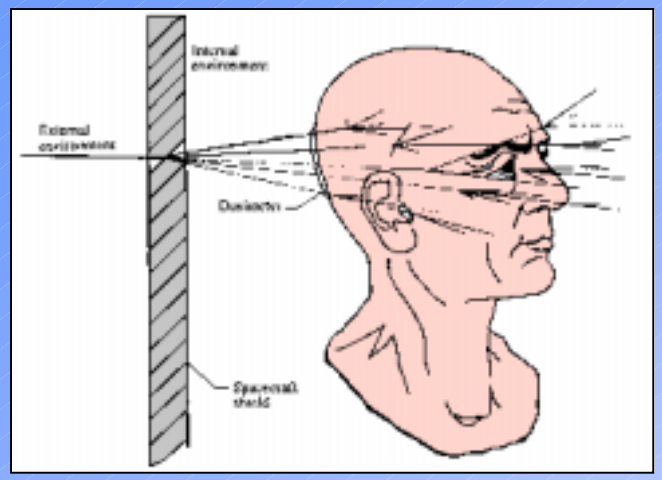
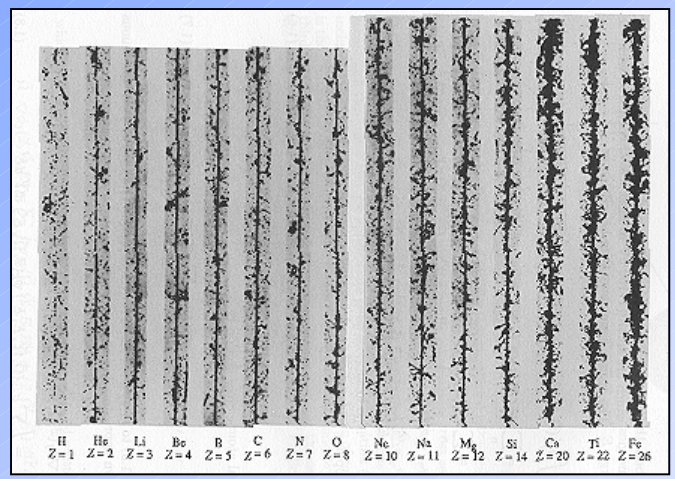
THE NEUROBEHAVIORAL AND NEURO-CHEMICAL CONSEQUENCES OF 1 GEV/n Fe PARTICLE EXPOSURE

ME Vazquez
SJ Gatley
MA Cosenza
BE Pyatt

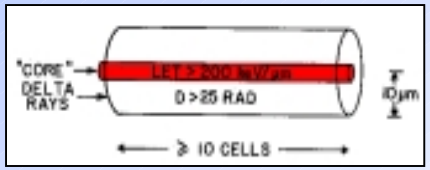
Medical Department
Brookhaven National Laboratory
Upton, NY 11973

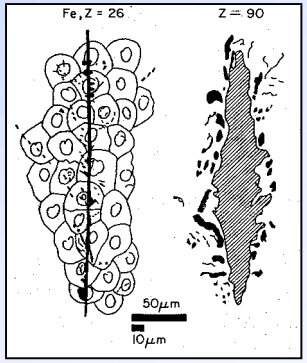
Effects of Galactic Cosmic Rays on the CNS

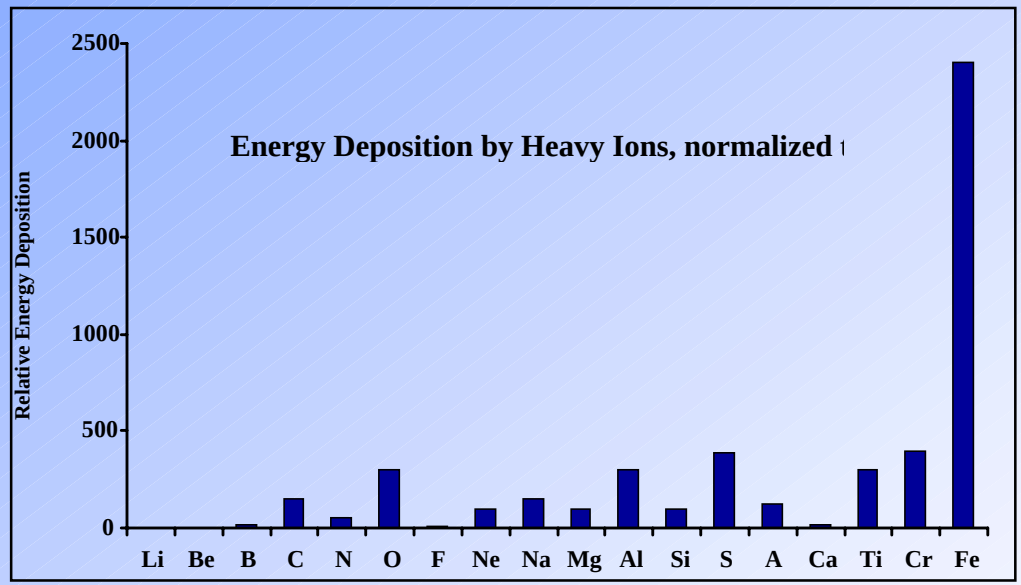


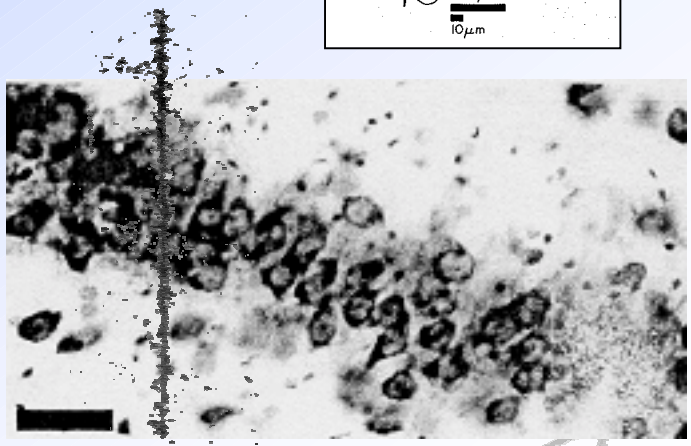


Microlesion Concept









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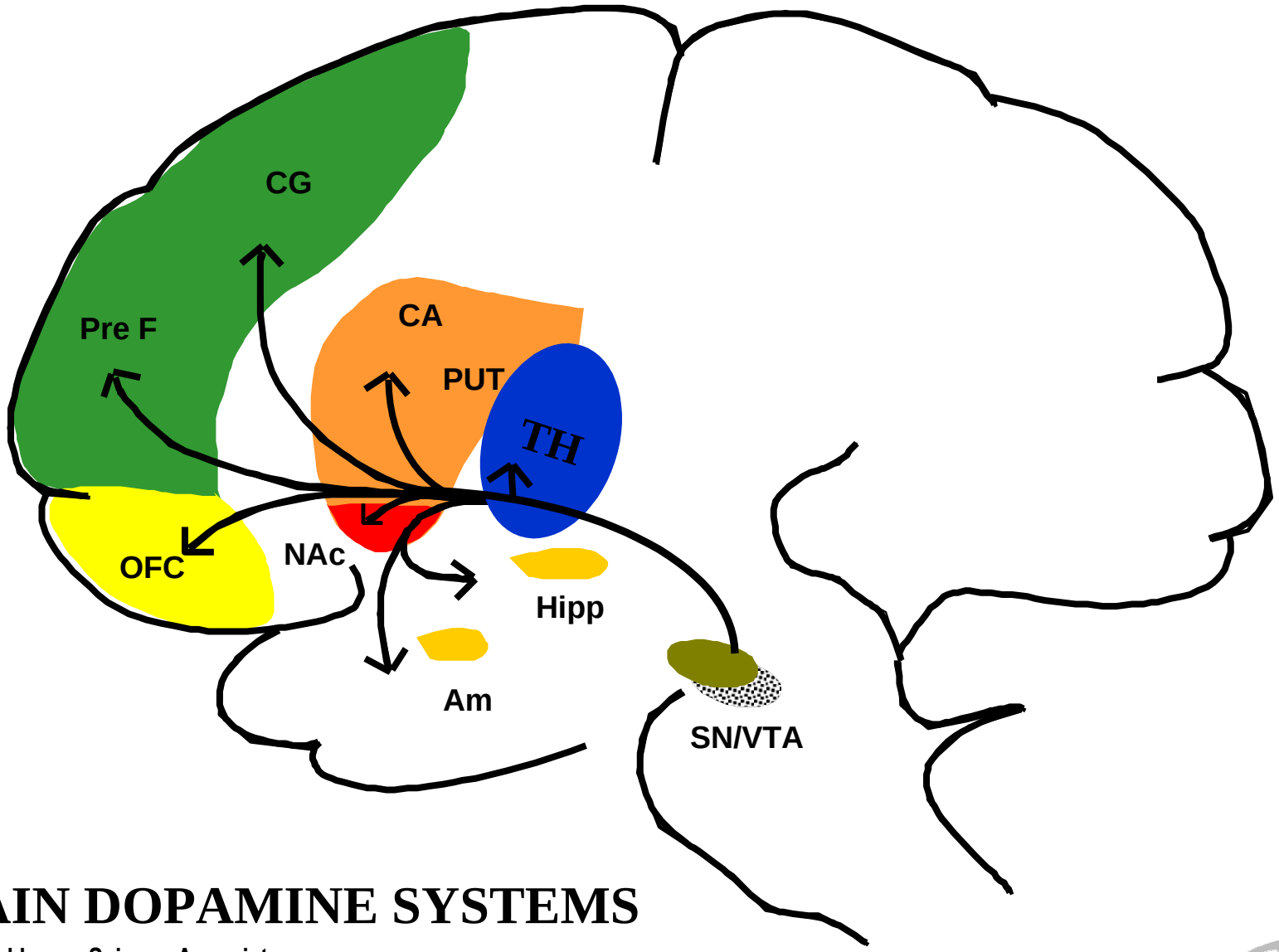

BRAIN DOPAMINE SYSTEMS

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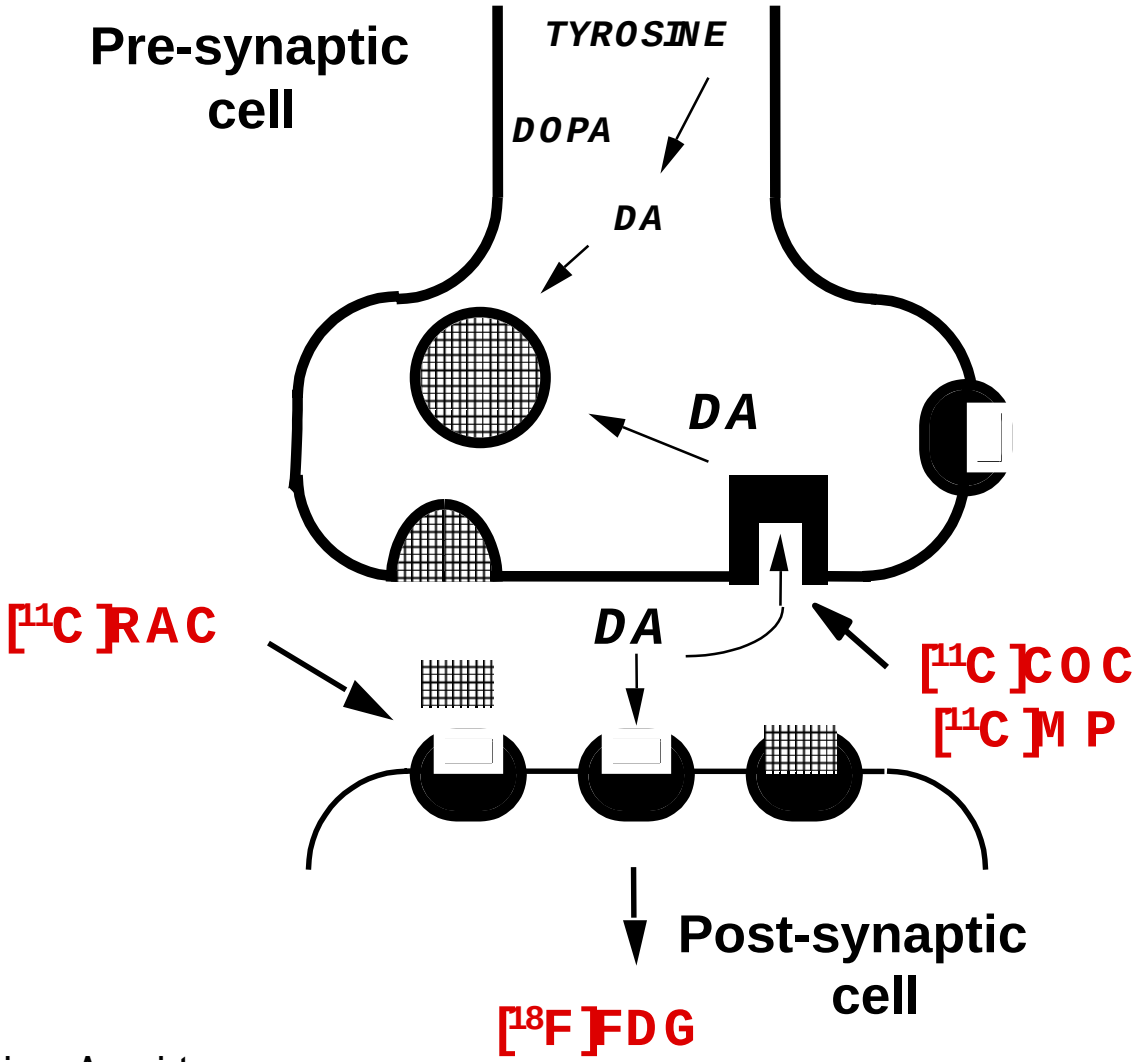

Pre-synaptic cell
TYROSINE
DOPA
DA
DA
DA
[11C]RAC
[11C]COC
[11C]MP
Post-synaptic cell
[18F]FDG

CNS Experiments at BNL

Early 1997, dopamine neuroreceptor assays in frozen rat brain supplied by Dr Alice Lindgren.

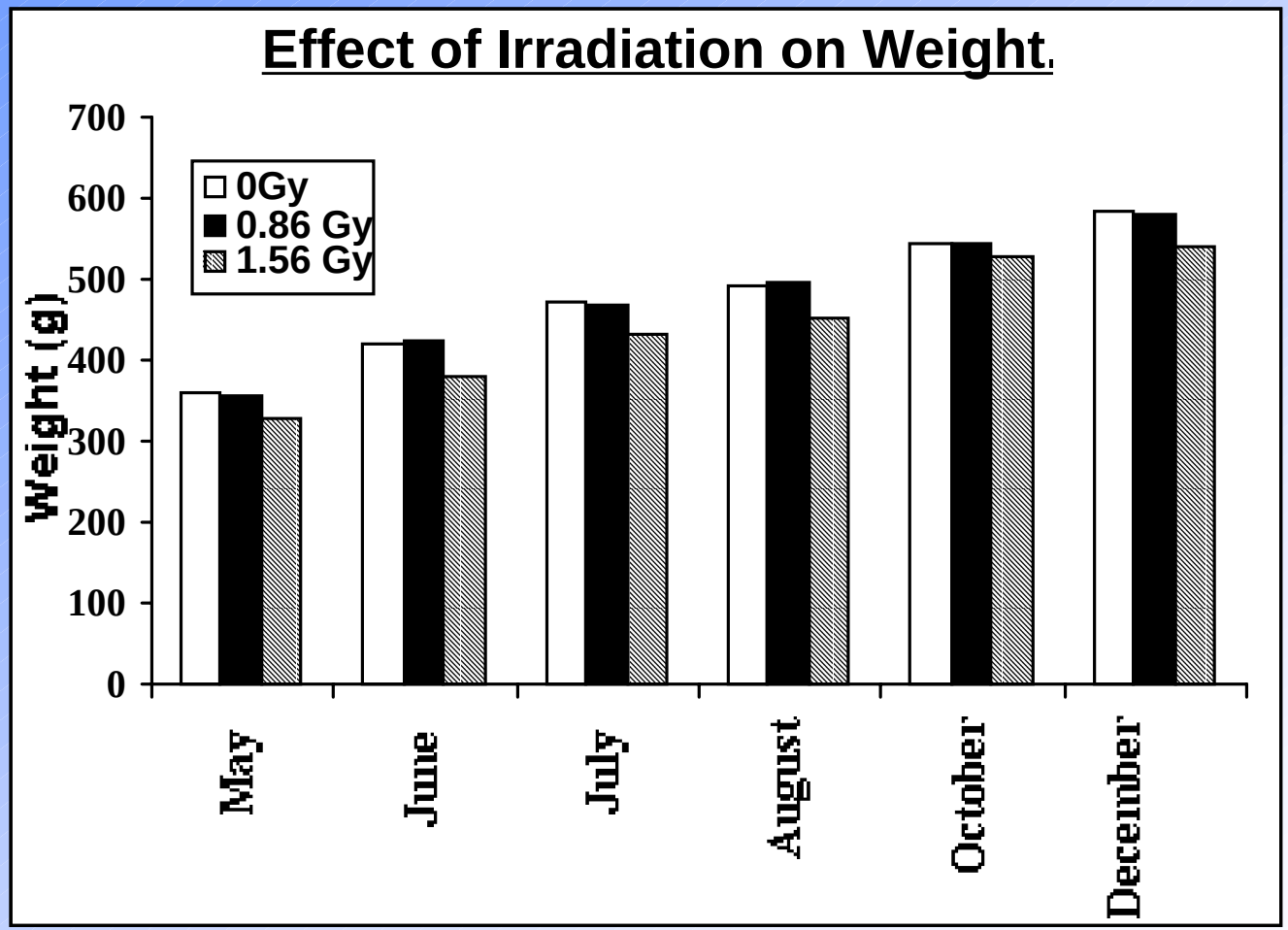
Late 1998, early 1999 behavioral tests in rats irradiated by Drs Bernie Rabin and Jim Joseph. These animals were sacrificed after 8 months and part of the striatum used immediately to conduct dopamine uptake assays. The remainder of each brain is in storage at -70 degrees awaiting neuroreceptor assays.

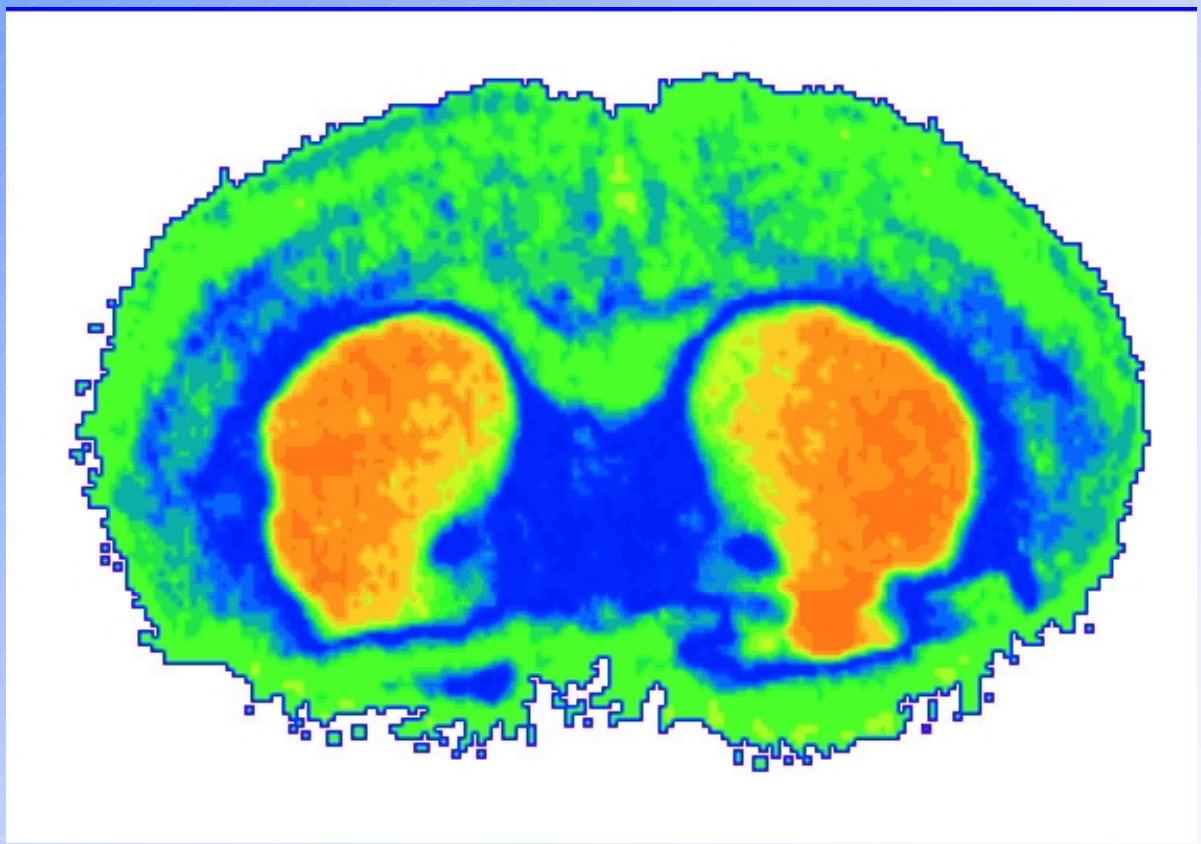
Hypothesis

The nigrostriatal system, which progressively loses capacity during normal aging and which is severely damaged in parkinsonism, will be adversely affected by HZE radiation.

This will result in attenuation of the locomotor activity response to cocaine in rats exposed to 1 GeV/n ^{56}Fe particles.

CAUTION

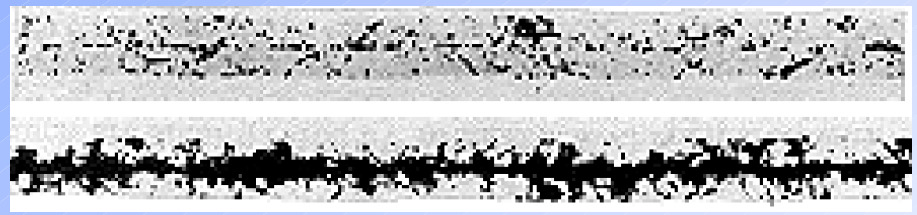

Effect of Irradiation on Weight.
0Gy
0.86 Gy
1.56 Gy
Weight (g)
700
600
500
400
300
200
100
0
May
June
July
August
October
December



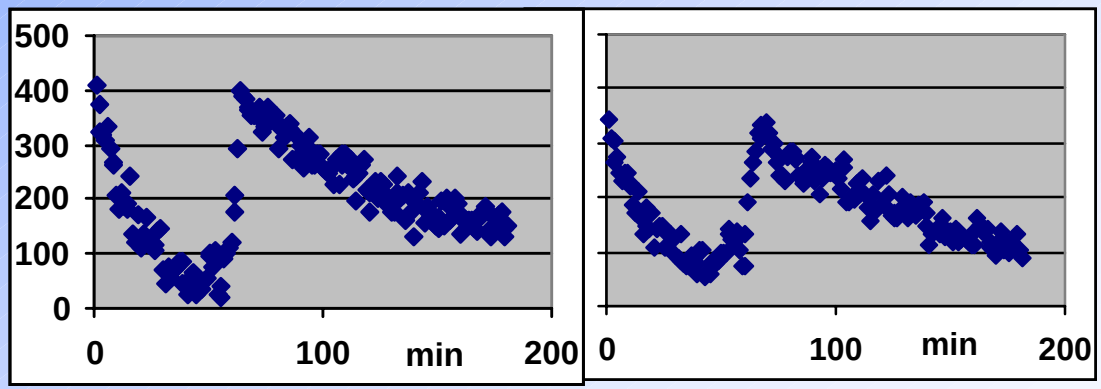
Is 1 GeV Fe-56 neurotoxic?

Ionization tracks of proton and Fe-56

~20 μm



Rats (8 per group) injected with cocaine 2 mo after irradiation at 156 cGy showed an attenuated increase in locomotor activity that disappeared at >3 mo.



Rats sacrificed 4 mo after irradiation at 100cGy showed only a trend towards decreased striatal D1 receptors

Binding site	0 cGy	100 cGy
D1 Receptor	46 ± 14 (8)	34 ± 3.9 (6)
D2 Receptor	50 ±19 (8)	50 ±16 (6)
Transporter	480 ± 150 (6)	430 ± 260 (6)

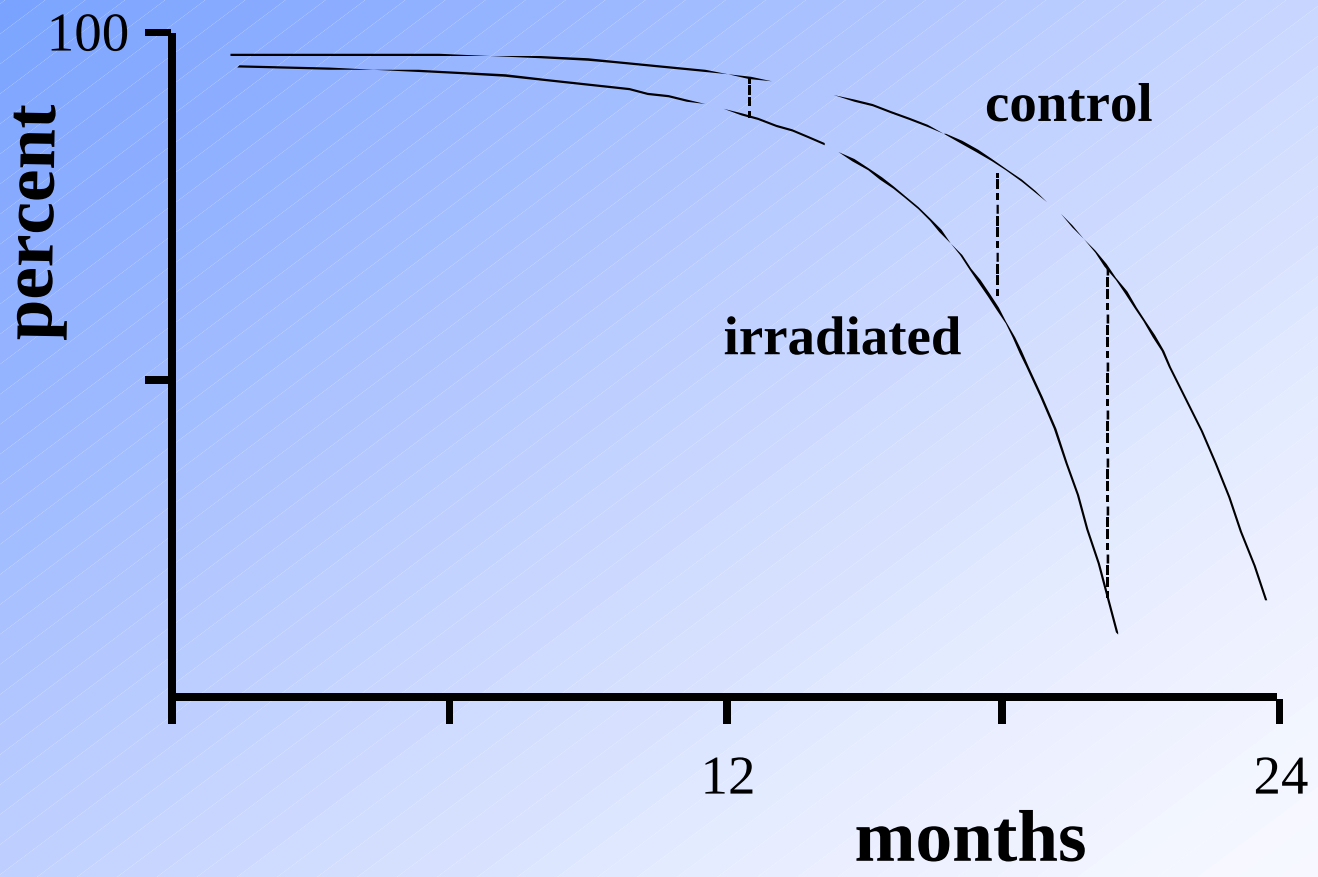
Tumor Induction.

Dose	Tumors
Controls	1/12
0.86 Gy	6/15
1.56 Gy	1/9

What have we learned so far?

Rats exposed to 1 GeV ^{56}Fe particles at doses of around 100 cGy, corresponding to about 4 hits/cell, do not exhibit large changes in locomotor activity or dopamine neuroreceptor density measured several months after irradiation.

Hypothesized functional loss after irradiation.



Good Behavioral Study

specific
systematic
methods well described
results statistically robust (adequate “n”)
results dose (fluence)-dependent
reproducible
backed by neurochemistry/histology

The idea that HZE radiation at relevant doses is associated with <u>persistent</u> neurological deficits is not well supported.

-mouse suspension work (1985): suspect

-oxotremorine-dependent K+-evoked DA release in striatal slices: dose-response relationship not observed

-CTA studies of Rabin: only short-term effects

-dramatic loss of DA cells in the rat substantia nigra: anecdotal

Thus insufficient data exist to conclude that dopaminergic systems are particularly targeted by HZE radiation.

The Problem Demands

large numbers of subjects to achieve adequate statistical power
***(because animal behavior is intrinsically variable*)**

long experimental times
(because evolution of neurological damage is likely to take a significant fraction of animals' life spans)

ergo: adequate funding

Equipment and Instruments
Imaging

Cyclotrons (2)
- RFQ accelerator
- PET Scanners (2)
- SPECT Scanner
- 4 Tesla MRI
- MicroPET (2000)