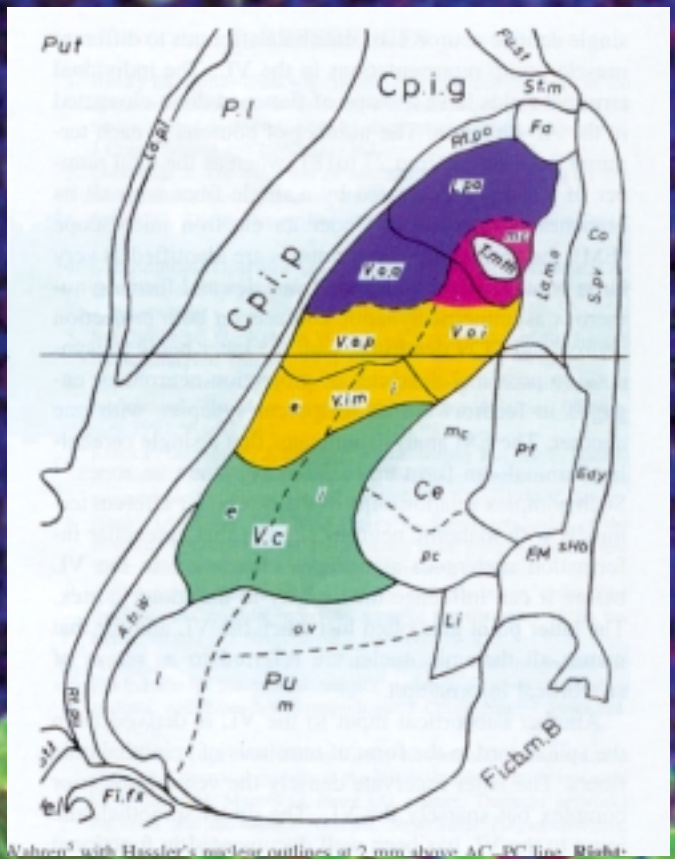
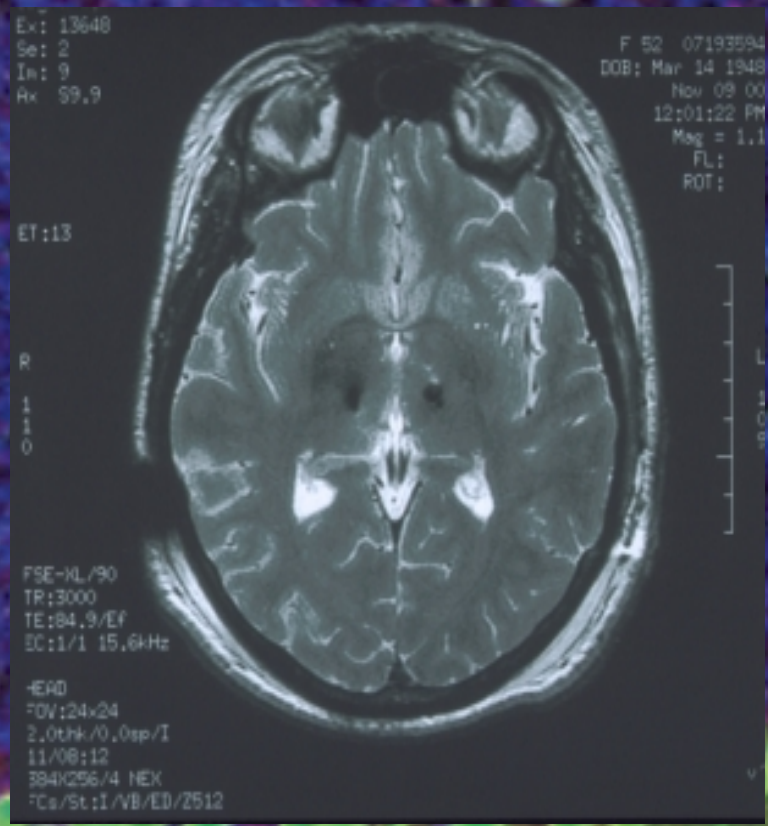
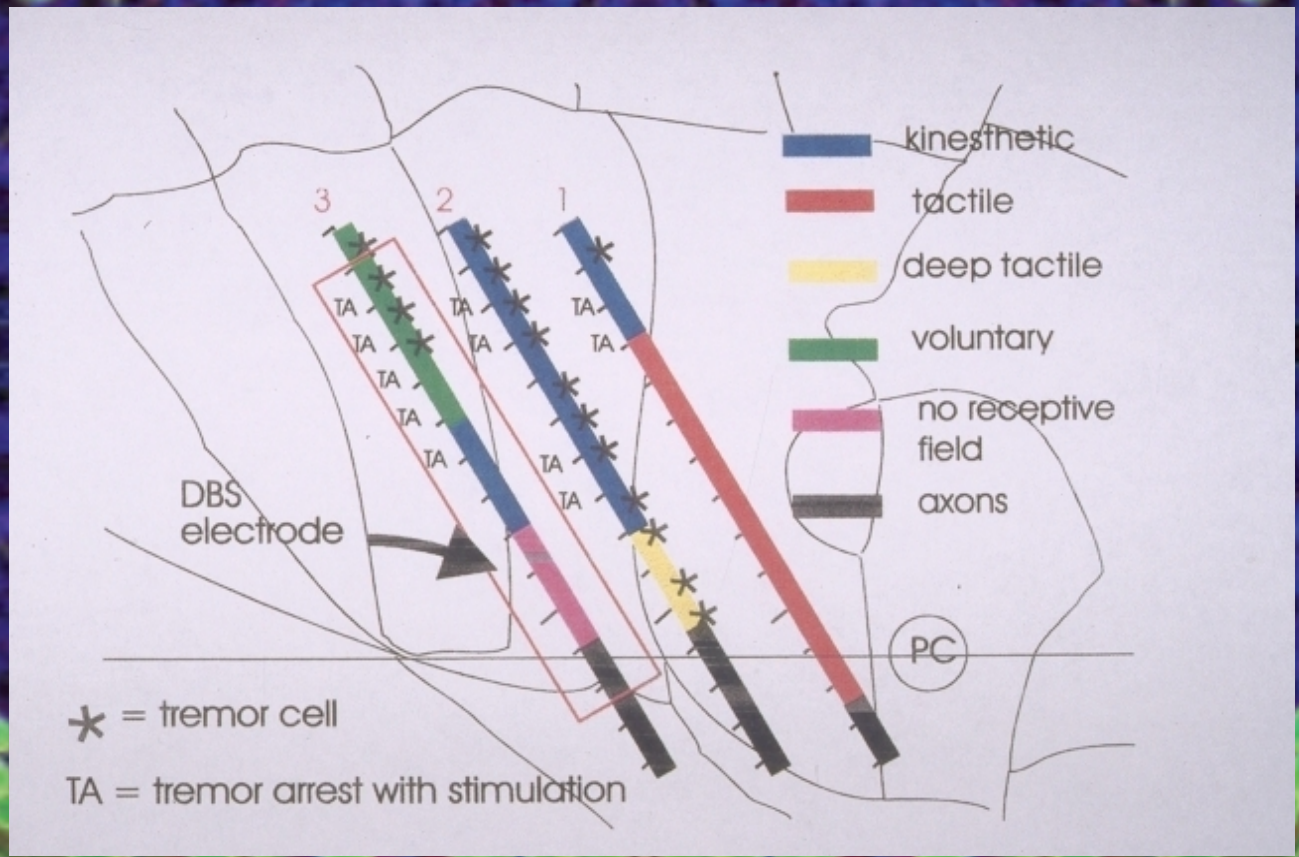
Thalamic targeting





Vim mapping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DBS electrode
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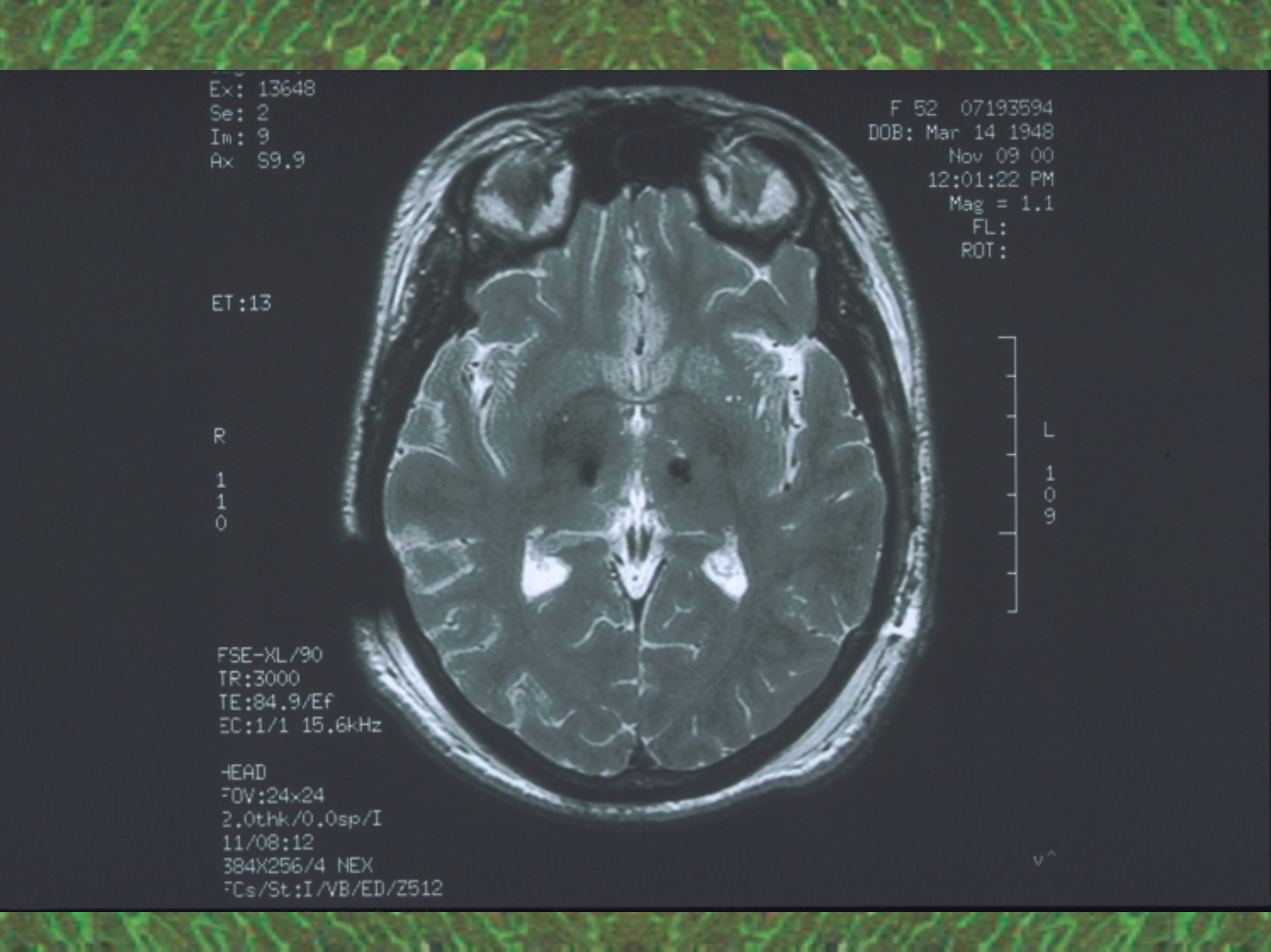
axons
PC
* = tremor cell
TA = tremor arrest with stimulation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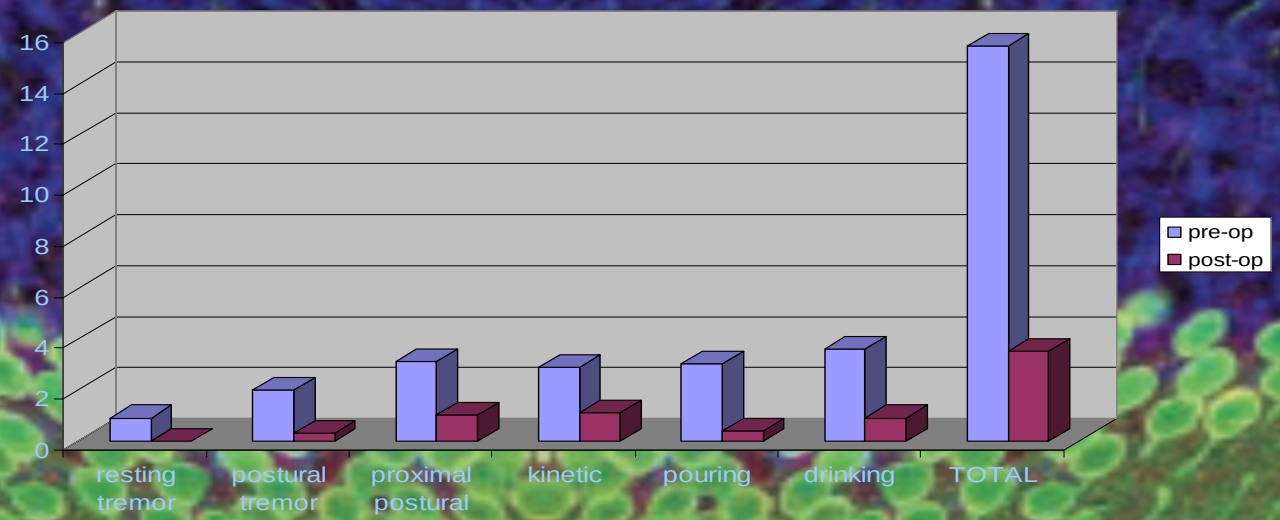
Results for essential tremor

- 80-100% improvement in arm tremor
- Helps hand tremor more than shoulder tremor
- Improvement in handwriting, drinking, eating, fine movements



Essential Tremor Pre- and Postoperative Writing Samples

Patient ET-0004

BEFORE

PATIENT ET-0006

BEFORE

Patient ET-0013

BEFORE

PATIENT ET-0018

BEFORE

Patient ET-0021

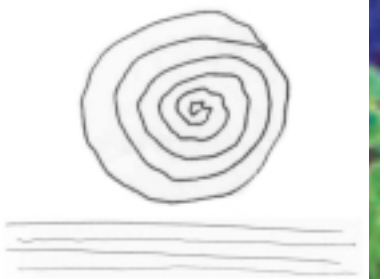
BEFORE

Patient ET-0004

AFTER

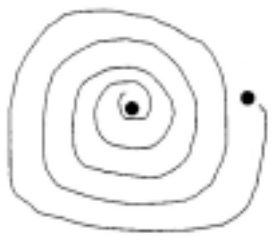
PATIENT ET-0006

AFTER



Patient ET-0013

AFTER



PATIENT ET-0018

AFTER

Patient ET-0021

AFTER

Complications of DBS

- Stroke <2%
- Seizure 3-5%
- Infection 5-10%
- Surgical/anesthesia complications: < 5% but may be life-threatening
- Cognitive decline 1-2%
- Bilateral DBS: worsening of speech
- Tremor rebound ?5-10%

Future directions

- Deep brain stimulation for tremor of upper limbs in ataxia?
- Further development of stem cell technology
  - More basic science research
  - Use stem cells to produce protective factors in the brain

Thank you

- National Ataxia Foundation
- UC Davis GHPP clinic
  - Terry Tempkin, nurse practioner
  - Rick Henry, Social worker
  - Rosy Chow, Physical therapist
  - Ron Risley, Psychiatrist
  - Barbara Briscoe, Genetics counselor
  - Donna Hopkins, Coordinator

Thanks, Keith!