Developmental Pesticide Exposure Models of Parkinson's Disease

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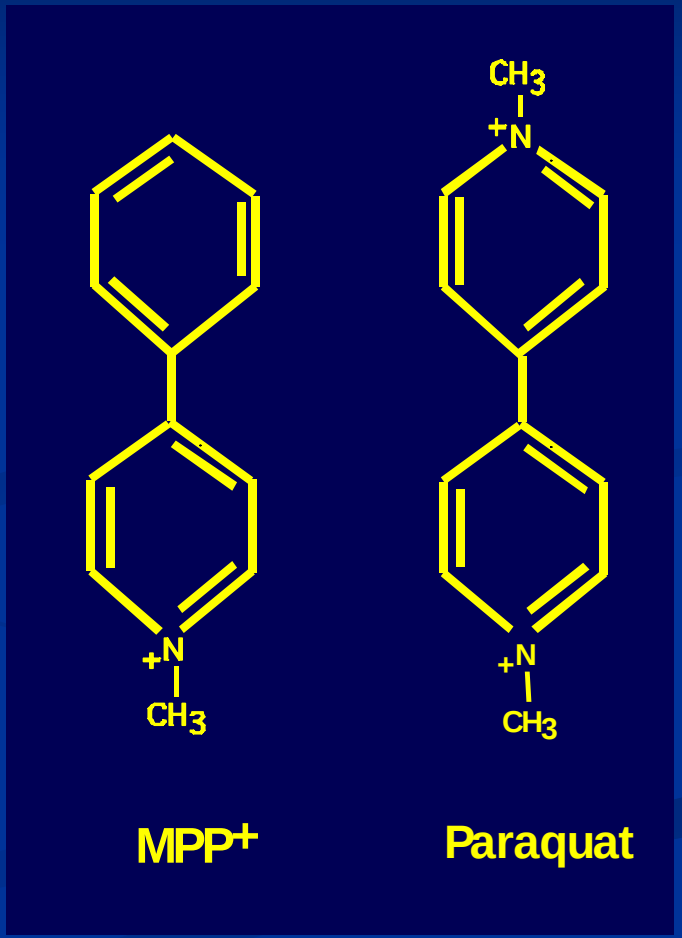
PARAQUAT

- Used as a herbicide and dessicant
- Impeded by blood brain barrier but gets into brain
- Age-related uptake
- Higher levels at 24 hours as compared to 0.5 hours
- Accumulates in melanin containing neurons
- Oxidative stressor - inhibits mitochondrial function

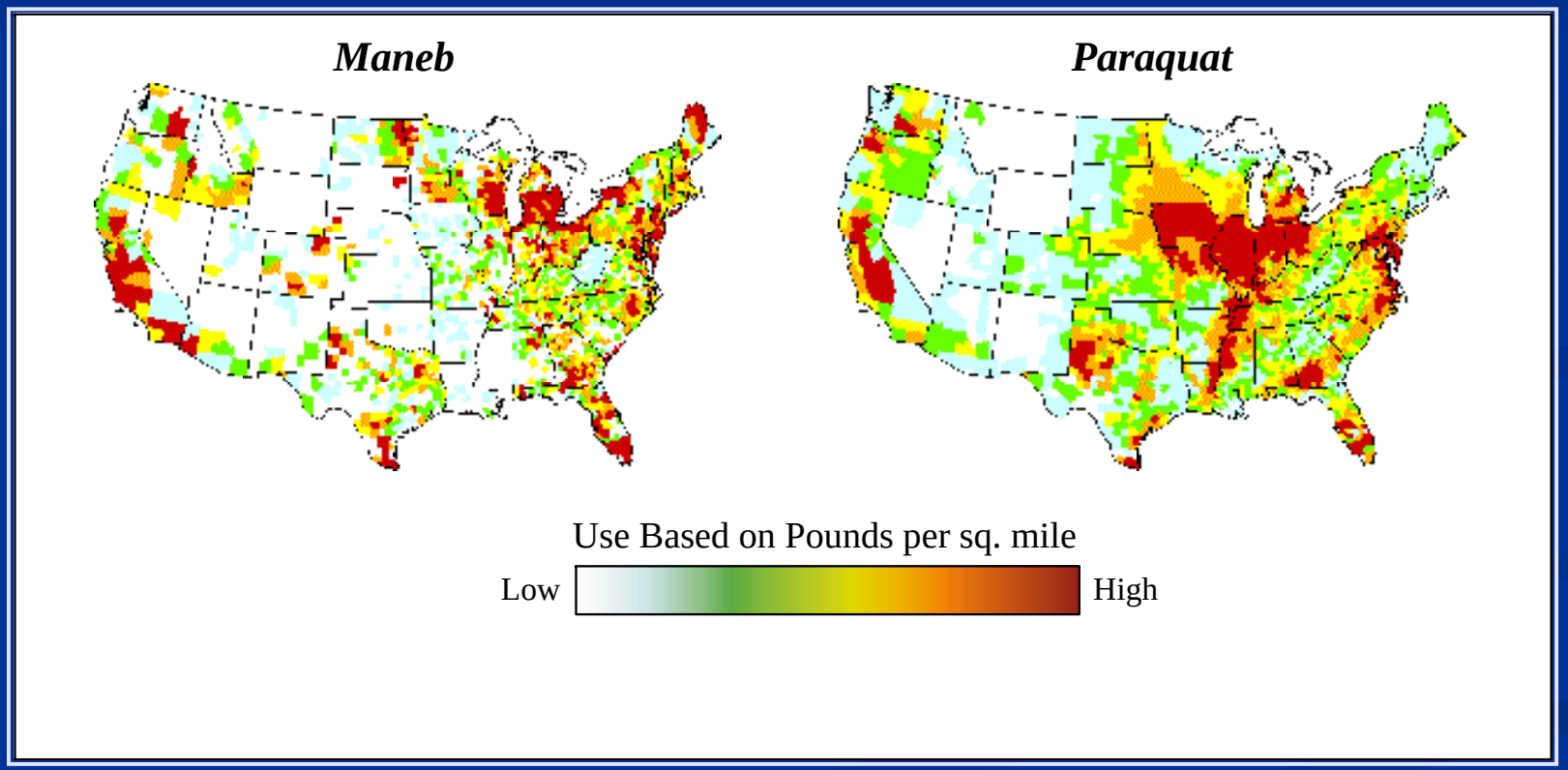


Manganese Ethylenebisdithiocarbamate - MANEB

- Commonly used fungicide
- Dose dependent decrease in locomotor activity
- Potentiates the effecfs of MPTP
- Increases uptake/decreases clearance of PQ
- Incidences of PD in humans following occupational exposure

Maneb

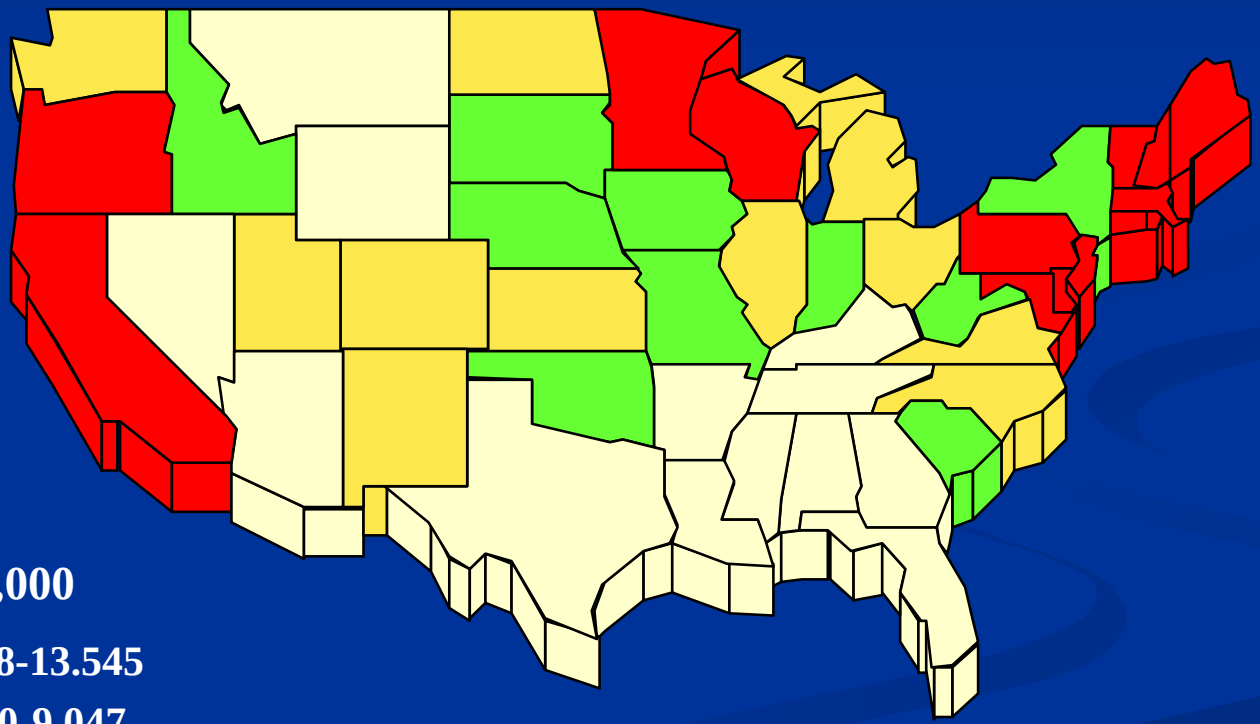
Overlapping Geographical Use of Agrichemicals



USGS Pesticide National Synthesis Project

Mortality Rate Due to Parkinson's Disease

- Age-adjusted mortality rate due to PD



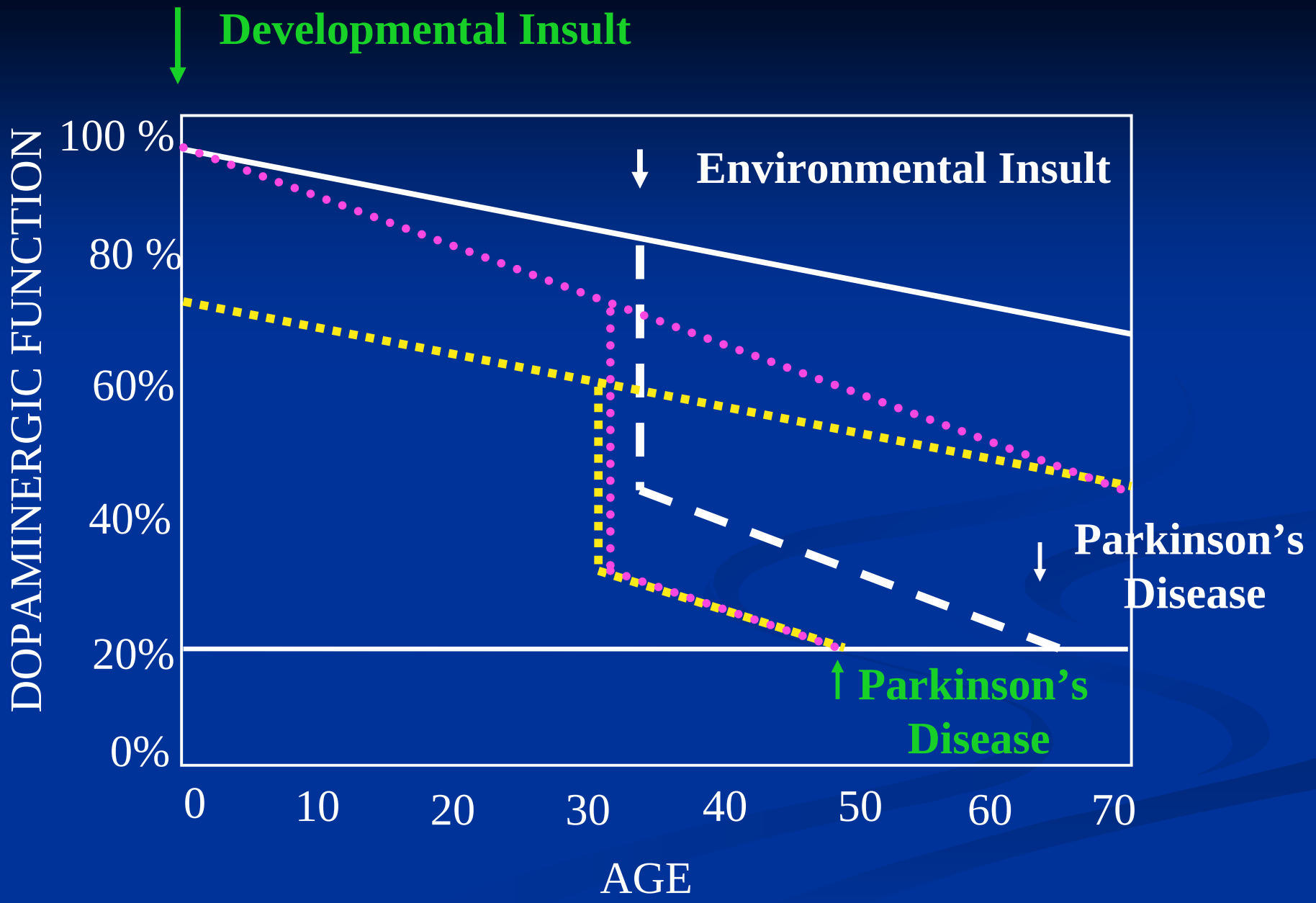
Rate per 100,000

- **9.048-13.545**
- **8.100-9.047**
- **7.355-8.099**
- **5.074-7.354**

Based on 1988 data from Lanska et al.

Combined Exposure to PQ and MB

- Produces potentiated effects
- Selective effects on the nigrostriatal system
- Changes are irreversible and progressive
- Produces age-related effects
- Effects are enhanced due to a genetic susceptibility
  - α-synuclein
- Developmental exposure produces permanent changes to the dopaminergic system
- Developmental exposure increases adult susceptibility to subsequent adult exposures
- Effects are gender-related

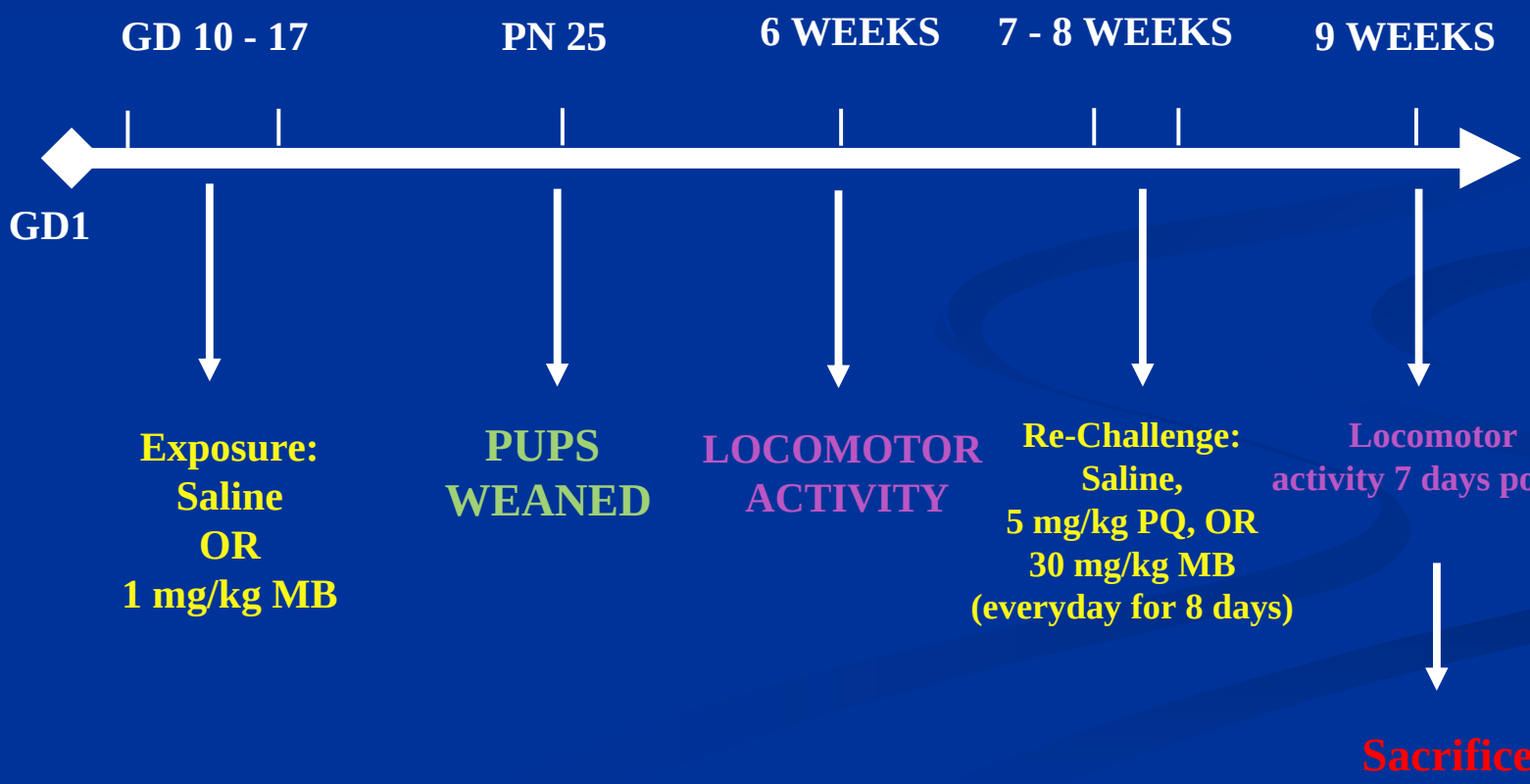

Developmental Insult
DOPAMINERGIC FUNCTION
100 %
80 %
60%
40%
20%
0%
Environmental Insult
Parkinson's Disease
Parkinson's Disease
0
10
20
30
40
50
60
70
AGE

Prenatal Maneb Exposure *-*

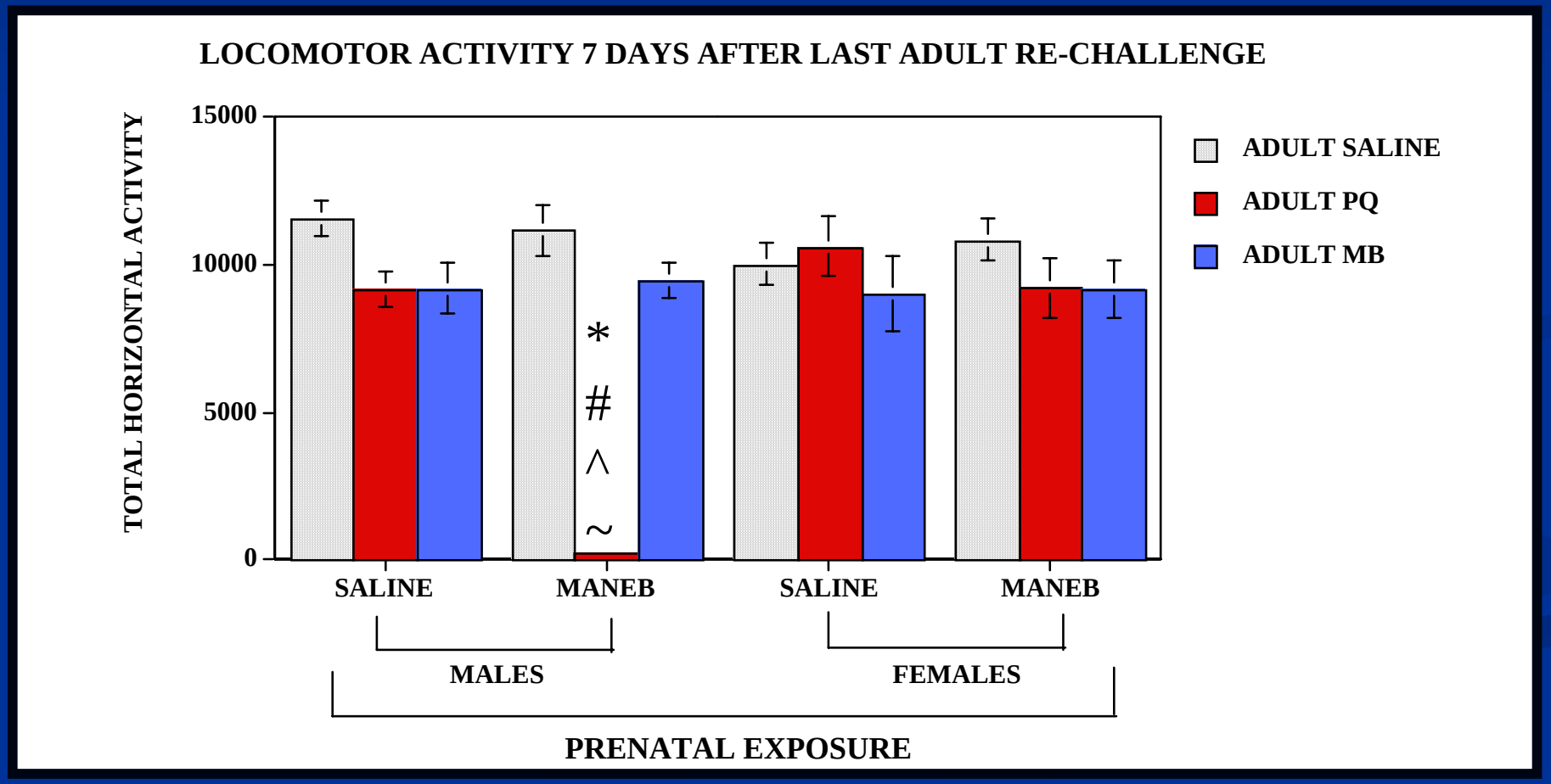
Do Paraquat and Maneb Need to Be Administered Concurrently: Experimental Evidence for Cumulative Neurotoxicity

Prenatal MB Exposure - Experimental Design

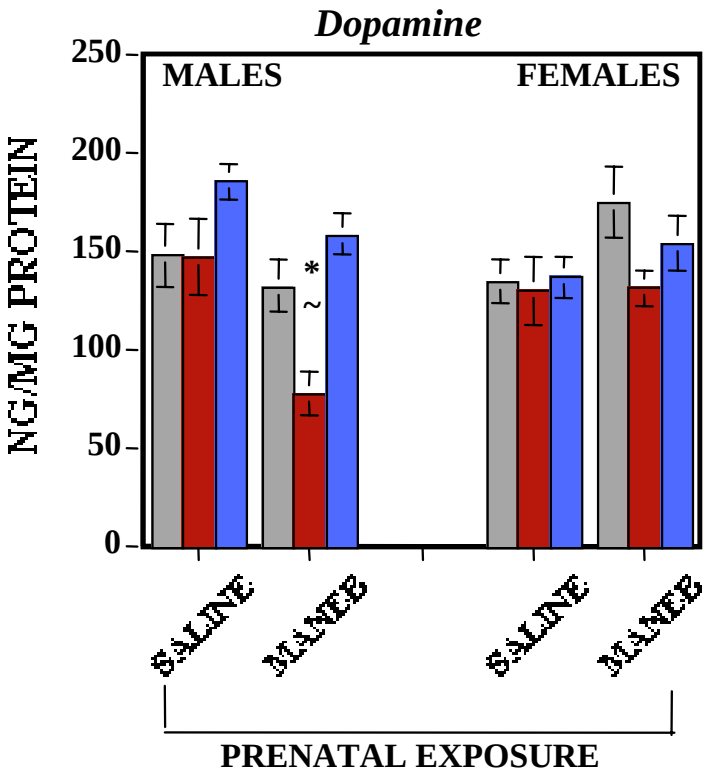
TIME - LINE

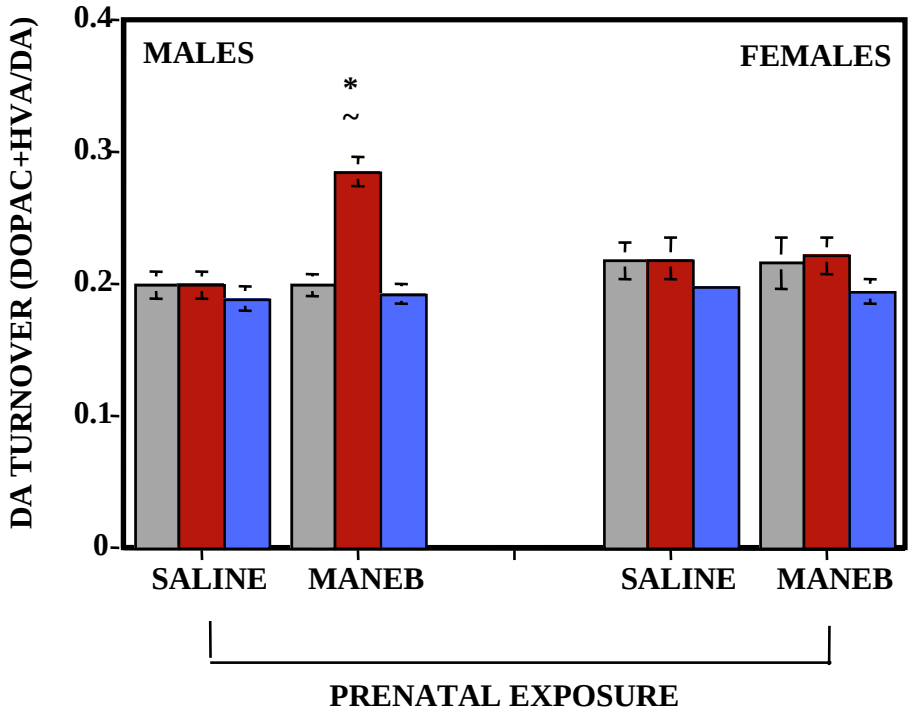


Effect of Prenatal MB Exposure Followed by Adult PQ or MB Exposure



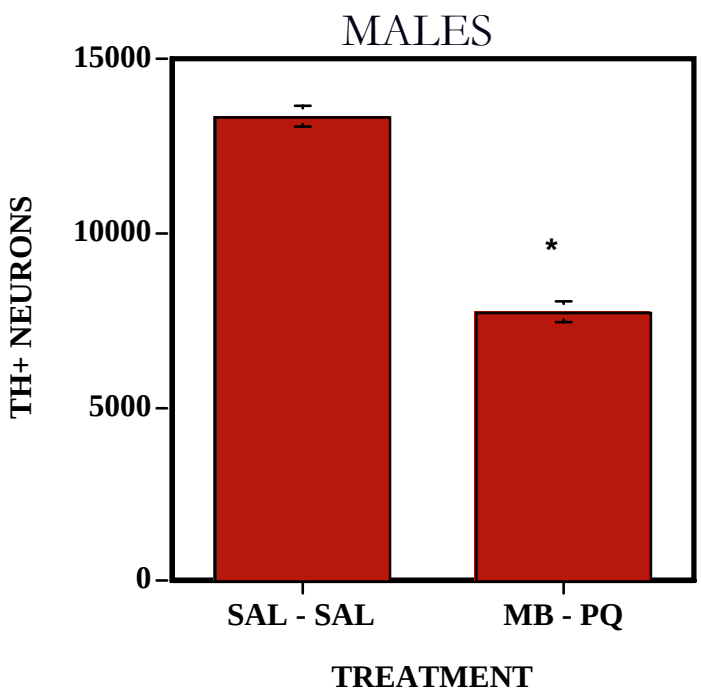
Changes in Striatal Dopamine and Dopamine Turnover

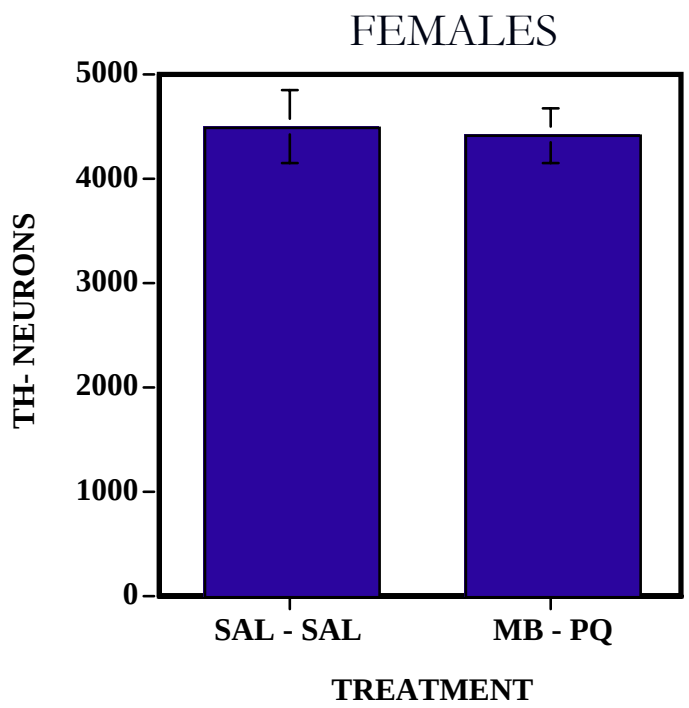




ADULT SALINE ADULT PQ ADULT MB

Loss of TH+ Neurons in the Substantia Nigra Pars Compacta

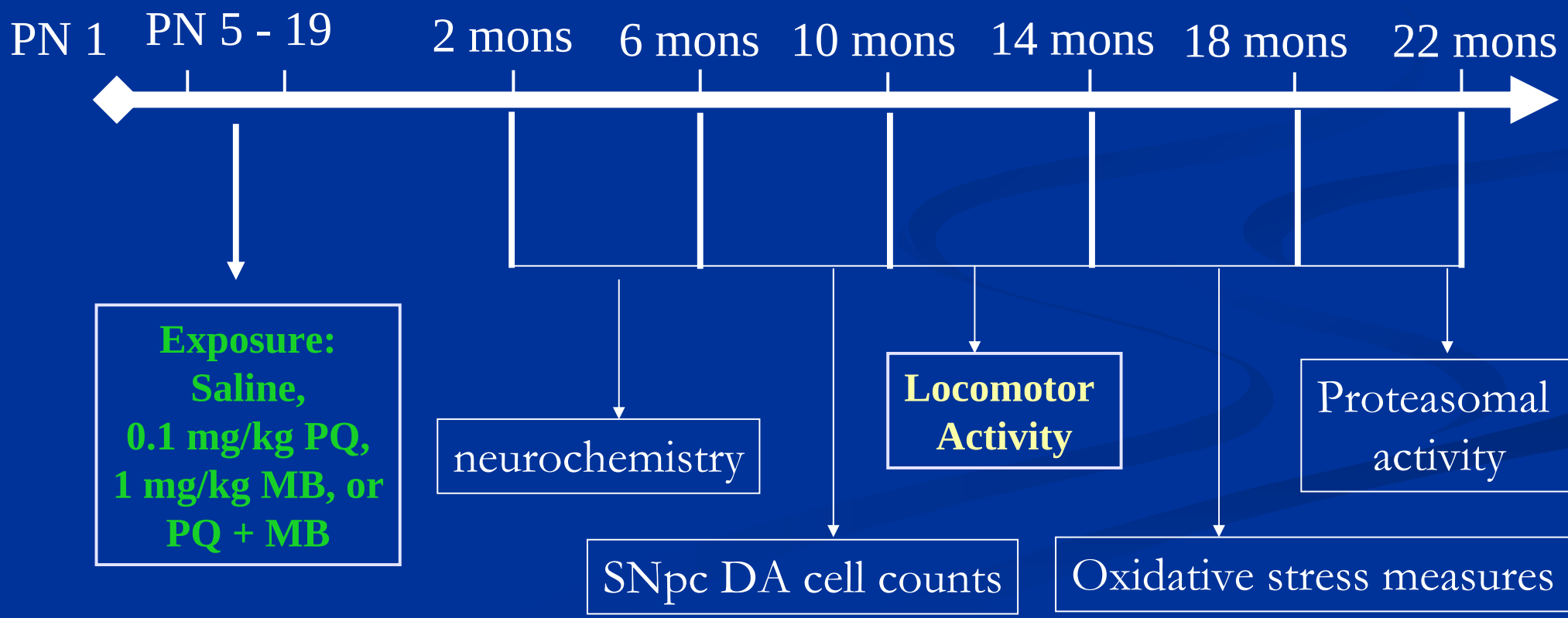




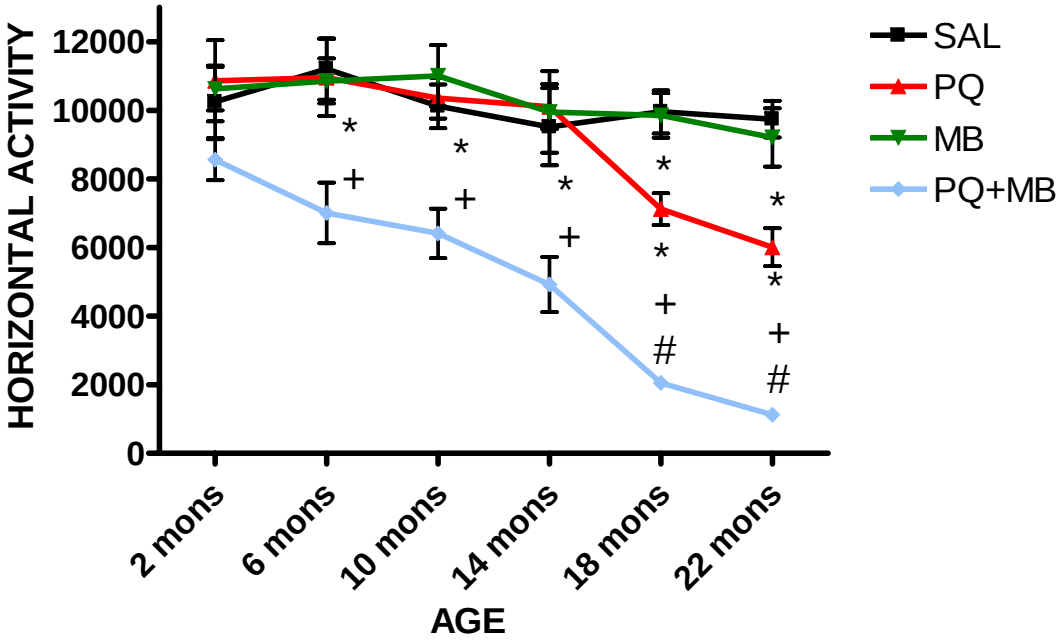
Progressive Neurotoxicity Following Postnatal Exposure to PQ & MB

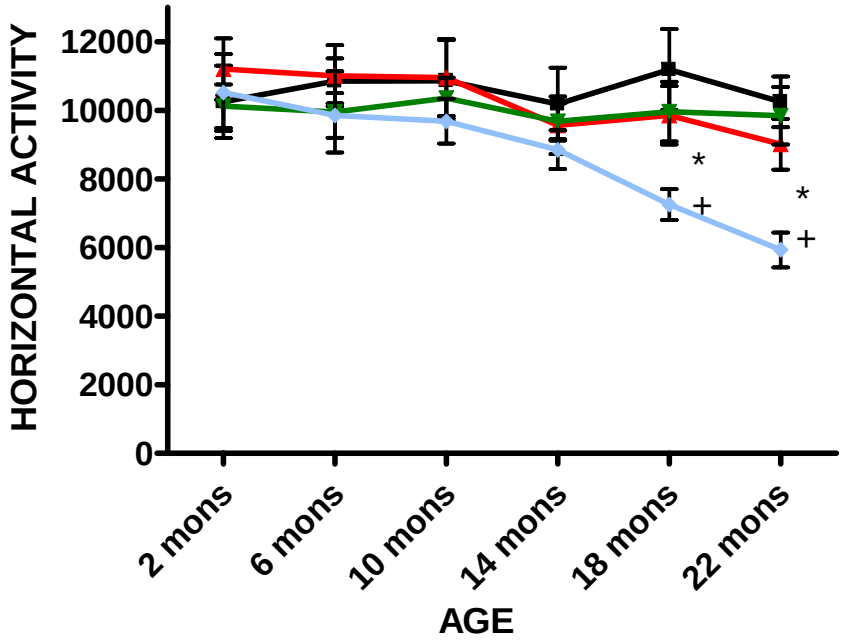
Postnatal PQ & MB Exposure - Experimental Design

TIME LINE

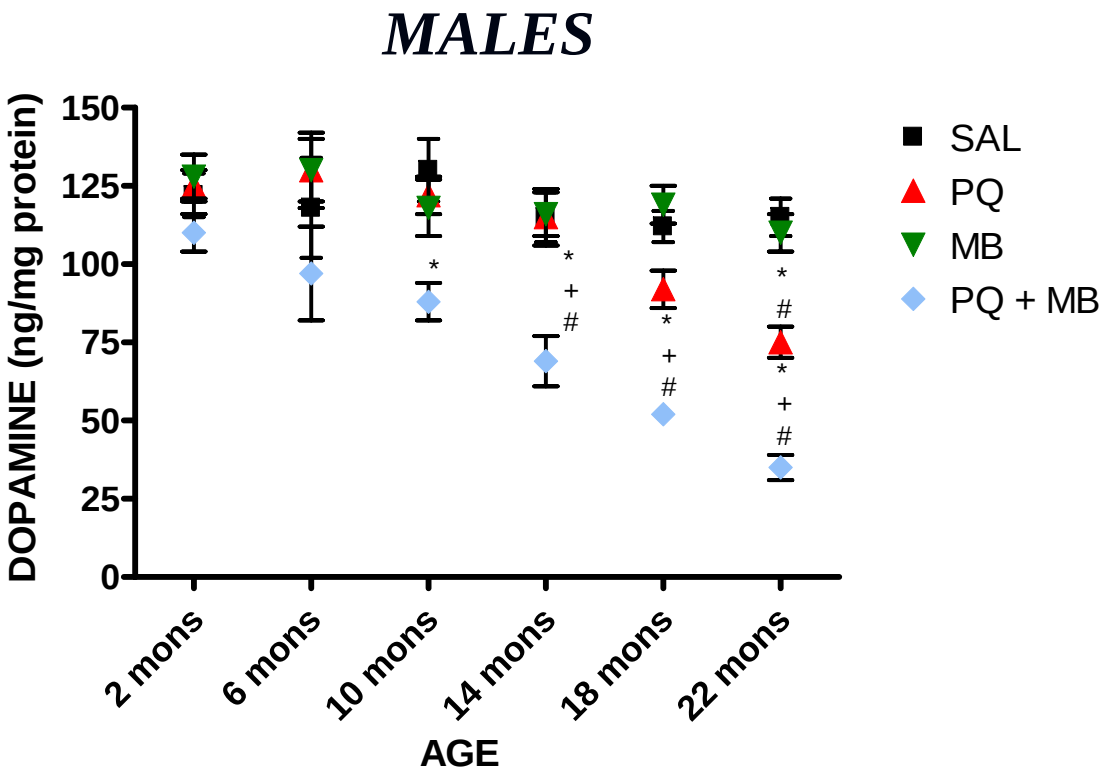


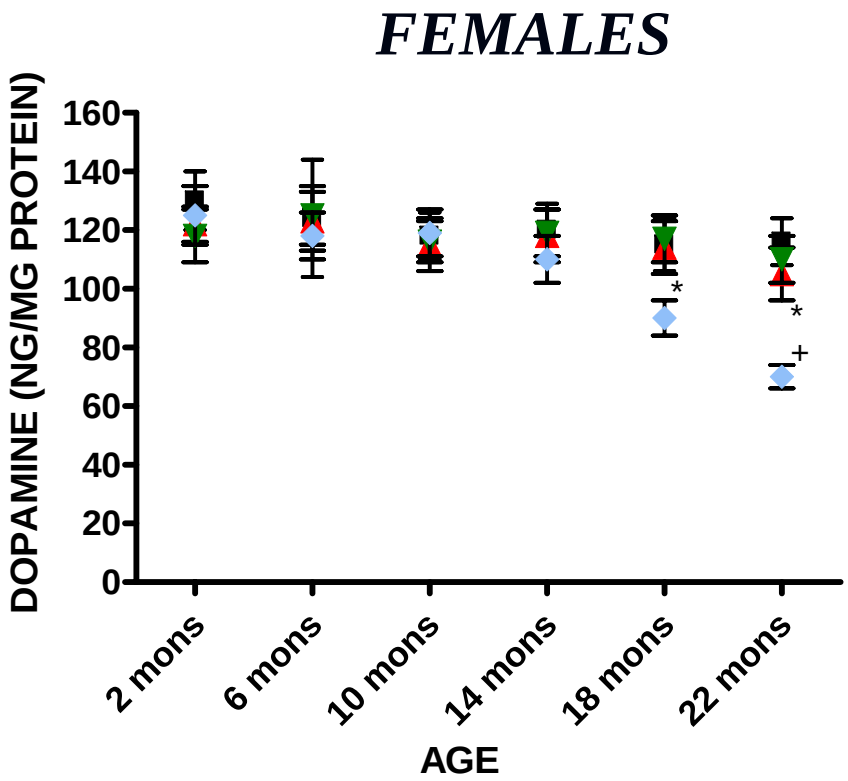
Progressive Decline With Age in Locomotor Activity





Progressive Decline With Age - Striatal Dopamine





Progressive Decline With Age - SNpc DA Cell Loss