



# Manganese neurotoxicity

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# Main uses

Fourth most used metal behind iron,  
aluminum and copper

With 20 million tons mined annually

Steel objects, batteries, beverage cans:  
manganese improves the properties of the  
alloys

# EXPOSURE SOURCES

## occupational

Mining

Ferroalloy

Alkaline battery

Welding

Mn-based pesticides

# **From high to low exposure levels with more ubiquitous diffusion:**

- **new applications in electronics,**
- **new steel and alloys with cryogenic and non-magnetic properties**
- **MMT in gasoline**

# EXPOSURE LEVELS

## Occupational:

- Above 1 mg/m<sup>3</sup> for clinical intoxication
- 200 µg/m<sup>3</sup> in “total dust” as current TLV
- 30 µg/m<sup>3</sup> in “respirable dust” as ACGIH intended change

## Environmental:

- WHO air quality standard: 0.15 µg/m<sup>3</sup>
- EPA Rfc: 0.05 µg/m<sup>3</sup>
- Canadian cities: from 0.01 to 0.02 µg/m<sup>3</sup>
- Higher levels in heavy industrial areas

# Exposure and effects

- High doses:

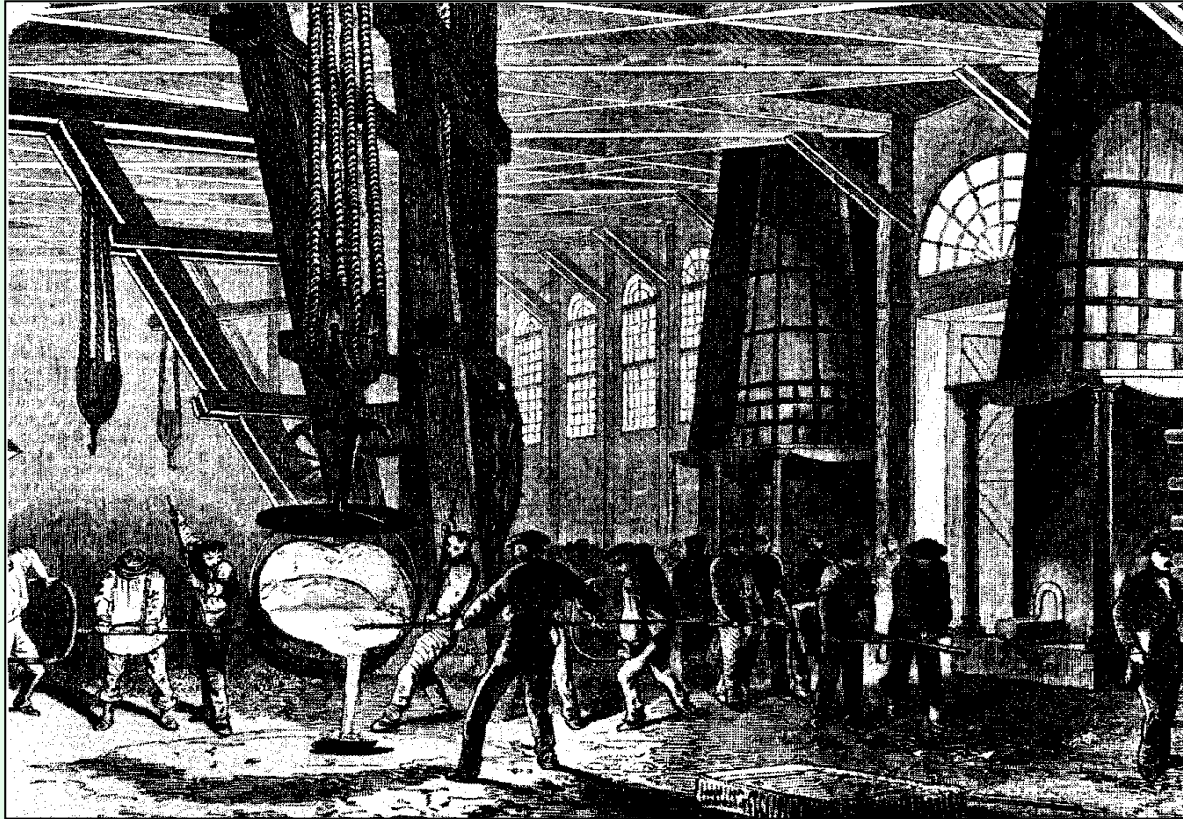
Clinical intoxication called manganism, with extra-pyramidal signs and psychiatric features (hallucination, aggressivity)

- Low doses:

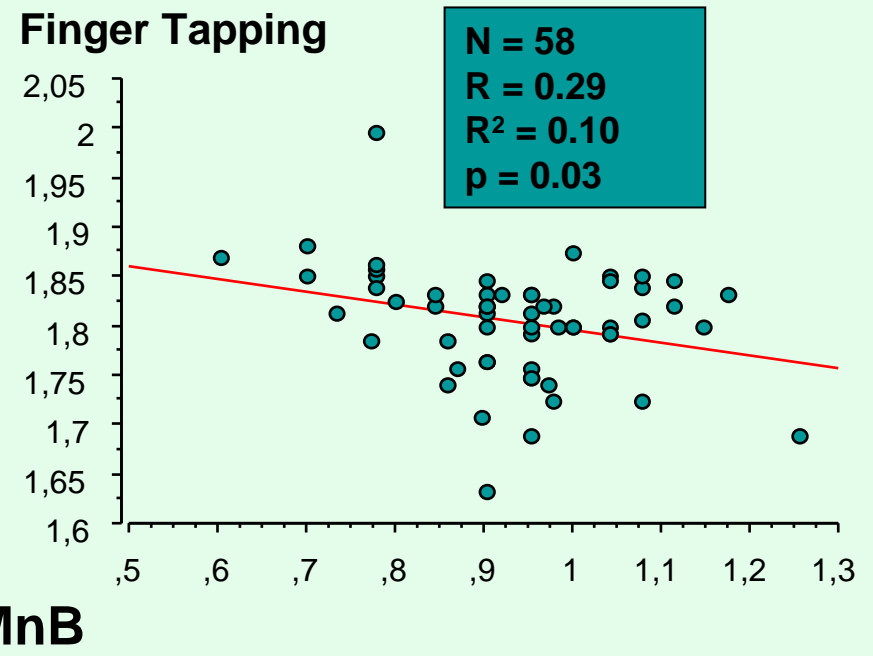
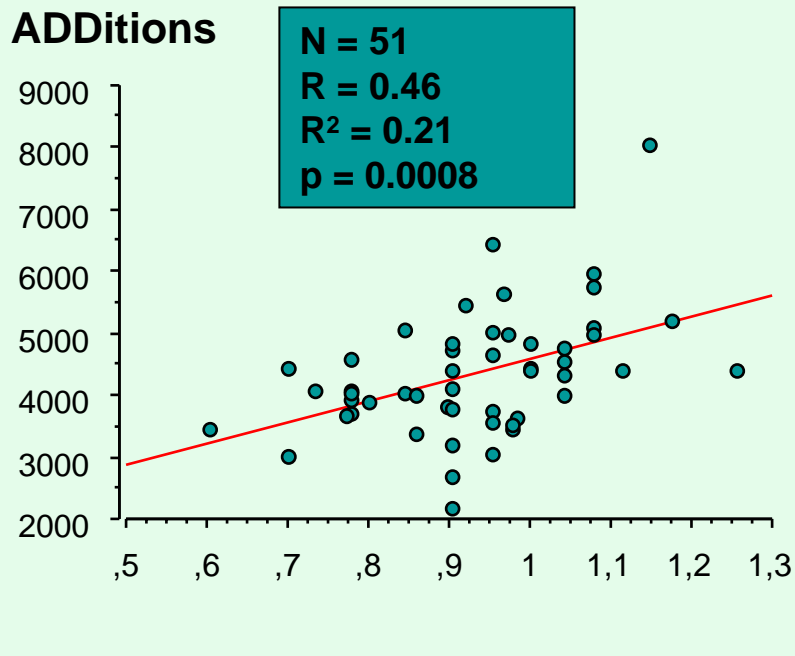
Neurobehavioral changes of motor function, associated with cumulative exposure

Age-related facilitating factor for the onset of parkinsonism ?

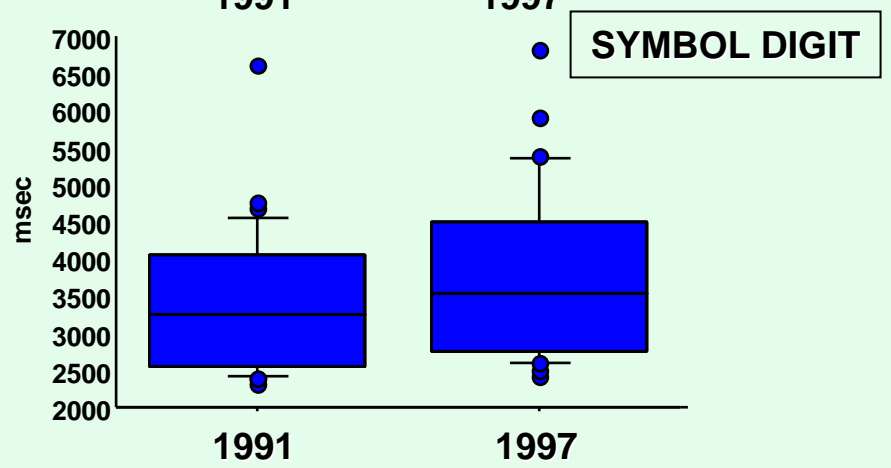
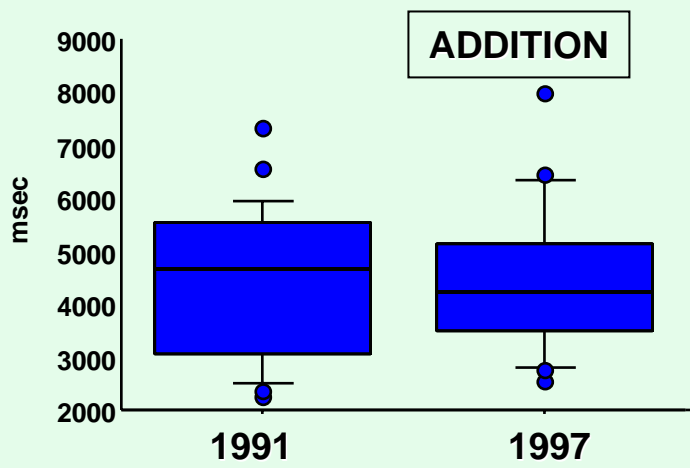
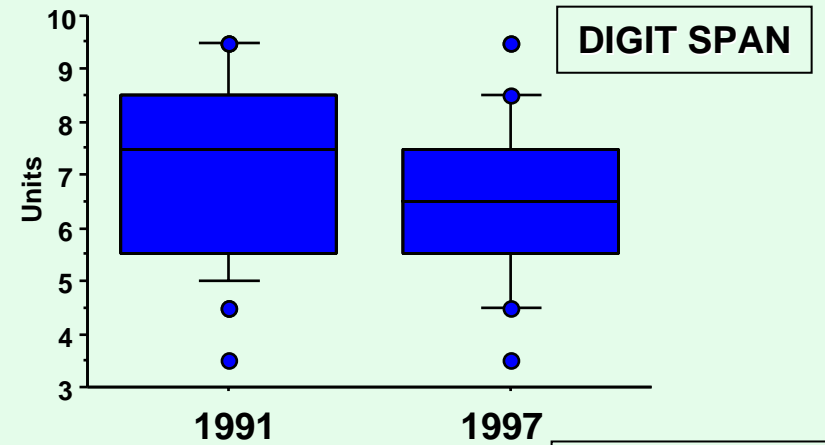
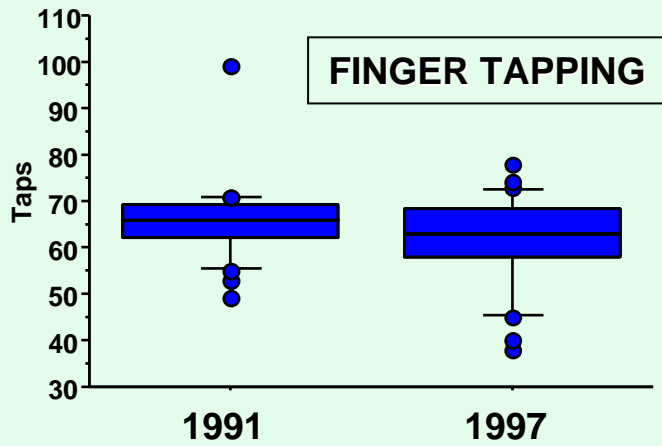
# Studies in Ferroalloy



# Neurobehavioral impairment



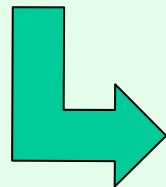
*Lucchini et al. (1995)*



*Lucchini et al. (1999)*

# ENVIRONMENTAL EXPOSURE

Chronic environmental exposure  
to Mn from ferroalloy plants

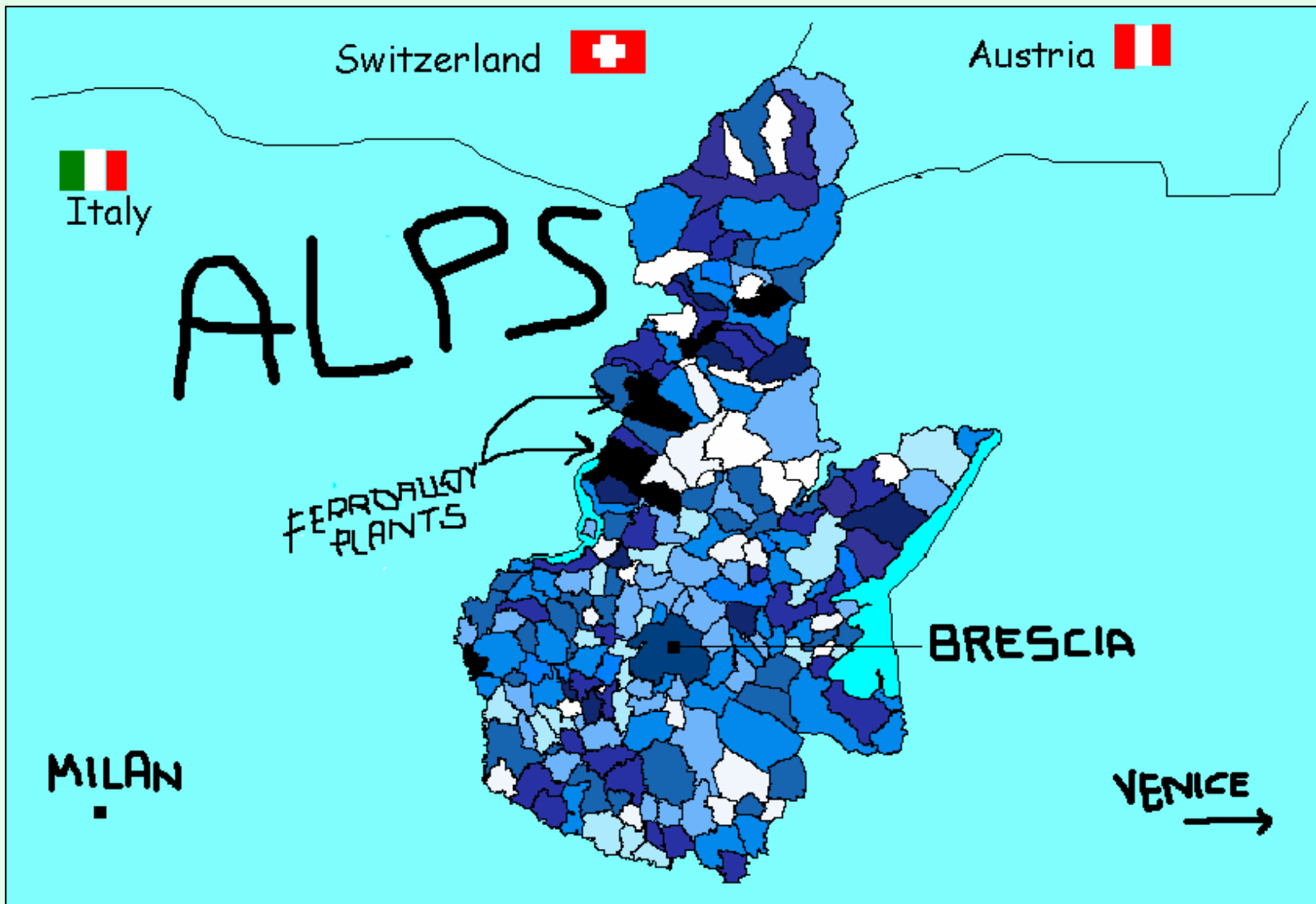


- Possible cause of Parkinsonian disturbances in the population ?

# EPI STUDY

## Sources of information

- a) registers from local medical clinics
- b) admission charts from local hospitals
- c) consumption of levo-dopa
- d) NHS list of exemption from prescription payment, due to the illness

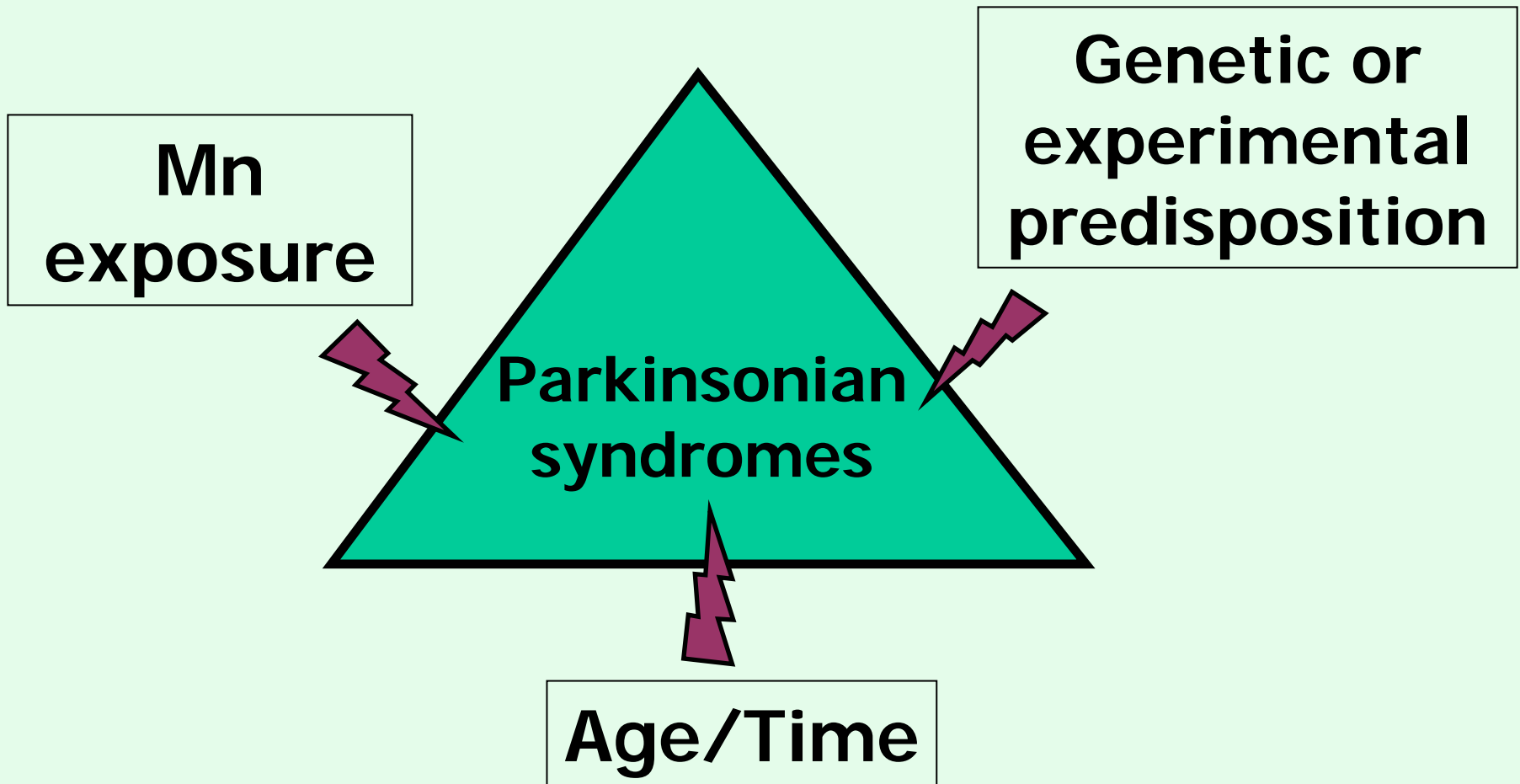


# Results

	Counties	Cases	Residents	Crude Preval
Counties with Mn exposure	29	290	81.060	358 438*
Counties without Mn exposure	177	2.387	1.007.286	237
Counties Tot	206	2.677	1.088.346	246

(Smr = 1.58; CI=1.41-1.76)

*(\*): Age-sex adj*



# Experimental evidence

- Normal neurobehavioral tests in rats treated with 6 hydroxydopamine (6-OHDA) to obtain dopamine depletion (pre-park condition)
- Behavioral/neuromuscular changes after chronic low exposure doses of Mn
- Alteration of striatal GABA - not striatal dopamine

*Witholt et al. (2001), Gwiazda et al. (2002)*

# Parkinsonism in welders ?

A case-control study on PD patients comparing 15 career welders vs. 100 non welders at the Movement Disorders Center, Washington University School of Medicine (St. Louis, MO)

*Racette et al. (2001)*

# Differences

	15 welders	100 seq. registered	Age-sex matched
<b>Age of onset *</b>	46 yrs	63 yrs	/
<b>Family history</b>	53%	32%	41%

\*  $p < 0.0001$

## *Hypothesis:*

1. PD in welders cannot be distinguished except from younger age of onset

2. Onset accelerated by Mn exposure, **environmental trigger** in individuals with genetical predisposition ?

# Mn toxico-kinetics

- Essential element with highly effective homeostatic mechanism
- Adjusting absorption and excretion rates
- Keeping Mn concentration within a strict range to avoid intoxication/deficiency

# Absorption through inhalation

Different oxidation states and chemical forms with different solubility and lung bio-availability

## Ingestion

Ingestion through water, diet  
(tea, cereals, legumes)

## Olfactory pathway ?

Bypass of blood/brain barrier

## Competition with iron ?

- Serum binding protein (transferrin)
- Divalent Metal Transporter (DMT1)

Enters the brain through rapid carrier-mediated mechanism

*Crossgrove et al. (2003)*

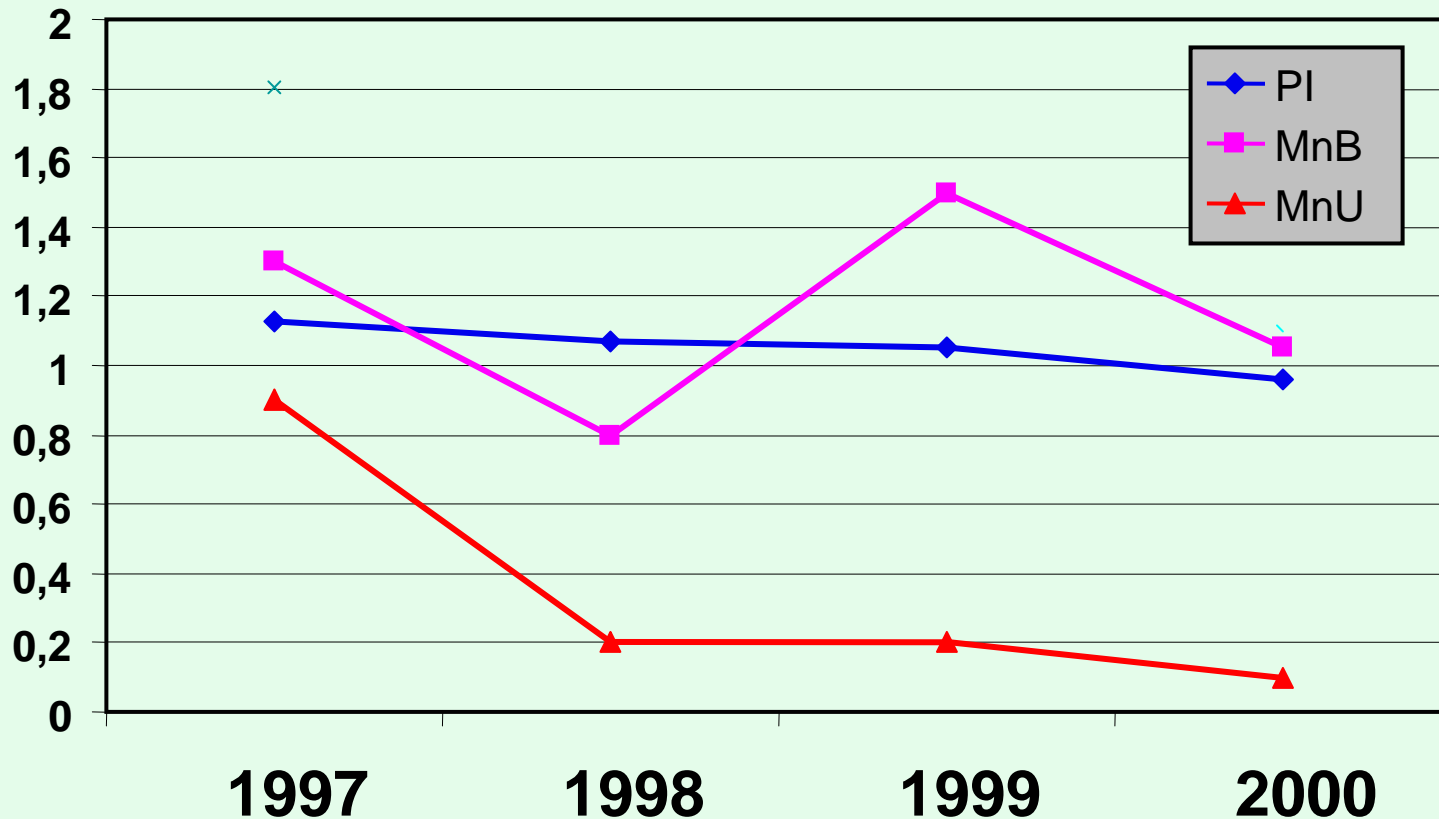


Efflux from the brain with slower passive diffusion mechanism

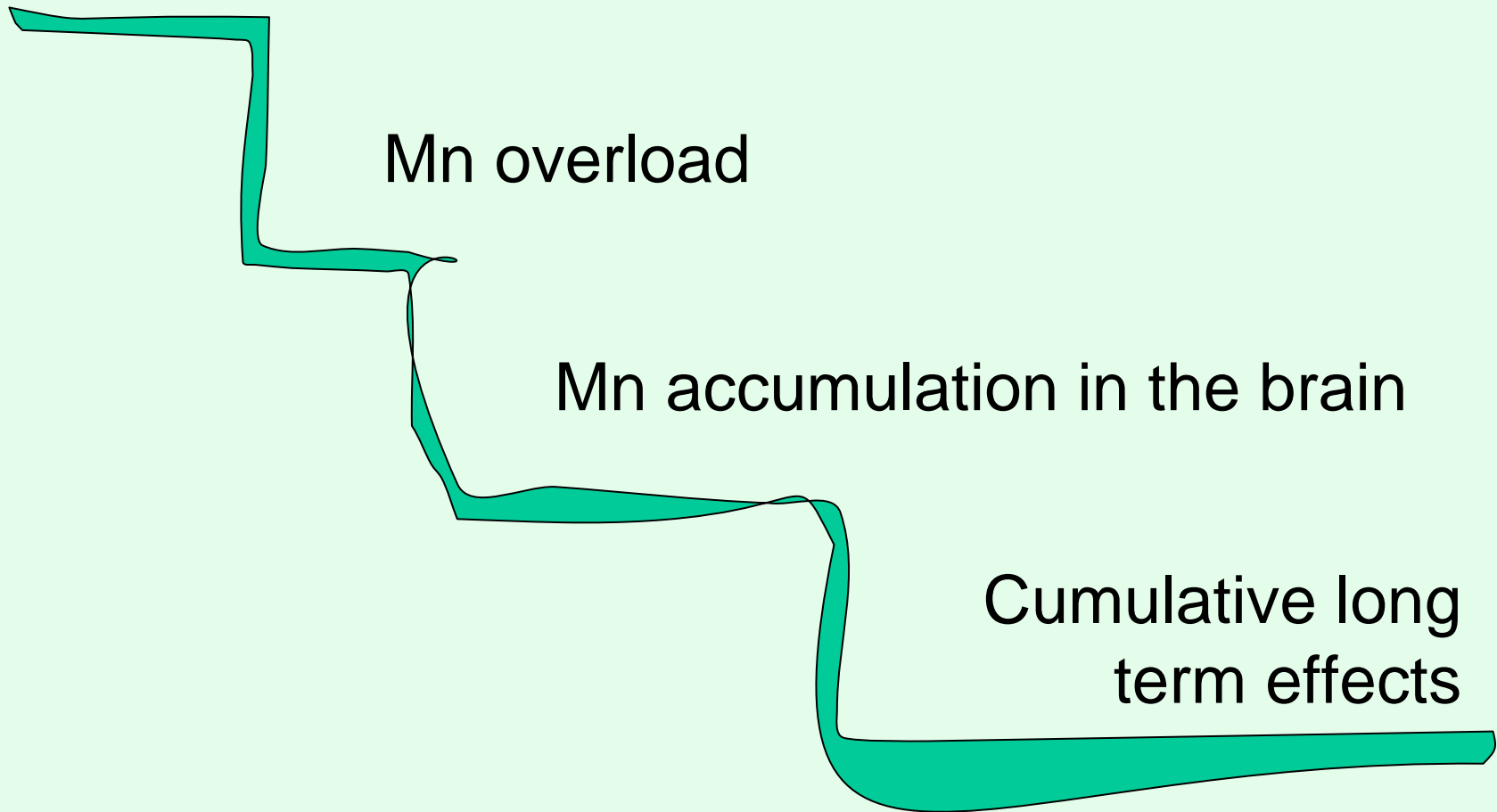
*Yokel, et al (2003)*

<b>Mn in tissues (µg/g weight)</b>	<b>HUMANS Tipton 1963</b>	<b>HUMANS Sumino 1975</b>	<b>RATS Rehnberg 1982</b>
Liver	1,68	1,2	2,6-2,9
Pancreas	1,21	0,77	No data
Adrenals	0,20	0,69	2,9
Kidney	0,93	0,56	0,9-1,0
<b>Brain</b>	<b>0,34</b>	<b>0,30</b>	<b>0,4</b>
Lung	0,34	0,22	No data
Heart	0,23	0,21	No data
Testes	0,19	0,20	0,4
Ovary	0,19	0,19	No data
Muscle	0,09	0,09	No data
Spleen	0,22	0,08	0,3
Fat	No data	0,07	No data
Bone (rib)	No data	0,06	No data
Pituitary	No data	No data	0,5

# Mn elimination after retirement



# Prolonged exposure to Mn low levels



# CONCLUSIONS

- Manganese can be accumulated in the CNS and cause long term effects
- Further study is needed to assess the safe occupational and environmental exposure levels, in view of a cumulative mechanism of neurotoxicity



**Thank you for  
your attention !**