Session I-6

High Signal Intensities on T1-Weighted MRI as a Biomarker of Manganese

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Abstract

Increased signal in T1-weighted images was observed in the experimental manganese (Mn) poisoning of the non-human primate and a patient with Mn neurointoxication. However, our study showed that the increased signals in magnetic resonance images (MRI) were highly prevalent (41.6%) in Mn-exposed workers. Blood Mn concentration correlated with pallidal index. These changes in MRI tend to disappear following the withdrawal from the source of Mn accumulation, despite permanent neurological damage. Thus increased signal intensities on a T1-weighted image reflect exposure to Mn, but not necessarily manganism. Our study also showed that the concentration of Mn required to produce increased signal intensities on MRI is much lower than the threshold necessary to result in overt clinical signs of manganism. Increased signal intensities in the globus pallidus were determined by manganese accumulation in the animal experiment. Reanalysis of the previous data with the structural equation model revealed that pallidal index (PI) on MRI reflects target organ dose of occupational Mn exposure

Introduction

Several valuable studies (Kim et al., 1999a; b; c; 2002; Park et al., 2003; Ahn et al, 2003) have been published on the relation of manganese (Mn) exposure with high signal intensities on T1-weighted brain magnetic resonance images (MRI) in Korea since the detection of high signals in Korean welders exposed to Mn in 1997. However, the fact that high signal intensities on T1-weighted MRI can be a useful biomarker of exposure to Mn was relatively unknown in the field of occupational health. The objectives of the present paper are 1) to review the history and the present issue of the research on the high signals on T1-weighted MRI as a biomarker of Mn, and thus 2) to contribute to improving the human health risk assessments of Mn exposure.

Mn causes the shortening of T1-relaxation time and an increase in signal intensity on T1

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weighted MRI. Because of the paramagnetic quality of Mn, the bilateral symmetrical increase in signal intensities, confined to the globus pallidus and midbrain, can be observed on T1-weighted MRI, but with no alteration on the T2 weighted image. However, Mn induced high signals in T1-weighted MRI do not show any abnormal findings in brain computed tomography (CT) (Ahn et al., 2003). The increased signal in T1-weighted images was observed in the experimental Mn poisoning of the non-human primate (Erikson et al., 1992). Nelson et al. (1993) also reported increased signal intensities in a patient with Mn neurointoxication. The Mn-induced high signals in MRI usually disappear within six months or one year following the withdrawal from the source of Mn accumulation (Kim et al., 1999a; c). Furthermore, the characteristic high signals were reported to be also frequently observed in asymptomatic workers exposed to Mn (Kim et al., 1999b). A similar MRI pattern has been also observed in patients receiving total parenteral nutrition, because of excessive Mn intake (Mirowitz et al., 1991), and in patients with liver failure, due to their inability to clear Mn through biliary excretion (Butterworth et al., 1995; Park et al., 2003).

Signal intensities in T1-weighted MRI as a target site dose

The increased signal in T1-weighted images was observed in the experimental Mn poisoning of the non-human primate (Erikson et al., 1992) and a patient with Mn neurointoxication (Nelson et al., 1993). However, our study (1999b) showed for the first time that the characteristic high signals were also frequently observed in asymptomatic workers exposed to Mn. We showed that the increased signals in MRI were highly prevalent (41.6%) in Mn-exposed workers. Especially 73.5% of the welders showed increased signal intensities although none of the non-exposed clerical workers showed the increased signal. Blood Mn concentration correlated with pallidal index (PI) which was defined as the ratio of the signal intensity of globus pallidus to subcortical frontal white matter in axial T1-weighted MRI planes multiplied by 100 (γ=0.41). Blood Mn concentration also increased PI and exposed workers also had higher PI than non-exposed manual as well as clerical workers. These changes in MRI tend to disappear following the withdrawal from the source of Mn accumulation, despite permanent neurological damage (Kim et al., 1999). All these findings suggest that increased signal intensities on a T1-weighted image reflect exposure to Mn, but not necessarily manganism. Compatible with some experimental animal studies (Olanow et al., 1996; Shinotoh et al., 1995) our study showed that the concentration of Mn required to produce increased signal intensities on MRI is much lower than the threshold necessary to result in overt clinical signs of manganism (Kim et al., 1999b). Our reanalysis of the previous data with the structural equation model revealed that PI on MRI reflects target organ dose of occupational Mn exposure (Kim et al., 2005). Hence, signals intensities in T1-weighted MRI reflect a target site dose in a biologically-based dose-response model21).

Mn-induced high signals should be differentiated from high singnals due to others

Similar patterns of increased T1-weighted signal intensities can be associated with lipid (Markesberry et al., 1984), hemoglobin breakdown products (Gomori et al., 1985), melanoma (Gomori et al., 1986), neurofibromatosis (Mirowitz et al., 1989), and calcification (Dell et al.,

1988). However, iron deposits cause a more marked shortening of T2-relaxation time compared to T1-relaxation time, which results in a low signal intensity in the T2-weighted image, allowing clear distinction of iron and Mn deposits. Melanoma and neurofibromatosis can also be differentiated from Mn deposits from knowledge of the site and symmetry of the signals. The signal intensity of calcification can be shown as diminished, null effect, or increased in T1-weighted MRI (Dell et al., 1988; Holland et al., 1985). However, in all situations, the extent and degree of calcification are much clearer at brain CT (Norman et al., 1978). Calcification-induced signals therefore can be ruled out by normal CT findings (Ahn et al., 2003).

Diagnosis of manganism

The diagnosis of manganism in industrial workers can usually be made when an extrapyramidal symptom complex such as parkinsonism develops in workers exposed to Mn. Clinical features of manganism are, however, similar to those of idiopathic Parkinson disease (IPD). It may be difficult to distinguish manganism and IPD from each other. There are several clinical distinctions between the two clinical entities (Kim et al., 1999c; Calne et al., 1994). Lack of tremor as a predominant feature, early dystonia, postural impairment early in the course of the illness, peculiar walking, the so-called "cock walk", difficulty in backward walking, and the failure to have a response to levodopa therapy may help to differentiate manganism from IPD. Increased signal intensities on a T1-weighted image do not necessarily indicate manganism although they are very sensitive indicies of Mn exposure. Moreover, the Mn-induced high signals usually disappear within one year following the withdrawal from the source of Mn accumulation, despite permanent neurologic damage (Kim et al., 1999a). Hence, the findings of 18^{F}-6-fluorodopa positron emission tomography (PET) or dopamine transporter single -photon emission computed tomography (SPECT) should be provided in discriminating between IPD and manganism in addition to increased signal intensities on a T1-weighted MRI (Kim et al., 1999a; c; 2003).

Conclusion

Signals intensities in T1-weighted MRI reflect a target site dose of Mn.

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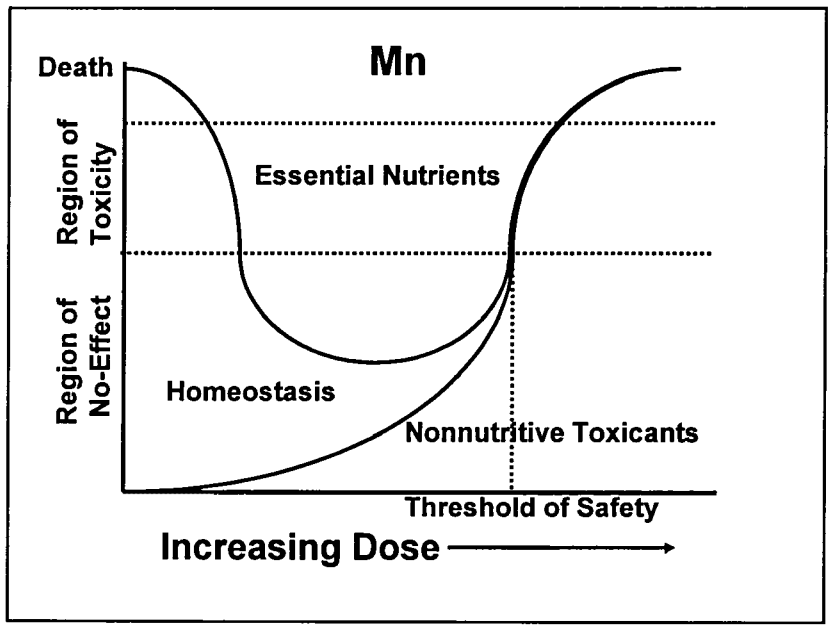

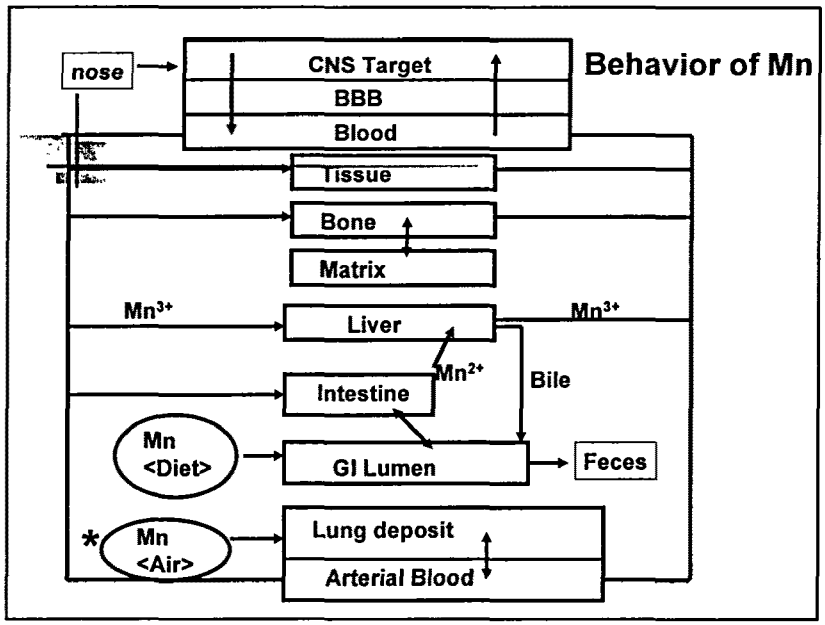
Behavior of Mn
nose
CNS Target
BBB
Blood
Tissue
Bone
Matrix
Liver
Intestine
Bile
Mn
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GI Lumen
Feces
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Mn
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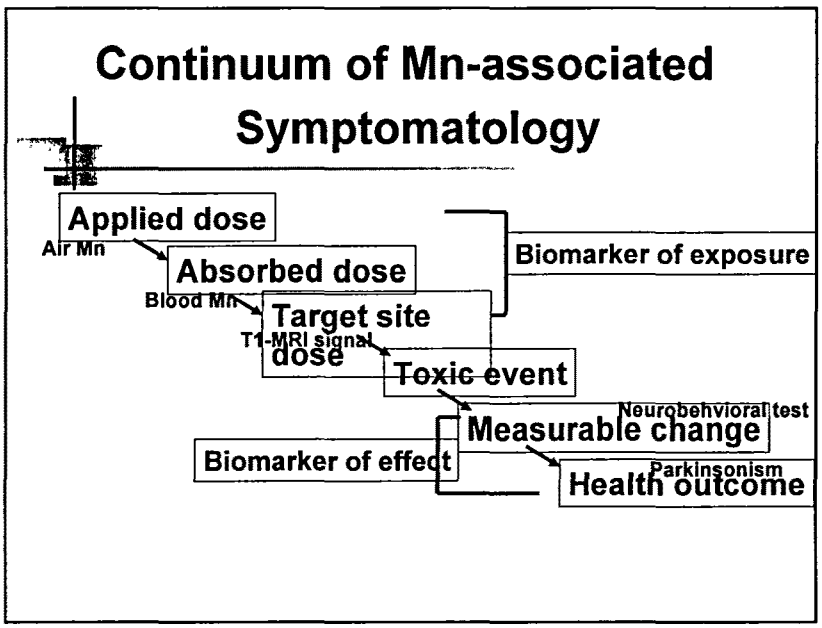
Lung deposit
Arterial Blood
Mn3+
Mn3+
Mn2+


Continuum of Mn-associated Symptomatology
Applied dose
Air Mn
Absorbed dose
Blood Mn
Target site dose
T1-MRI signal
Toxic event
Measurable change
Neurobehvioral test
Biomarker of effect
Health outcome
Parkinsonism
Biomarker of exposure

Paramagnetic qualities of manganese

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Shortening of T1 relaxation time

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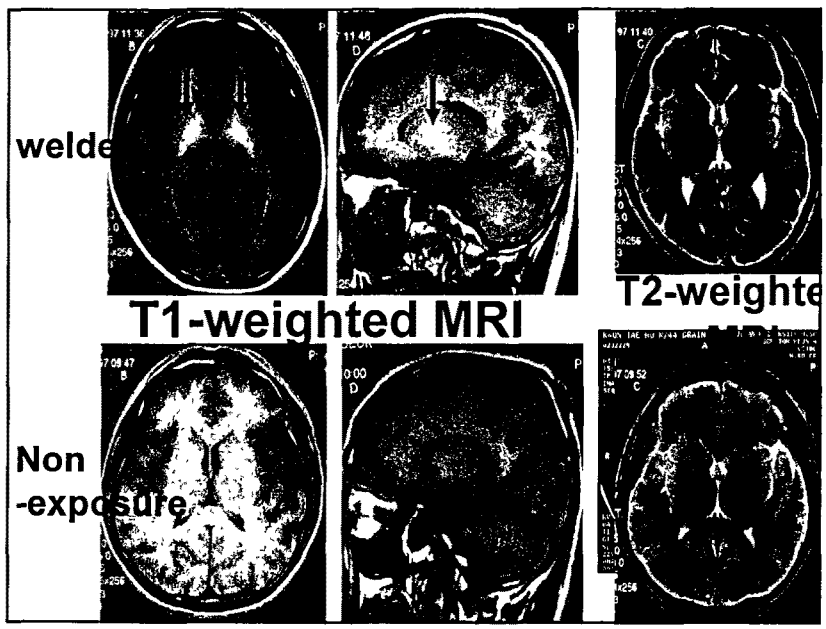
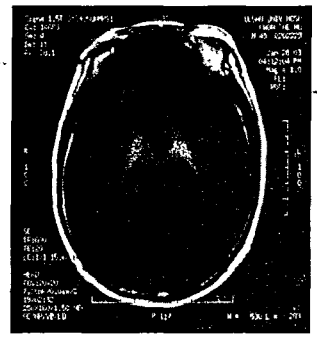
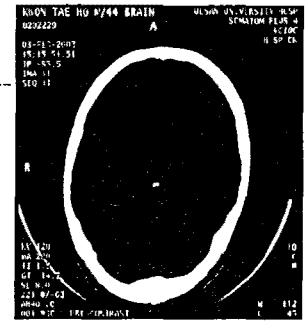
Increased signal intensities
in T1-weighted MRI



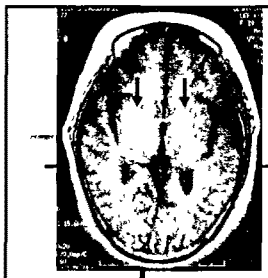




T1-weighted MRI CT (normal finding)

Other high signal on T1-Weighted MRI should be differentiated from Mn-induced high signals

- Fat
- Fe: low signal in T2-Weighted MRI
- Hemoglobin breakdown products: site and symmetricity
- Melanoma : site and symmetricity
- Neurofibromatosis : site and symmetricity
- Calcification: CT

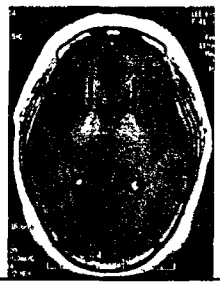


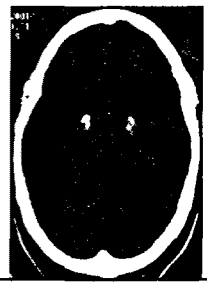
CALCIFICATION MIMICKING Mn-INDUCED INCREASED SIGNAL INTENSITIES IN T1-WEIGHTED MRI IN A PATIENT TAKING HERBAL MEDICINE

Ahn et al. Neurotoxicology. 2003;24:835-8

1 year later

CT





Characteristic bilateral increase in the signal intensities, confined mainly to globus pallidus on T1-weighted MRI

- Experimental Mn poisoning of non-human primate (Newland et al., 1989)
- Mn poisoning case (Nelson et al., 1993)
- Prevalent in asymptomatic workers exposed to Mn (Kim et al., 1999)

Characteristic bilateral increase in the signal intensities, confined mainly to globus pallidus on T1-weighted MRI

- Total parenteral nutrition due to excessive intake
- Chronic liver disease due to impaired excretion via bile juice

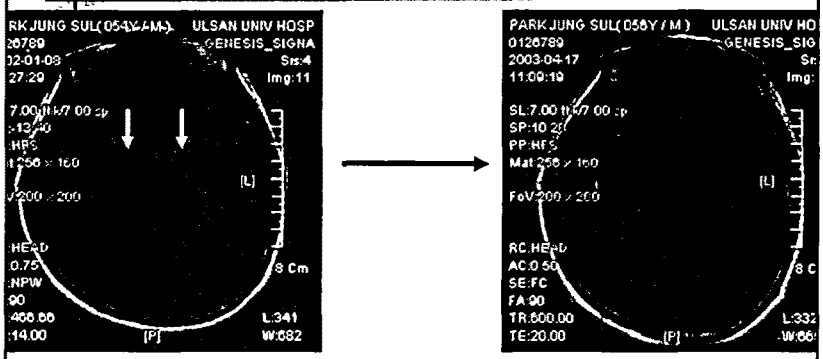
Whole blood manganese correlates with high signal intensities on T1-weighted MRI in patients with liver cirrhosis

Neurotoxicology Park et al. 2003:24:909-15

- High signals were in 27 (81.8%) of 33 patients with liver cirrhosis
- High signals correlate with severity of liver disease and total bilirubin level
- High signals correlate with whole blood Mn rather than plasm Mn

Whole blood and red blood cell manganese reflected signal intensities of T1-weighted MRI better than plasma manganese in liver cirrhotics

Choi et al. J Occup Health 2005;47:68-73



Liver transplanation

Blood manganese concentration increased markedly, however, the increase in the signal intensities in the globus pallidus is not remarkable in IDA

Yangho Kim et al.

Neurotoxicology 2005;26:107-111

Blood manganese concentration increased markedly, however, the increase in the signal intensities in the globus pallidus is not remarkable in IDA

- MnB is elevated in IDA patients
- Iron therapy resulted in increased hemoglobin levels and decreased MnB levels
- Globus pallidus MRI signal intensities are minimally affected
- This stands in contrast to patients suffering chronic liver disease or occupational Mn exposure, in which signal intensity is elevated remarkably

Increase in signal intensities on T1-weighted magnetic resonance images in asymptomatic manganese-exposed workers

Yangho Kim et al.

Neurotoxicology 1999;20:901-908

OBJECTIVES

Increased signal intensities in T1-weighted MRI

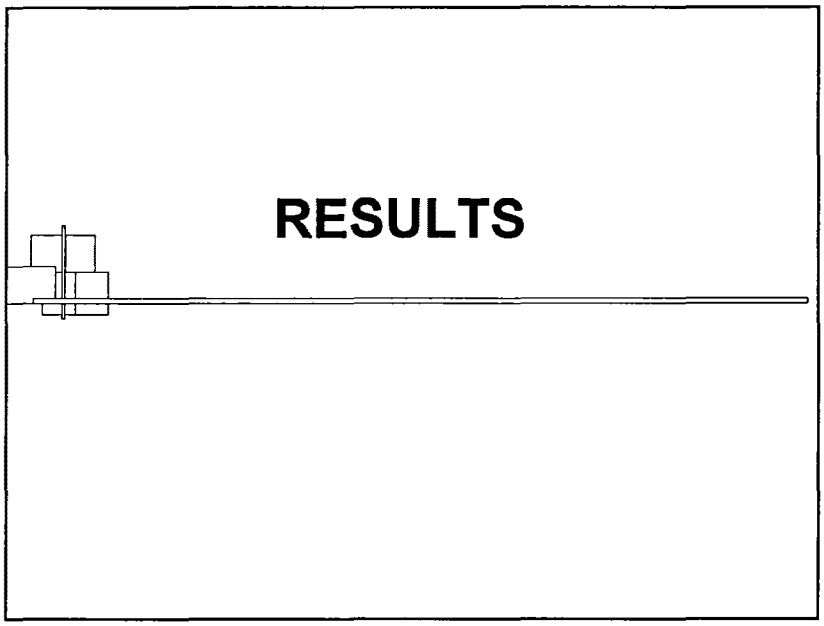
- *Appear in Mn-exposed workers only?*
- *How prevalent among exposed workers?*
- *Correlate with other Mn exposure indices?*
- *Workers with them show signs of manganism?*
- *Enhanced signals resolve after withdrawl of Mn?*

Type	Facil-ities	Exposed A	Exposed B	Exposed B/A	Manual Non-exposed A	Manual Non-exposed B	Manual Non-exposed B/A	Clerical Non-exposed A	Clerical Non-exposed B	Clerical Non-exposed B/A
Welding	1	46	8	17.4	18	3	16.7	8	0	0
	2	5	1	20.0	12	2	16.7	6	1	16.7
	3	26	3(1)	11.5	8	1(1)	12.5	5	1(1)	20.0
	4	48	4(2)	8.3	12	1	8.3	9	2	22.2
	5	66	6(1)	9.1	13	2	15.4	14	2	14.3
	6	89	16	18.0	3	1	33.3	15	3	20.0
Smelting	7	39	12	30.8	8	1	12.5	6	1	16.7
	8	70	20	28.6	18	4	22.2	11	2	18.2
	9	74	7	9.5	6	1	16.7	18	3(1)	16.7
Welding-rod	10	78	16	20.5	1	1	100	18	3	16.7
Total(n=750)		*541*	*93(4)*	*17.2*	*99*	*17(1)*	*17.2*	*110*	*18(2)*	*16.4*

A:Eligible Workers B:Selected Workers B/A:Selection Rate(%)

MRI

- Subjective evaluation
  - Signal intensity of the globus pallidus relative to frontal white matter graded into 3 categories
- Pallidal index (PI)
  - Ratio of the signal intensity of globus pallidus to subcortical frontal white matter in axial T1-weighted MRI planes multiplied by 100
- Regional distribution of increased signal intensities



Demographic, clinical and laboratory features

Group Characteristic	Exposed (n=89)	Manual Non-exposed (n=16)	Clerical Non-exposed (n=16)
Mean age (y)	43.3	42.3	40.4
Duration of employment (y)	15.3	13.9	14.5
Proportion of smoker (%)	70	56	50
Proportion of drinker (%)	72	56	75
Blood Mn level (μg/dl)	1.42(0.53)	1.17(0.37)	1.18(0.33)
No. of increased signal intensities [proportion]**	41[46.1%]	3[18.8%]	0[0%]
Pallidal indices*	107.7(6.5)	104.7(3.8)	103.1(2.8)
RBC (10^6 cells/μl)	4.97(3.88)	4.67(0.45)	4.84(0.27)
SGOT (IU/l)	30.4(14.5)	28.1(8.8)	28.8(15.4)
No. of workers with tremor	6	0	1

*p<0.05, **p<0.01, compared for non-exposed clerical workers

Exposure Evaluation

- Geometric mean and range (mg/m^3) of ambient Mn concentrations among the total exposed eligible workers
  - Welders : 0.53 (0.1-1.56, n=148)
  - Smelters : 0.14 (0.08-1.4, n=40)
  - Welding-rod manufacturing workers : 0.15 (0.02-0.42, n=17)

Increased Signals

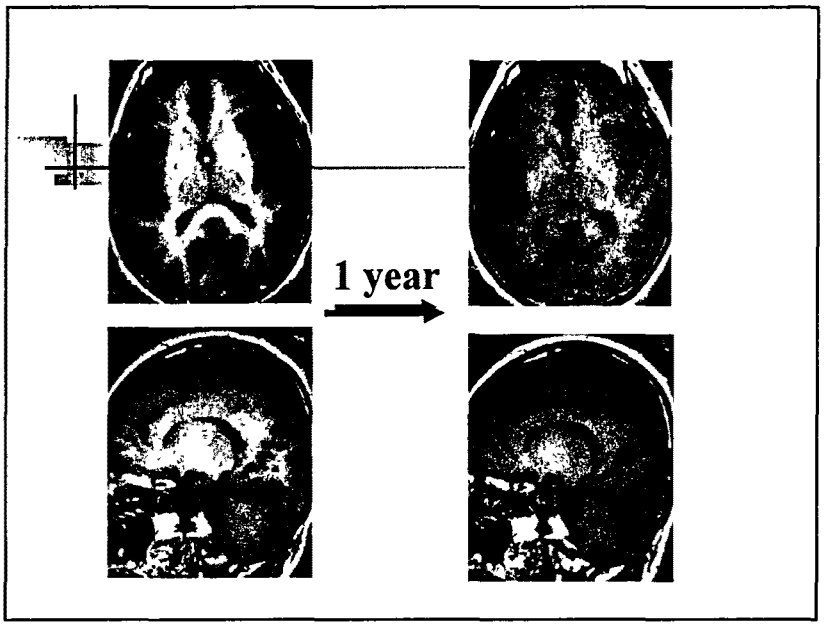
- Proportion of workers with increased signals in exposed groups
  - *Welders: 73.5%*
  - *Mn smelters: 41%*
  - *welding rod manufacturers: 0%*
- Regional distribution of increased signal
  - *globus pallidus : 100%*
  - *midbrain: 80%*
  - *pituitary gland: 43%*
  - *putamen: 16%*

Multiple regression analysis for PIs

Variables	b-coeff (95% CI)	P	R^2
Model 1 (with blood Mn concentration)		0.0001	0.22
Blood Mn concentration	6.06 (4.25 to 7.87)	0.0001	
Exposure duration	0.01 (-0.45 to 0.46)	0.92	
Age	0.11 (-0.39 to 0.62)	0.24	
Alcohol consumption	0.98 (-0.84 to 2.81)	0.43	
Smoking (pack-year)	0.01 (-0.39 to 0.42)	0.87	
Model 2 (with study groups)		0.0177	0.11
Exposed *v* non-exposed clerical workers	5.47 (3.16 to 7.79)	0.0068	
Exposed *v* non-exposed manual workers	3.94 (1.66 to 6.22)	0.0422	
Exposure duration	-0.11 (-0.63 to 0.42)	0.2971	
Age	0.15 (-0.34 to 0.64)	0.09	

Clinical Signs

- Isolated mild postural tremor in hand of some workers
  - essential tremor or enhanced physiological tremor
- Nor was the proportion of workers with the tremor significantly different among the three groups
- In no subject, clinical signs of manganism were observed



DISCUSSION

Increased Signal Intensities as Useful Biomarker of Mn

- Highly prevalent in asymptomatic workers
- Increased signals, confined mainly to globus pallidus as target organ of Mn
- Increased signals correlated with blood Mn
- Increased signals resolved within one year after withdrawal of Mn

Clinical Significance of Increased Signal in MRI

- Increased signals in MRI reflect target organ exposure to Mn, but not necessarily manganism
- Mn level required to produce enhanced signal is much lower than the threshold necessary to result in overt clinical signs of manganism

Further research issues

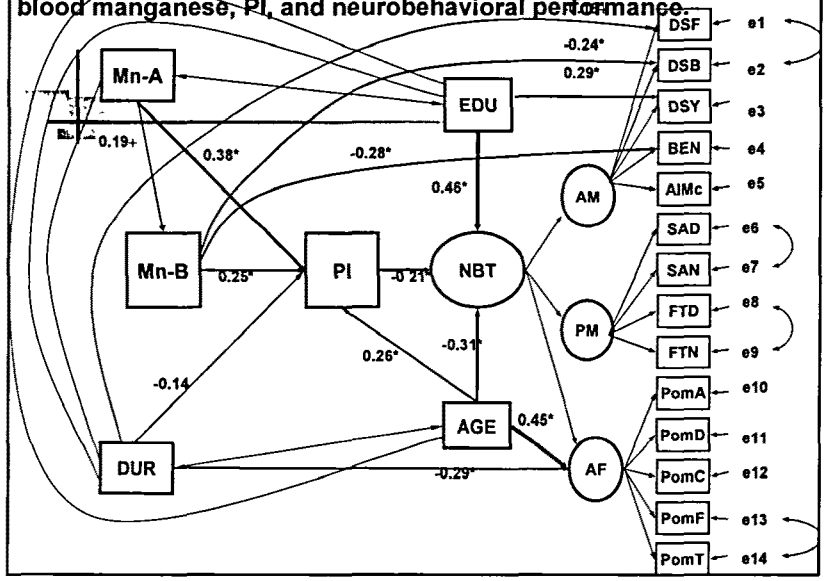
- At which increase of signal intensity the progression of manganism from Mn exposure occurs remains to be solved
  - Prospective studies on changes of high signal in Mn-exposed workers
- New biomarkers reflecting high signal in MRI should be developed
  - Which species of blood Mn is reflecting high signal

Pallidal index on MRI as a target organ dose of manganese: structural equation model analysis

Euna Kim et al.

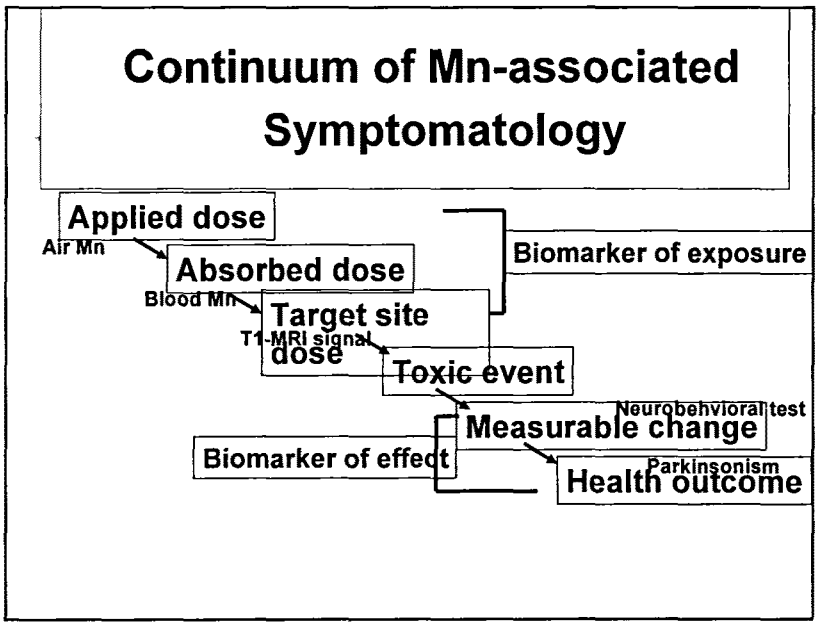
Neurotoxicology 2005 (in press)

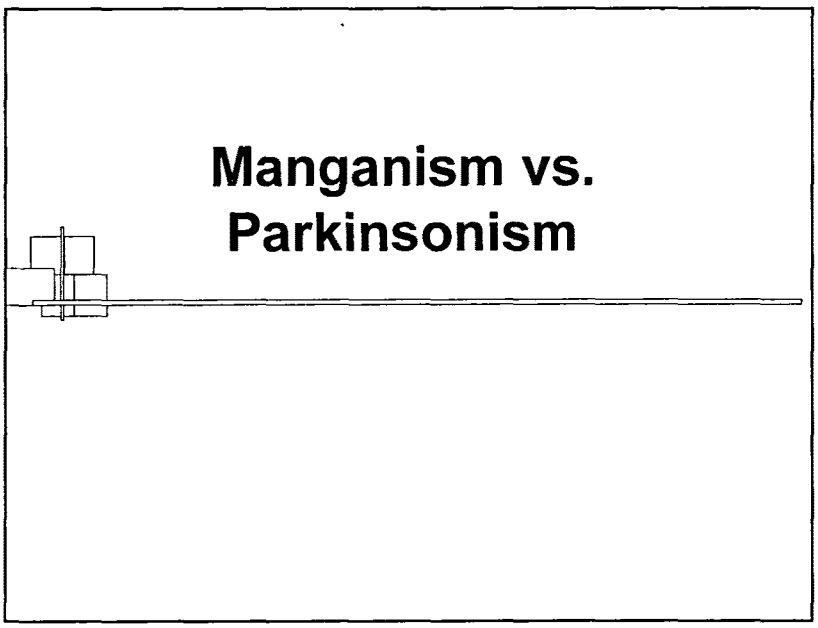
Fig Model of interrelationships among airborne manganese, blood manganese, PI, and neurobehavioral performance.



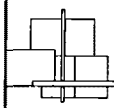
SEM: to assess the interrelationships among airborne manganese, blood manganese, MRI signal index, and neurobehavioral function

- Airborne manganese contributes to PI, which is the most effective predictor of neurobehavioral performance after adjusting for age and level of education
- Pallidal index on MRI as a target organ dose of manganese


Continuum of Mn-associated Symptomatology
Applied dose
Air Mn
Absorbed dose
Blood Mn
Target site dose
T1-MRI signal
Toxic event
Measurable change
Neurobehvioral test
Biomarker of effect
Health outcome
Parkinsonism
Biomarker of exposure


Manganism vs. Parkinsonism

Idiopathic parkinsonism with superimposed manganese exposure : utility of positron emission tomography
Kim et. al. Neurotoxicology 1999;20:249-52



Dopamine transporter density is decreased in parkinsonian patients with a history of manganese exposure; what does it mean?
Kim et. al. Mov Disord 2002;17:568-575

Similarities and differences between IPD and manganism have been recently discussed in some papers

- **The differential diagnosis is important from determining the plan of treatment and prognosis as well as medico-legal aspects regarding workers' compensation**
- **The differential diagnosis is also important for clarifying pathophysiology of manganism**

Manganism vs. Parkinsonism

- I'll present 4 cases of parkinsonism with concurrent Mn exposure
- discuss the value of ^{18}F-dopa (fluorodopa) positron emission tomography (PET) or (1r)-2β-carboxymethoxy-3β-(4-iodophenyl)tropane ([^{123}I]-ß-CIT) single photon emission computed tomography (SPECT) and MRI in differential diagnosis of manganism

Occupational Histories

	Age	Occupation	Mn exposure period
Case 1	52	Preparing of Mn powder by crushing ferromanganese	1984.11 - 1985.10
Case 2	49	Welder	1988.1 - 1996.10
Case 3	49	Welder	1991.1 - 1999.1
Case 4	56	Foundry worker	1970 - 1998.8

Occupational Hx & Lab findings

	Onset(Age)	Air Mn	Blood Mn
Case 1	1985.9 (39)	No data	No data
Case 2	1996.9 (47)	0.63 (0.34-0.86)	3.26
Case 3	1998.1 (48)	0.28 (0.02-2.70)	3.06
Case 4	1998.2 (55)	0.007 (0.001-0.039)	1.41

Clinical features

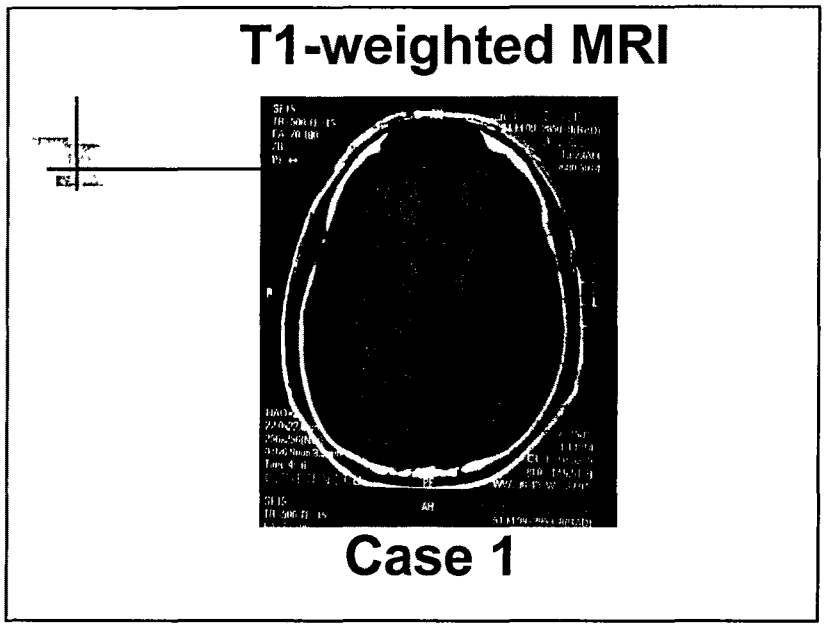
	Tremor, rigidity bradykinesia	Bilaterality	Gait disturbance	Dystonia
Case 1	+ resting < action	Rt > Lt	+	+
Case 2	+ resting > action	Rt only	-	-
Case 3	+ resting > action	Rt > Lt	-	-
Case 4	+ resting > action	Rt = Lt	-	-

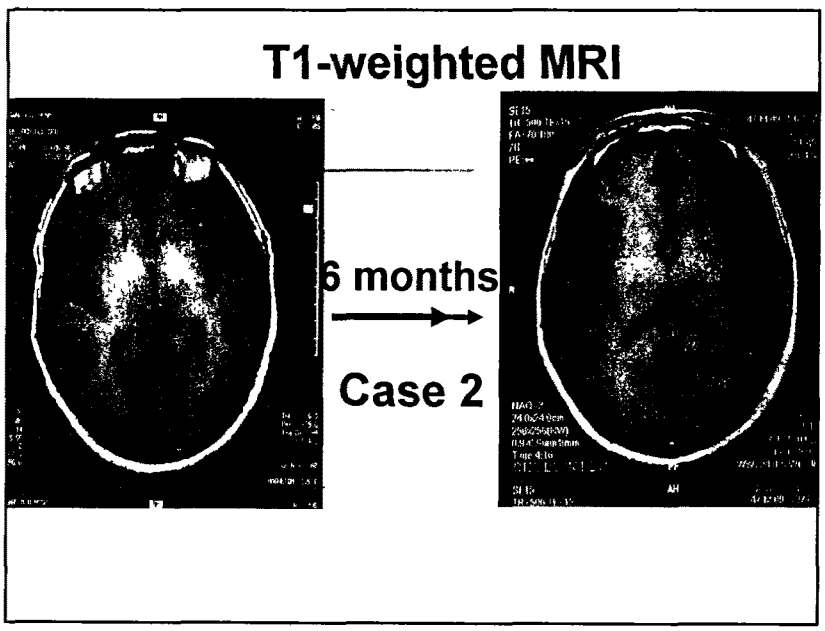
Clinical features

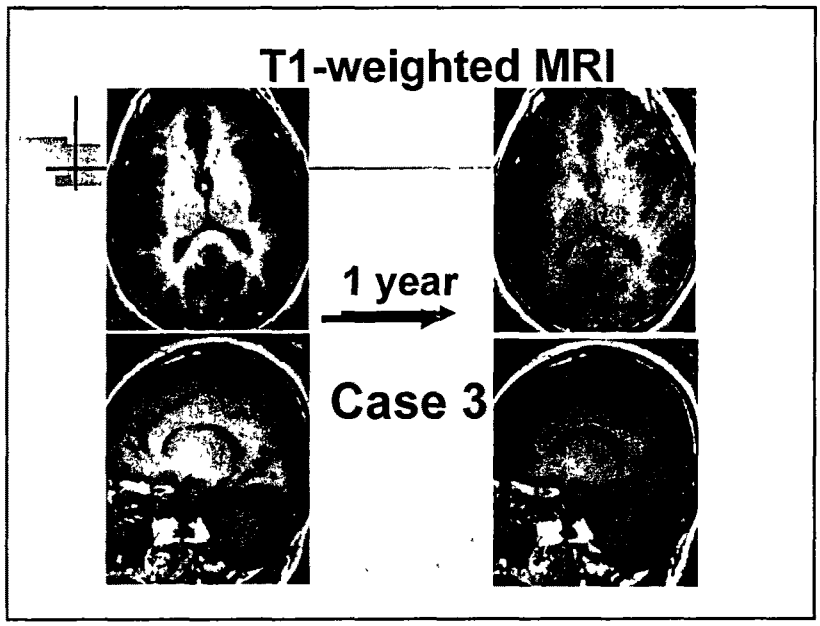
- The clinical signs in all cases were compatible with parkinsonism
- Typical neurologic features in case 1 suggest manganism
  - Severe postural instability
  - A particular propensity to fall in backward gait
  - Cock walk
  - Dystonia

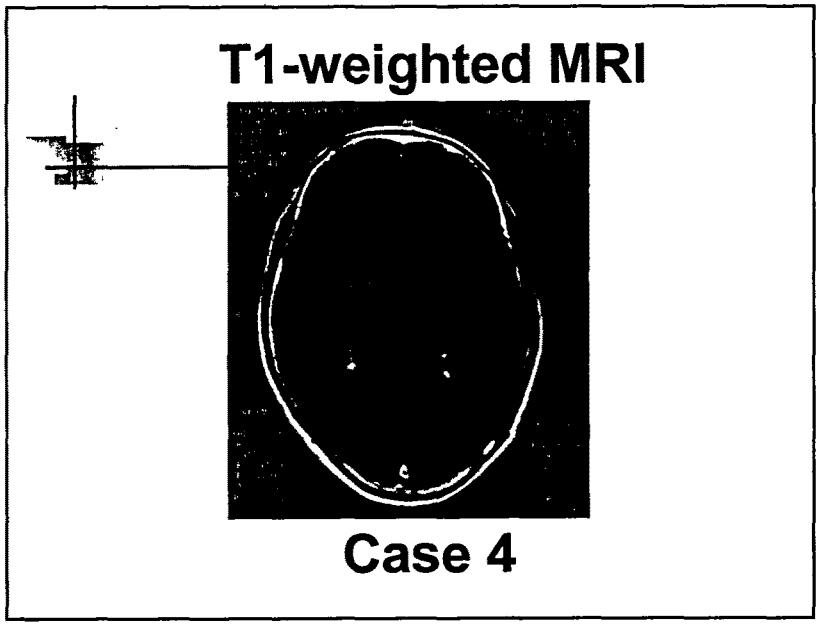
Clinical features

- The clinical signs in 3 cases (case 2,3,4) were compatible with IPD although it is somewhat difficult to make the final diagnosis with clinical signs only
  - Predominantly resting tremor,
  - Favorable response to levodopa,
  - Lack of typical neurologic features as severe postural instability, a particular propensity to fall in backward gait, the so-called cock walk, and dystonia


T1-weighted MRI
Case 1


T1-weighted MRI
6 months
Case 2


T1-weighted MRI
1 year
Case 3


T1-weighted MRI
Case 4

Increased signal (MRI)

Case 1 - : 12 yr after cessation

Case 2 + , - : 6 month after cessation

Case 3 + , - : 1 yr after cessation

Case 4 - : 3 month after cessation

PET

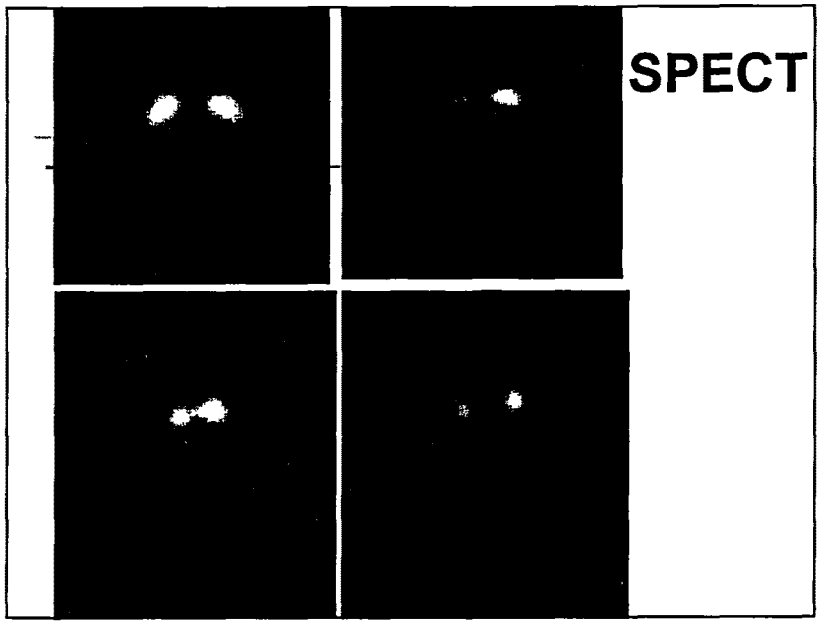
Normal Case 1 Case 2

Fluorodopa PET in IPD

- Fluorodopa PET provides an index of the integrity of the dopaminergic nigrostriatal pathway, the primary focus of neurodegeneration in IPD where it is abnormal
- There is reduced uptake in the striatum, particularly the posterior putamen
- This finding is in accord with the knowledge that there is a 40 to 60% loss of dopaminergic cells in the nigrostriatal pathway

Fluorodopa PET in manganism

- In nonhuman primates and humans that had been intoxicated with Mn, the fluorodopa PET scan was normal
- This suggests that the nigrostriatal pathway is relatively preserved in manganism and is consistent with pathological observations noting that damage induced by Mn occurs primarily in pathways postsynaptic to the nigrostriatal system



[^{123}I]-β-CIT SPECT (1)

- While fluorodopa PET is not available in many medical facilities, [^{123}I]-ß-CIT SPECT is more easily accessible
- Dopamine transporter imaging with β-CIT as a SPECT ligand shows the density of dopamine transporters, and therefore examines the nigrostriatal dopaminergic integrity

[^{123}I]-β-CIT SPECT (2)

- In IPD, [^{123}I]-β-CIT SPECT shows that the specific striatal β-CIT uptake is reduced
- In manganism, [^{123}I]-β-CIT uptake is expected to be normal in manganism

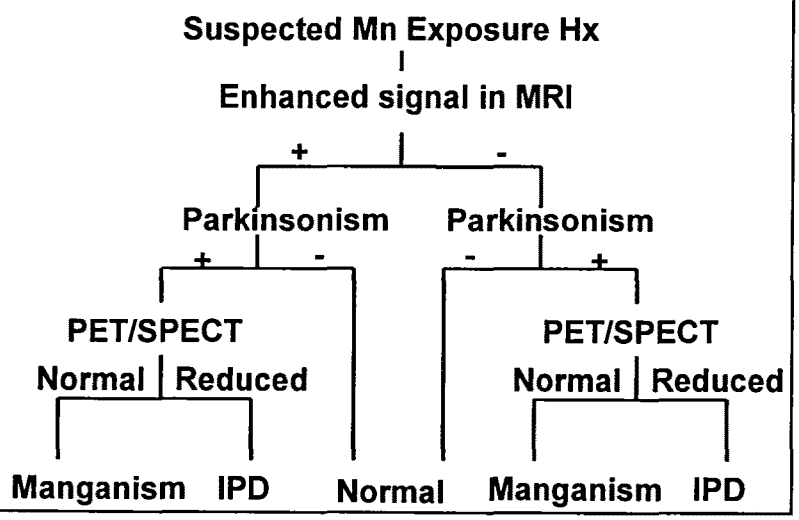
Summary

- Reduced β-CIT uptake on SPECT or reduced fluorodopa uptake on PET further supported the clinical diagnosis of IPD in case 2, 3, 4
- Hence 3 cases except case 1 would be IPD with superimposed Mn exposure

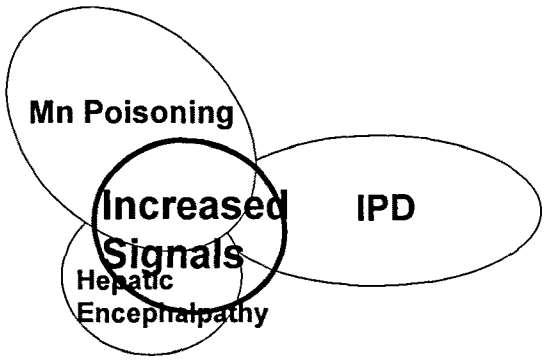
Similarities and differences

	IPD	Manganism
Rigidity / bradykinesia	+	+
Resting tremor	more frequent	less frequent
Backward gait difficulty	less frequent	more frequent
Dystonia	less frequent	more frequent
Mn exposure Hx	-/ +	+
MRI (high signal)	-/ +	+/-
Response to L-dopa	sustained	-
PET/SPECT	reduced uptake	normal
Nigrostriatal pathway	degeneration	intact

Implication of Enhanced signal in MRI

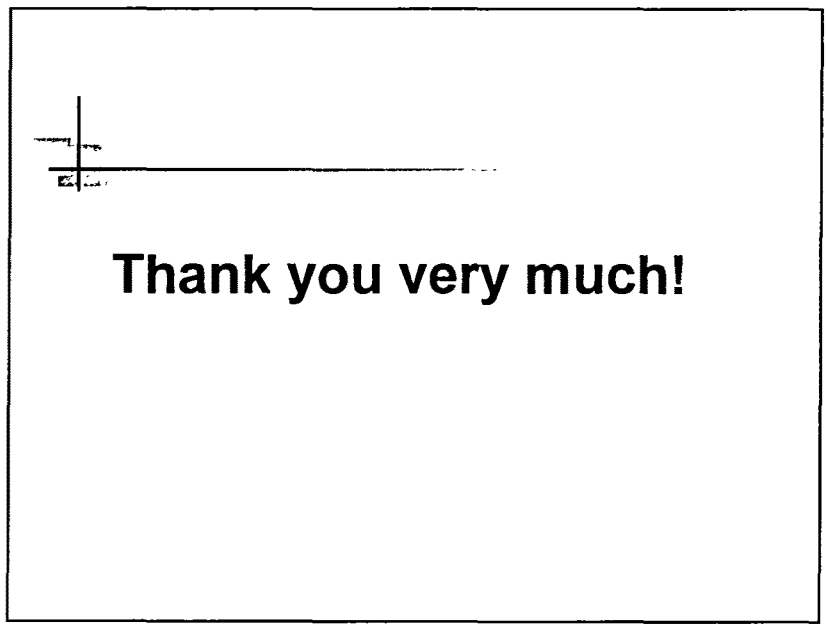


Clinical Significance of Increased Signal in MRI



FURTHER RESEARCH ISSUES

- Whether Mn exposure may act as a risk factor of IPD is controversial
- Human research on the minimum dose to bring about enhanced signals in MRI


Thank you very much!