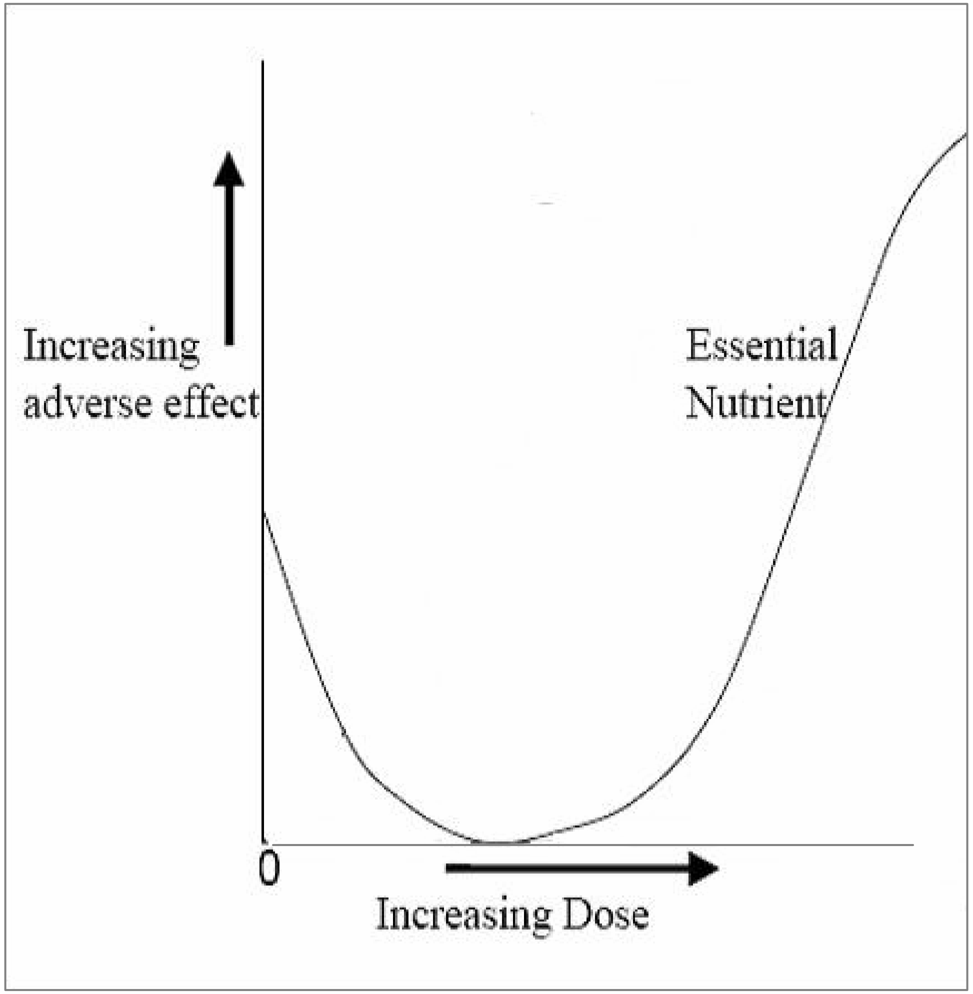
MANGANESE AS A NEURODEVELOPMENTAL TOXICANT

Roberto Lucchini, Silvia Zoni, Elisa Albini
(Occupational Health, University of Brescia, Italy)
Cynthia Kern, Donald Smith
*(Environmental Toxicology
University of California, Santa Cruz, USA)*

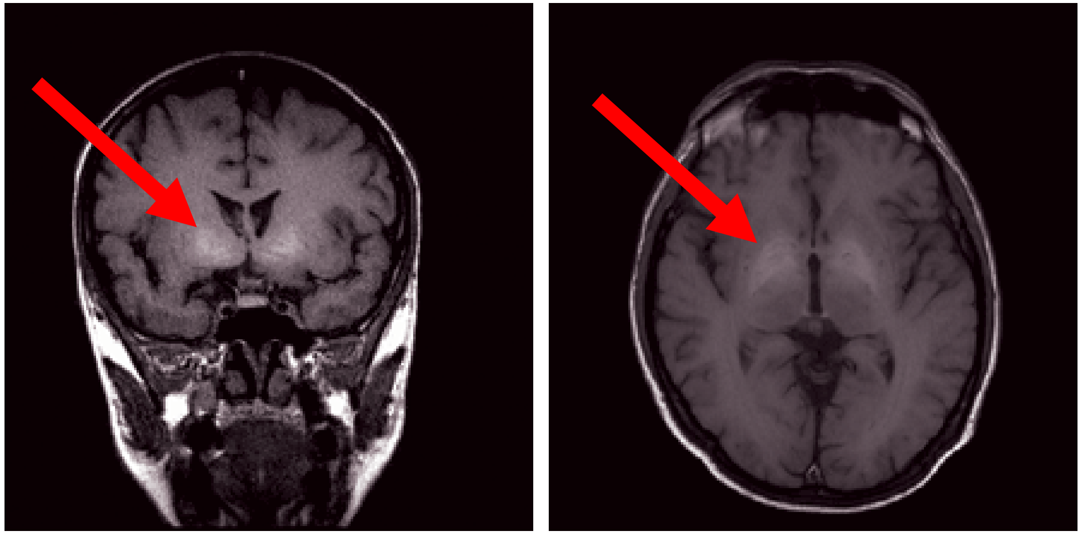
Avoid deficiency and toxicity

- Complicated dynamics based on complex kinetics



Mn adult neurotoxicity

- **Occupational:** **mines, ferroalloy, welders, etc**
  - fine motor impairment, gait deficits, dystonia
  - Mood changes towards aggressivity



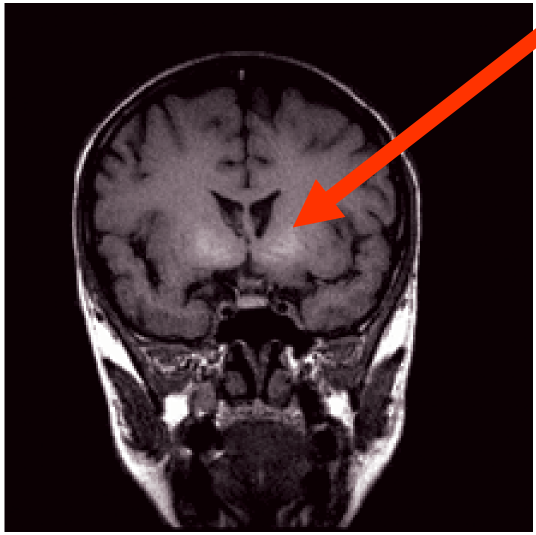
T(1)-Weighted MRI hyperintensity

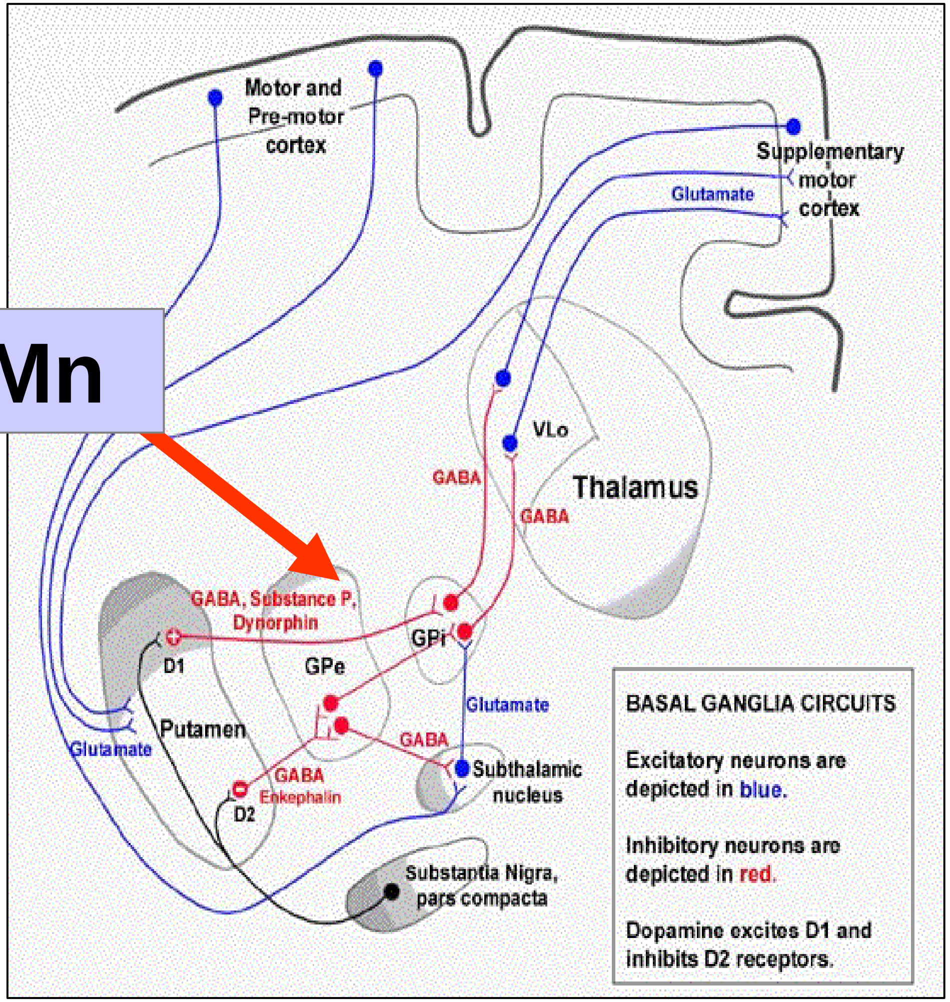
- **Globus pallidus as critical target**

Target Globus pallidus

- GP: domaninergic and GABAergic control of motor functions and mood

Mn





Mn adult neurotoxicity

<u>Environmental:</u>

- Increased frequency of parkinsonism from
  - Mexican mines (Rodriguez-Agudelo et al, 2006)
  - Italian ferroalloy plants (Lucchini et al., 2007)
  - Canadian industrial sites and car traffic MMT (Finkelstein and Jerrett, 2007)

OR for PD = 1.034 (1.00-1.07)
per 10 ng/m^3 increase of Mn in TSP

Prenatal exposure: animals

- Drinking water exposure to dams:
  - increased brain Mn levels in pups and adolescent (Seth 1977, Chandra and Shukla 1979, 1980, 1981)
  - increased activity at PND 17 (Pappas 1996)
- Inhalation study to dams:
  - aberrations in offspring behavior (Lown 1984)
- Maternal dietary intake increases fetal Mn levels (Jarvinen 1975, Kirchgessnes 1981)
- Placenta partially sequesters inhaled manganese, limiting fetus exposure (Dorman et al 2005)

Pre/post-natal: humans

- Learning disabilities in Chinese children 11-13 yrs associated with MnW 241- 346 μg/L (300 EPA lifetime health advisory level)

  (He et al 1994)

- Mn tooth enamel (which develops 20 gestational wk - 7 mo postnatal) associated to behavioral outcomes

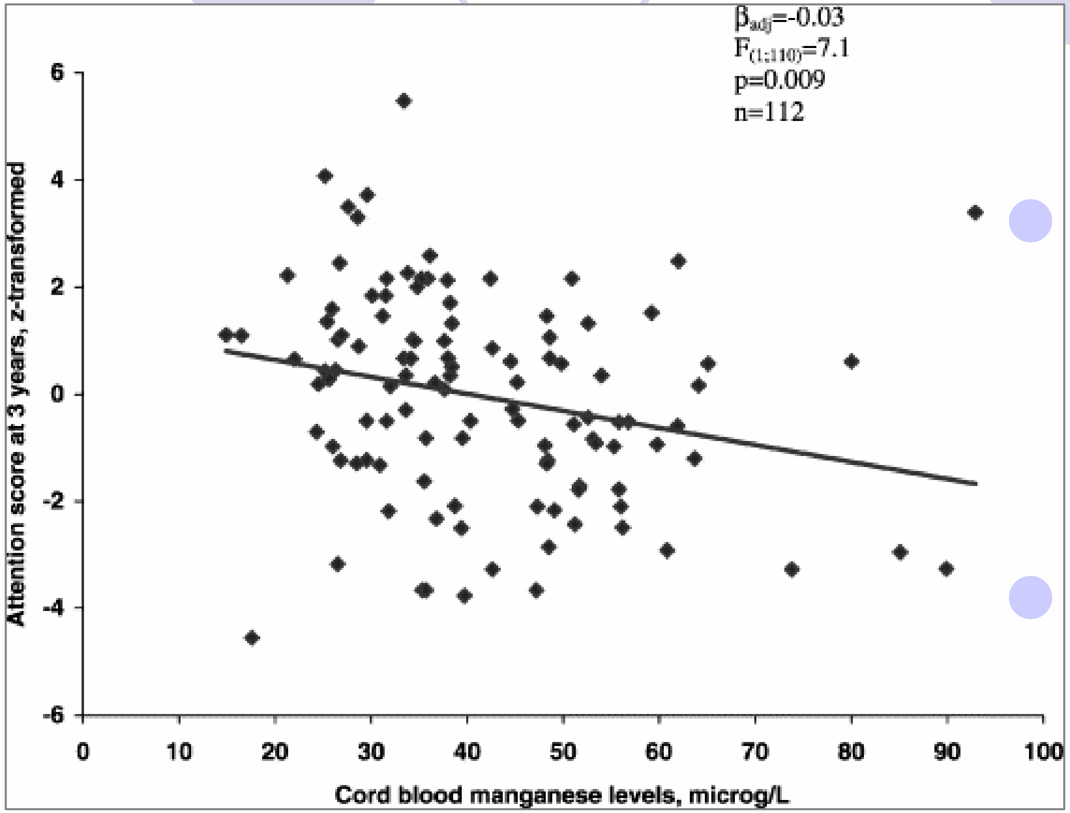
  (Ericson et al 2007)

Manganese levels in mother's and cord blood, mother's and newborn hair, and placental tissue in initial population and the sample followed up to 6 years

Manganese levels	Initial population		Follow-up sample at 6 years of age	
	Mother	Cord/newborn	Mother	Cord/newborn
Blood manganese (μg/l)				
n	222	222	91	91
Geometric mean	20.4	38.5	20.8	38.6
5th–95th percentiles	11.1–40.4	19.1–71.2	12.7–3.1	22.0–67.7
Range	6.3–151.2	14.9–92.9	6.8–94.1	14.9–92.9
Hair manganese (μg/g)				
n	173	173	69	69
Geometric mean	0.36	0.75	0.35	0.77
5th–95th percentiles	0.16–0.87	0.22–4.25	0.15–0.92	0.22–4.25
Range	0.10–3.24	0.05–13.33	0.10–3.24	0.18–11.17
Placental manganese (μg/g)				
n	200		95	
Geometric mean	0.10		0.10	
5th–95th percentiles	0.06–0.16		0.06–0.15	
Range	0.01–0.49		0.01–0.49	

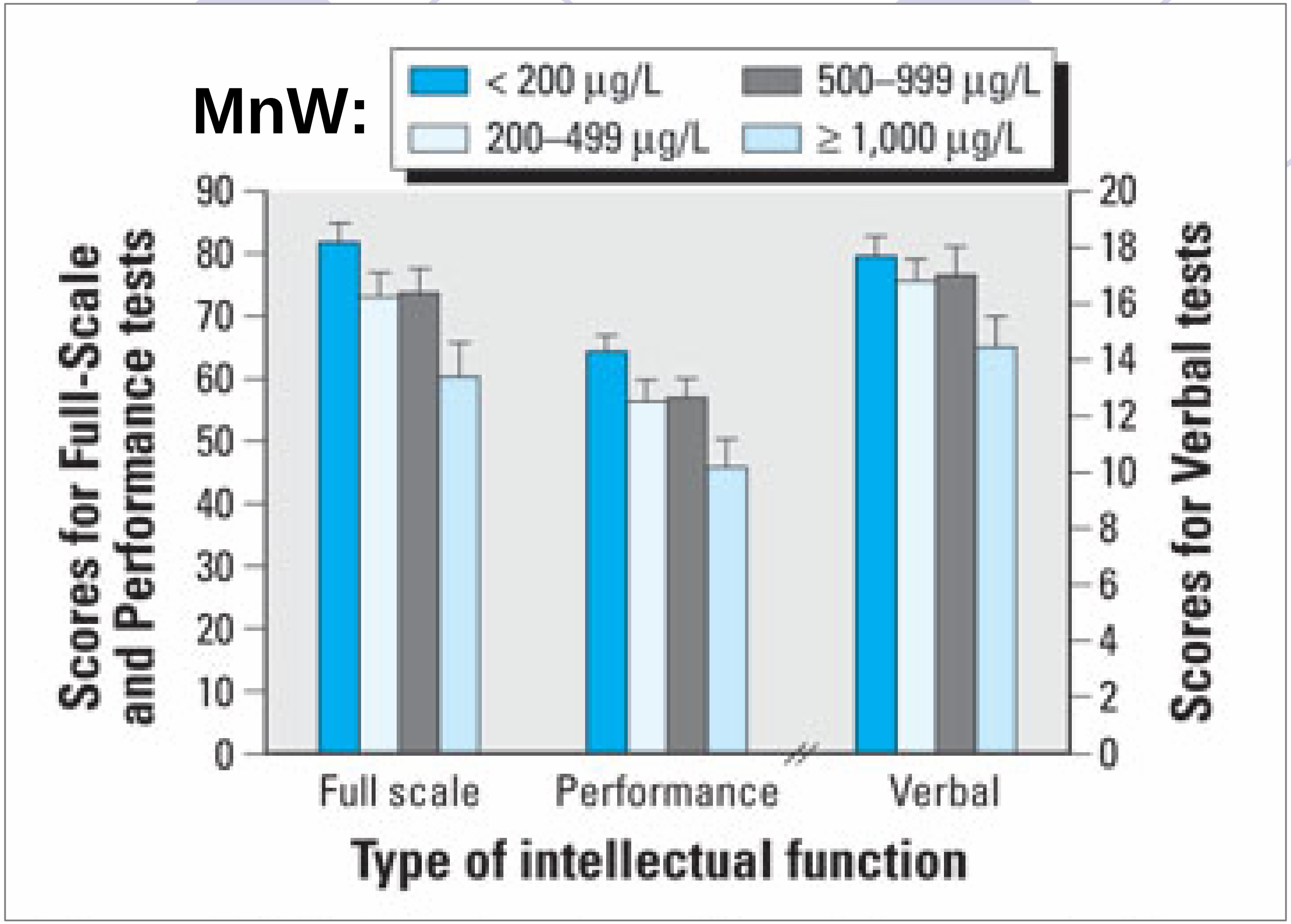
No significant differences were observed between initial and follow-up populations (*t*-test was used).

- Takser et al., 2004



- Mn at birth associated with pyschomotor sub-tests at 3 yrs not 9 mo not 6 yrs
- No association with cognitive tests

- Takser et al., 2004

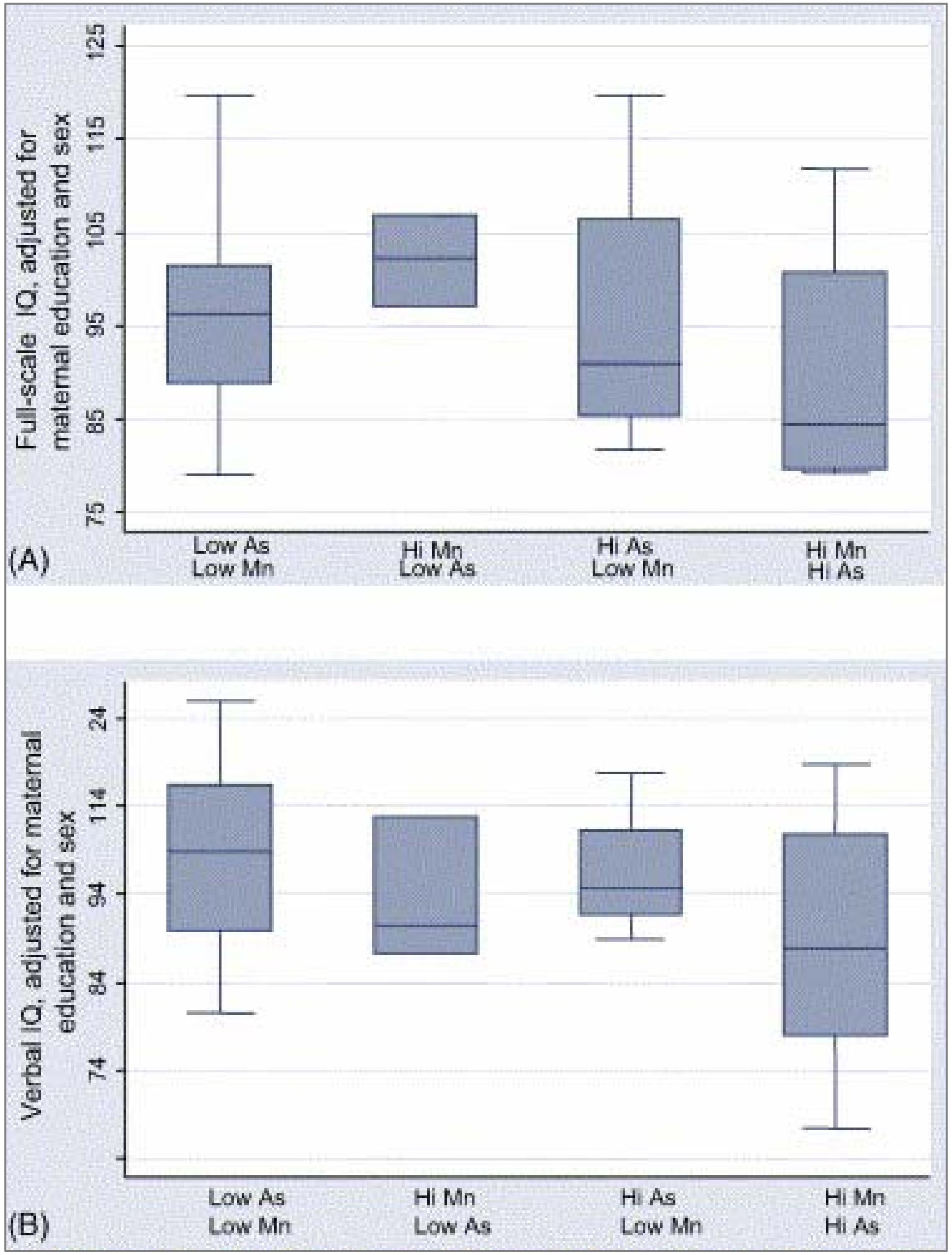


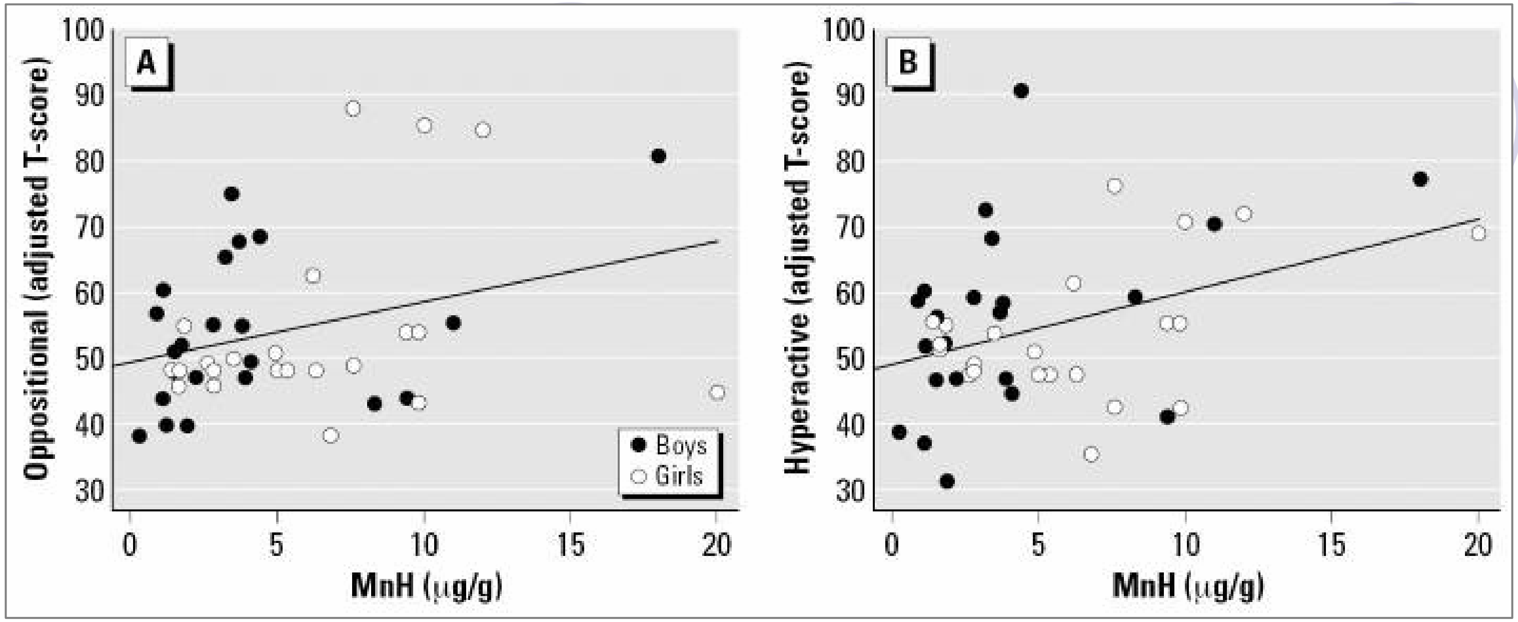
High MnW and low AsW in Bangladesh

- Wasserman et al., 2006

Interaction Hair Mn/As on IQ from Tar-Creek, OK

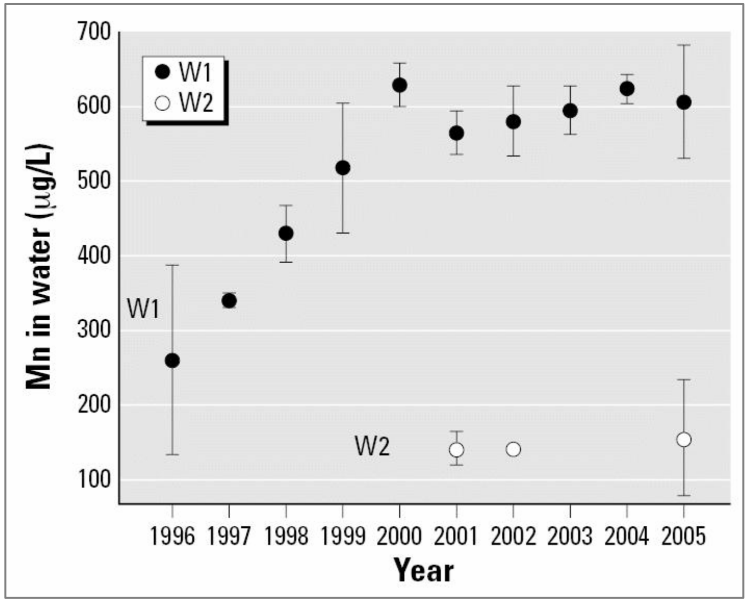
- Wright et al., 2006





MnH from high MnW associated wiht hyperactive behavior

- Bouchard et al., 2007

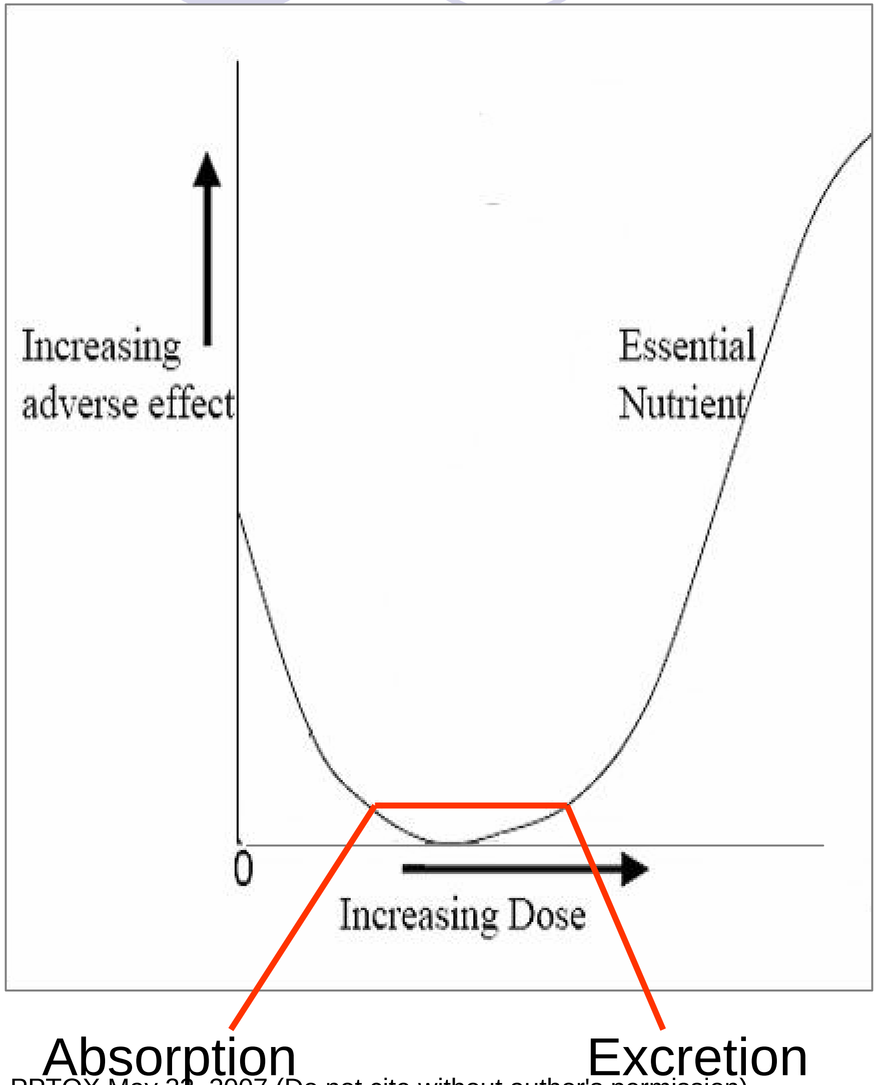


Mn essentiality

- **For metaloenzymes:** arginase, glutamine synthetase (nitrogen methabolism), pyruvate carboxylase (carbohydrates synthesis)
- In tissues with high metabolic rate (brain for glutamine in astrocytes)
- Free radical defense (MnSOD)

developing brain needs Mn

Homeostatic control



- **V**ery efficient in regulating absorption and excretion rates <u>in aduls</u>

Adult vs Infant homeostasis

- **Dietary Mn Intake**
  - Adult **~ 10mg/kg/day**
  - Breast-fed infants **~ 0.0005mg/kg/day**
  - **20,000-times less than adults!**

- **GI Mn Absorption**
  - Adults – 3-4% of ingested Mn
  - Infants ~ 80%
- **Mn Excretion / Retention**
  - Adults – significant hepato-biliary excretion
  - Infants – little hepato-biliary excretion
- **Brain Mn Uptake**
  - Adults – BBB regulates Mn uptake
  - Infants –immature BBB –Mn uptake poorly regulated

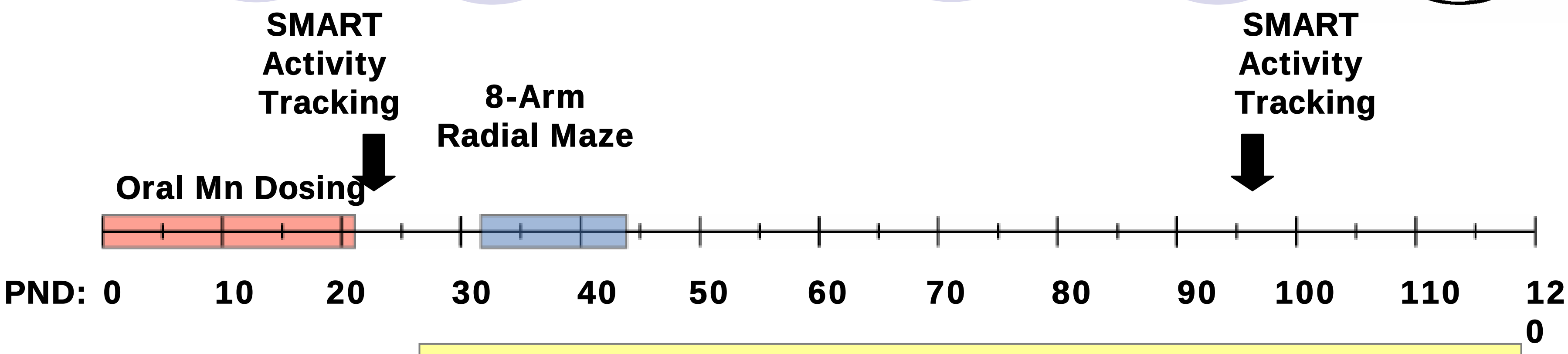
- Therefore, there is a delicate balance between a great need for Mn and a possible overload, especially in infants

Mn in Infant Formula

Human milk:		**4ug/L Mn (ppb)**
Cow milk:		**30ug/L**
Formulas		
Cow based:	**Similac**	**73ug/L**
Soy based:	**Isomil:**	**436ug/L**
	ProsoBee:	**749ug/L**
(Stastny,1984)	**Enfamil:**	**1,289ug/L**

*In the U.S. 20% of infants are fed soy formula, with 750,000 infants receiving soy formula every year *(Mercola, 2001)*.

Rodent model by UCSC



<u>Oral Mn Expsoure</u>

- Vehicle (Sucrose sol'n)
- 25mgMn/kg/day
- 50mgMn/kg/day **(MIMICKS HIGH LEVEL IN FORMULA)**
- N=14 – 18 /treatment/outcome

<u>Outcomes:</u>

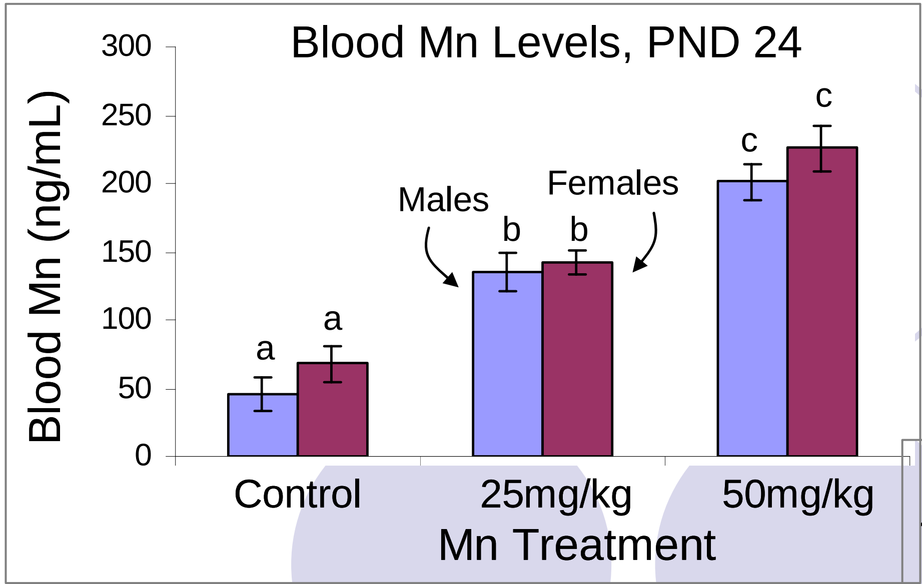
•<u>Activity</u> – motor activity and behavior (SMART)

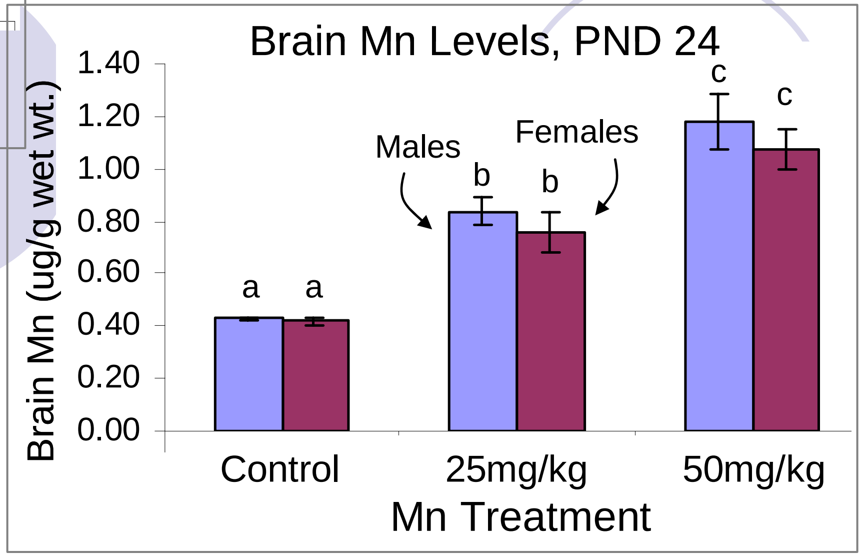
*Analysis of Zones within arenas

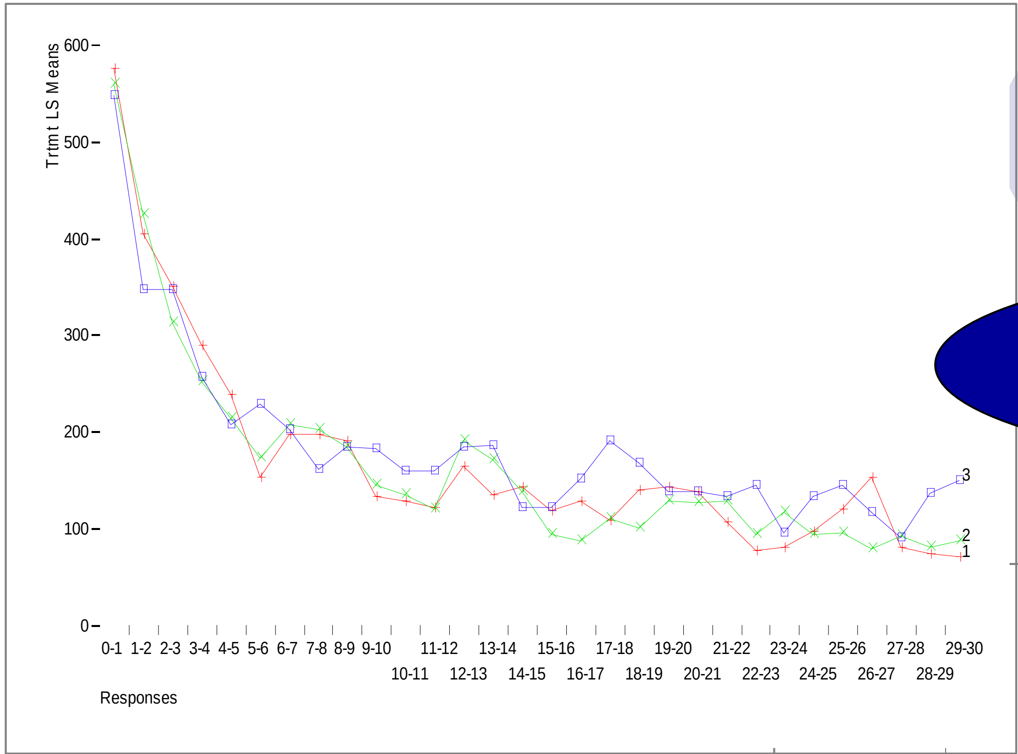
*Time spent and distance traveled

•<u>Learning / Memory</u> – 8-arm radial maze

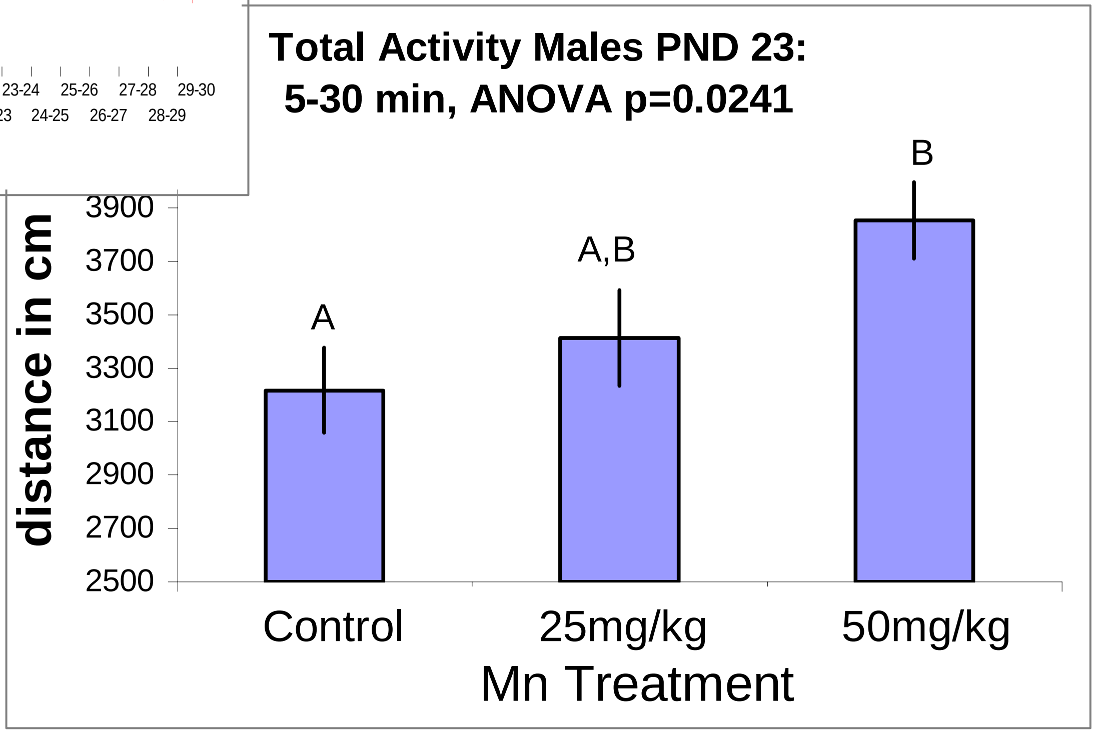
Blood and Brain Mn increased by the end of Treatment on PND 21



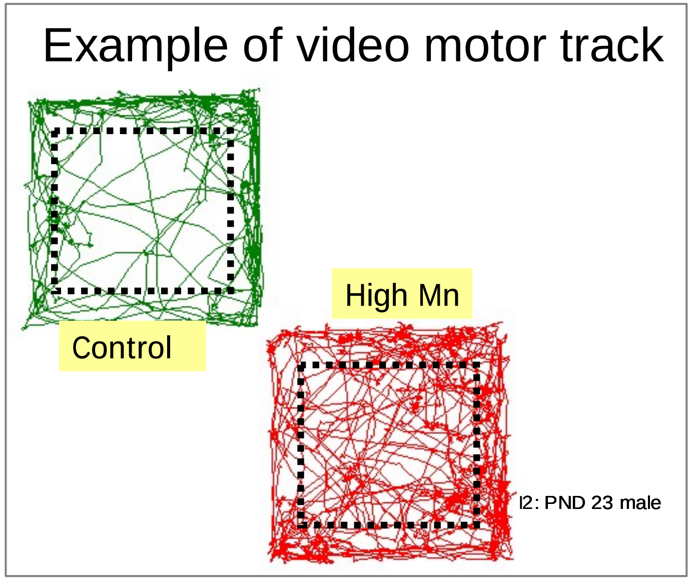


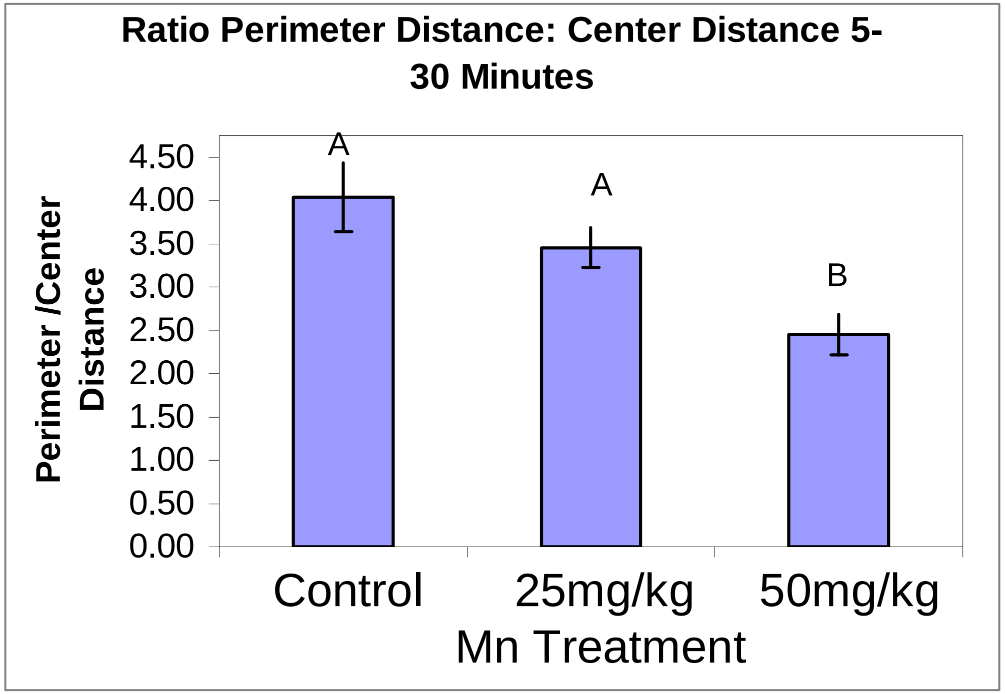


Mn increased activity



Increased activity in the center



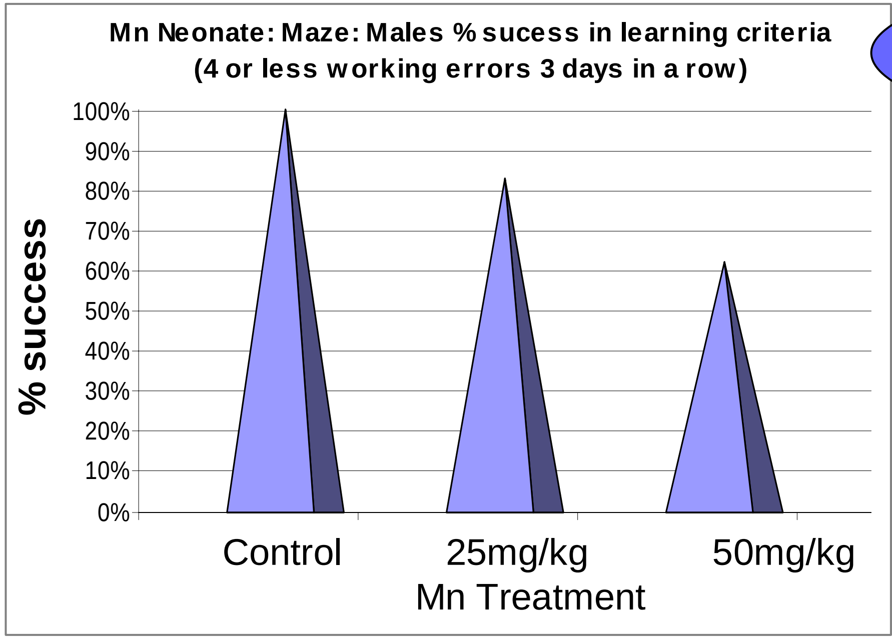


Rodents usually prefer periphery of arena—favor thigmotaxis

Open arena is a measure of gross motor activity and reaction to a stressful event; not on exploration

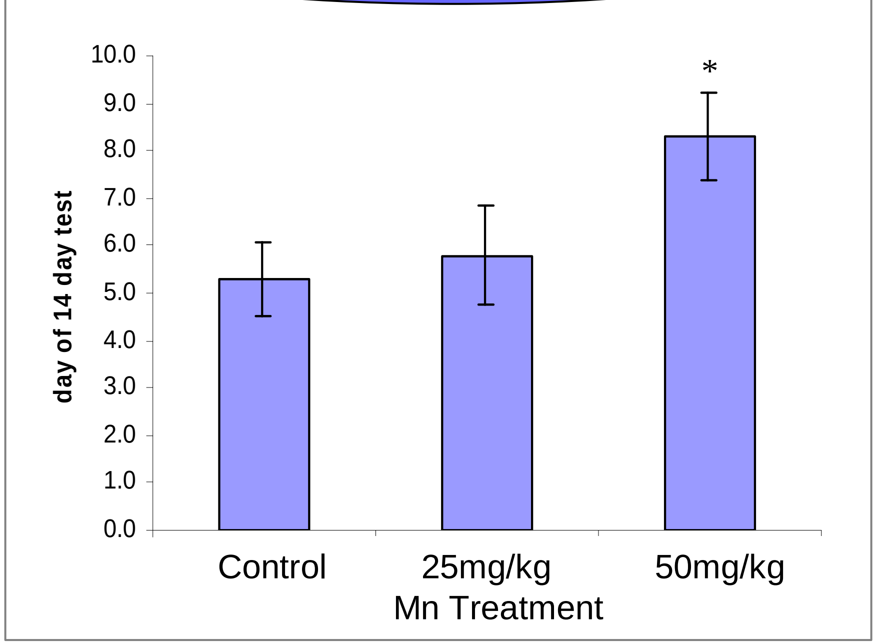
Increase time in center indicates decrease response to stressful event

Mn decreases ability to learn



Percent of animals per treatment who reached the maze criteria

Mn increases time needed to learn



No **of days to reach learning criteria**

In summary

- Pre- and post-natal exposure increase Mn levels and cause motor and cognitive impairment
- Pre- and post-natal exposure + adult environmental and occupational ⇒
- Neurodegeneration as cumulative long term effect ?