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# Neuroimaging in Manganese-Induced Parkinsonism

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## 1. Introduction

Over the last 20 years, the impact of imaging on the clinical sciences has been immense. Tremendous progress has been made in medical imaging of the human body since the invention of computed tomography (CT) and magnetic resonance imaging (MRI). Neuroimaging of patients with metal neurotoxicity can be divided into two types: morphological neuroimaging (anatomy-based imaging) including CT and MRI; and functional neuroimaging (physiology-based imaging) such as magnetic resonance spectroscopy (MRS), single-photon emission computed tomography (SPECT), positron emission tomography (PET), diffusion tensor imaging (DTI), and functional MRI (fMRI). Neuroimaging is undergoing a shift from morphological to functional imaging as new technologies are introduced and technical problems associated with the local production of radioisotopes are solved (Lang, 2000; Walker et al., 2004). MRI, PET, and SPECT have been used for 10 years or more to evaluate workers exposed to manganese (Mn), and to examine the neurological consequences of such exposure. Very recently, functional neuroimaging modalities such as fMRI, MRS, and DTI have been applied to this end.

The objectives of this chapter are (1) to review the use of neuroimaging in Mn-induced parkinsonism, and (2) to discuss recent developments in the functional neuroimaging in Mn-induced parkinsonism.

## 2. The pallidal MRI T1-signal reflects the target organ dose of Mn exposure

The Mn ion ( $Mn^{2+}$ ) has five unpaired electrons in the 3d orbital, which results in a large magnetic moment, resulting in the shortening of proton T1-relaxation time and an increased signal intensity on T1-weighted MRI. Because of this paramagnetic quality of  $Mn^{2+}$ , a bilateral symmetrical increase in signal intensity, mainly confined to the globus pallidus and midbrain, can be observed on T1-weighted MRI, but with no concomitant alteration on the T2-weighted image (Kim et al., 1999a) (Fig. 1).

However, Mn-induced high signals on T1-weighted MRI do not correspond to any abnormal findings on brain CT (Park et al., 2003). The characteristic high signal caused by Mn can be differentiated from signals that increase in intensity for other reasons. Thus, high signals from fat, hemoglobin breakdown products, melanomas, neurofibromatosis, and

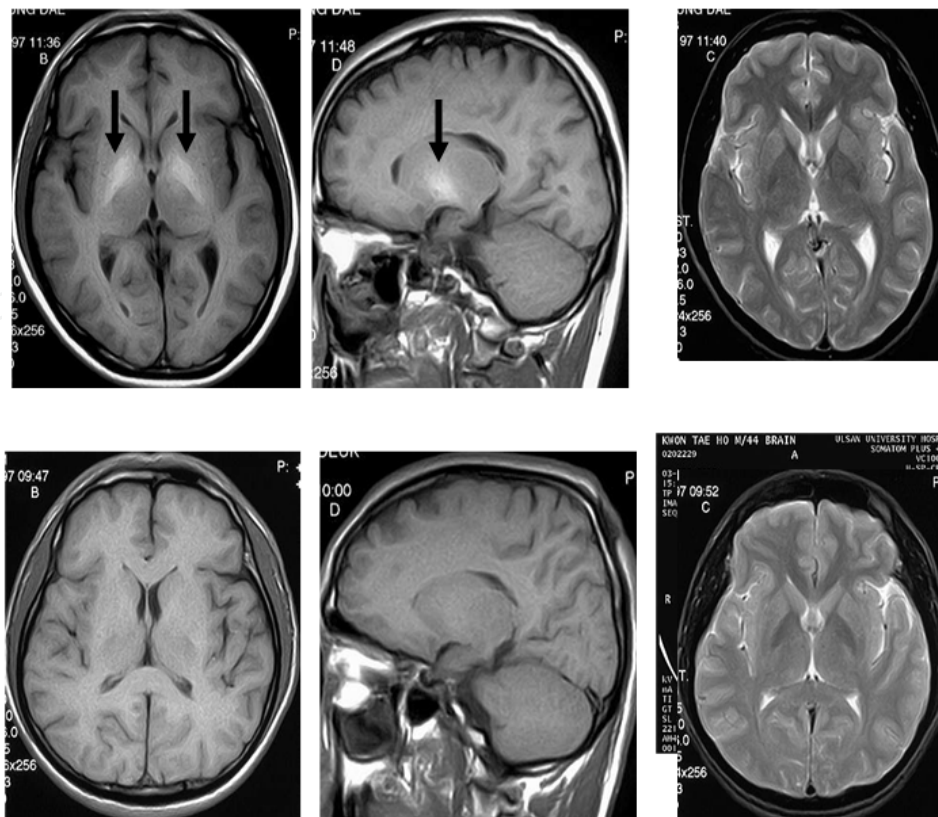


Fig. 1. T1-weighted MRI scans with or without increased signal intensities. Axial and sagittal sections show increase in signal intensities mainly confined to the globus pallidus, but with no concomitant alteration on T2-weighted image in workers exposed to manganese (Mn) in the upper row. In the lower row, worker without Mn exposure does not show increased signal intensities (Arrow indicates high signal. Left and middle column: T1-weighted image; right column: T2-weighted image).

calcification, can be seen on T1-weighted images. High signals from hemoglobin breakdown products, melanomas, and neurofibromatosis can be differentiated from Mn-induced high signals on the basis of signal site and symmetry. Iron deposits cause a greater shortening of the T2-relaxation time than the T1-relaxation time, resulting in low signal intensity upon T2-weighted imaging, distinct from that of an Mn deposit. Calcification can be easily identified by CT (Ahn et al., 2003). Krieger et al. (1995) coined the term “pallidus index” (PI) to quantify Mn accumulation in the globus pallidus, defined as the ratio of the signal intensity in the globus pallidus to that in the subcortical frontal white matter (WM) in axial T1-weighted MRI planes, multiplied by 100. An increase in signal upon T1-weighted imaging was observed during experimental Mn poisoning of non-human primates (Erikson et al., 1992; Newland et al., 1989). Nelson et al. (1993) were the first to report increased signal intensities in a patient with occupational Mn neurotoxication. A similar MRI pattern has also been observed in patients receiving total parenteral nutrition (TPN) by direct intravenous administration (Ejima et al., 1992; Mirowitz et al., 1991) and in patients with portal systemic shunts such as individuals with liver cirrhosis, leading to an inability to clear Mn via biliary excretion (Butterworth et al., 1995; Hauser et al., 1994, 1996; Krieger et al., 1995; Park et al., 2003; Spahr et al., 1996). A high pallidal signal is very frequently observed in patients with established liver cirrhosis, but who lack exposure to Mn (Park et

al., 2003). Mn-induced high signals can occasionally be observed in patients with severe iron-deficiency anemia (Kim et al., 2005). Kim et al. (1999a) showed, for the first time, that the characteristic high T1 signals were also frequently observed in asymptomatic workers exposed to Mn. The cited authors found a high prevalence (41.6%) of increased MRI signals in Mn-exposed workers, and, interestingly, 73.5% of welders showed increased signal intensities compared to none of the non-exposed clerical workers in the same factories. The cited authors found that the increased signal intensities resolved significantly approximately 1 year after Mn exposure ceased (Kim et al., 1999b). The disappearance of high signal abnormalities on MRI following withdrawal of the Mn source has been shown after the cessation of occupational exposure (Nelson et al., 1993), after discontinuation of TPN (Mirowitz et al., 1991), and after liver transplantation in patients with hepatic failure (Choi et al., 2005; Pujol et al., 1993). These findings suggest that increased signal intensities on a T1-weighted image reflect exposure to Mn, but do not necessarily indicate the presence of manganism. This is very important when the similarities and differences between idiopathic Parkinson's disease (IPD) and manganism are considered. Many reports have shown that blood Mn concentration is highly correlated with PI in liver cirrhotics (Hauser et al., 1996; Krieger et al., 1995; Spahr et al., 1996). In Mn-exposed workers, blood Mn concentration was also found to correlate with PI (Chang et al., 2009a; Dietz et al., 1999; Jiang et al., 2007; Kim et al., 1999a).

A recent study showed that PI was significantly associated with digit symbol test results, digit span backward ratings, scores on the Stroop Word and Stroop Error indices, and Grooved Pegboard (dominant hand) data (Chang et al., 2009a). This means that PI is a good predictor of neurobehavioral performance in welders without clinical manganism. In particular, PI was a better predictor of neurobehavioral performance than was blood Mn levels in such welders.

Taken together, the data suggest that PI on MRI may reflect a target organ dose of occupational Mn exposure (Kim, 2006). In addition, Mn in brain has a longer half-life than in blood (Lucchini and Kim, 2009). Thus, PI reflects the cumulative dose better than does blood Mn level. However, the level of signal intensity indicating progression to manganism from Mn exposure remains to be determined. The development of an animal model of manganism would assist in this regard, but the fact that the routes of exposure in humans differ, and that data on non-human species may not be transferable to human situations, are limiting factors. Hence, a prospective study correlating increases in T1 signal intensities with clinical and neuropsychological findings in Mn-exposed workers is needed.

### **3. PET/SPECT as an index of the integrity of the dopaminergic nigrostriatal pathway**

The dopaminergic nigrostriatal pathway is the primary focus of neurodegeneration in IPD (Brooks et al., 1990; Morrish et al., 1995, 1996). In IPD, dopamine uptake is reduced in the striatum, particularly the posterior putamen. This finding is in accord with the 40-60% loss of dopaminergic cells seen in the nigrostriatal pathway of patients with IPD. In non-human primates and humans intoxicated with Mn, [<sup>18</sup>F]-dopa (fluorodopa) PET scans are normal (Erikson et al., 1992; Kim et al., 1998; Shinotoh et al., 1995, 1997; Wolters et al., 1989). This supports the view that, in instances of Mn intoxication, the nigrostriatal pathway is relatively well preserved, consistent with many pathological observations showing that Mn-

induced damage occurs primarily in pathways postsynaptic to the nigrostriatal system. Dopamine transporter (DAT) imaging using (1r)-2b-carboxymethoxy-3b-(4-iodophenyl)tropine ( $\beta$ -CIT), employed as a SPECT ligand, reveals the density of DAT, and therefore explores the integrity of the nigrostriatal dopaminergic system. DAT is a protein located in the presynaptic nerve terminals of this system.  $\beta$ -CIT binds to DAT with high affinity and a low level of nonspecificity (Laruelle et al., 1993). In IPD, [ $^{123}\text{I}$ ]- $\beta$ -CIT SPECT reveals that specific striatal  $\beta$ -CIT uptake is reduced (Seibyl et al., 1995). Earlier data showed that this method can distinguish IPD patients from normal controls (Jeon et al., 1998a, 1998b). Further, striatal DAT uptake is nearly normal in patients with Mn-induced parkinsonism, but is markedly reduced in IPD patients (Huang et al., 2003). Various ligands that bind to DAT, such as [ $^{123}\text{I}$ ]- $\beta$ -CIT, [ $^{123}\text{I}$ ]-fluoropropyl-CIT, and [ $^{99\text{m}}\text{Tc}$ ]-TRODAT-1 have been used in SPECT studies (Huang et al., 2003; Kim et al., 2002). DAT SPECT is more easily accessible and less expensive than is fluorodopa PET. Fluorodopa and DAT uptake values are (nearly) normal in patients with manganism (Huang et al., 2003; Kim et al., 1998; Shinotoh et al., 1997; Wolters et al., 1989), whereas uptake is markedly reduced in IPD patients. However, Guilarte et al. (2008) reported that, in the non-human primate brain, chronic Mn exposure inhibited dopaminergic transmission, leading to motor deficits, in the absence of changes to presynaptic dopaminergic nerve terminals.

Racette et al. (2005) found relatively symmetrical and severely reduced fluorodopa uptake on PET in the posterior putamen of a patient with manganism secondary to liver failure, together with T1 hyperintensities in the basal ganglia on MRI. This is the only reported case of secondary manganism accompanied by abnormal fluorodopa PET findings. However, SPECT data from our secondary manganism patients (Kim et al., 2010) revealed two different patterns of clinical and neuroradiological features. Four of five patients showed atypical parkinsonism, with normal DAT density, which could be clearly differentiated from PD, whereas one patient showed levodopa-responsive parkinsonism with reduced DAT density (classical PD). These findings are remarkably different from those of Racette et al. (2005). PET/SPECT findings in patients with manganism caused by liver failure should be further studied, with respect to both clinical and pathological features. Further, the pathogenesis, clinical characteristics, and neuroimaging might differ between patients with primary and secondary manganism. Liver cirrhosis might confound the symptoms and accelerate the signs of parkinsonism. It is unclear whether secondary manganism caused by liver cirrhosis, for example, differs (from a neuroimaging standpoint) from manganism associated with occupational or environmental exposure to Mn.

Some welders showed clinical features and PET/SPECT findings typical of IPD, with concurrent Mn exposure (Kim et al., 1999b, 2002; Racette et al., 2001). Initially, Kim et al. (1999b) reported that one welder showed IPD with incidental exposure to Mn. However, they subsequently developed the hypothesis that Mn might have been a risk factor for development of IPD, although they could not exclude the possibility that the patient simply suffered from IPD, with coincidental exposure to Mn (Kim et al., 2002). Racette et al. (2001) suggested that welding might be a possible risk factor for development of early-onset IPD. However, it remains unclear whether Mn causes or accelerates IPD. The link between Mn exposure and an increased risk of IPD should be further examined in clinical, pathological, and epidemiological studies focusing on PET/SPECT findings.

Neuroimaging modalities such as MRI and PET/SPECT may be useful for the differential diagnosis of parkinsonism (Calne et al., 1994; Kim, 2006) (Fig. 2).

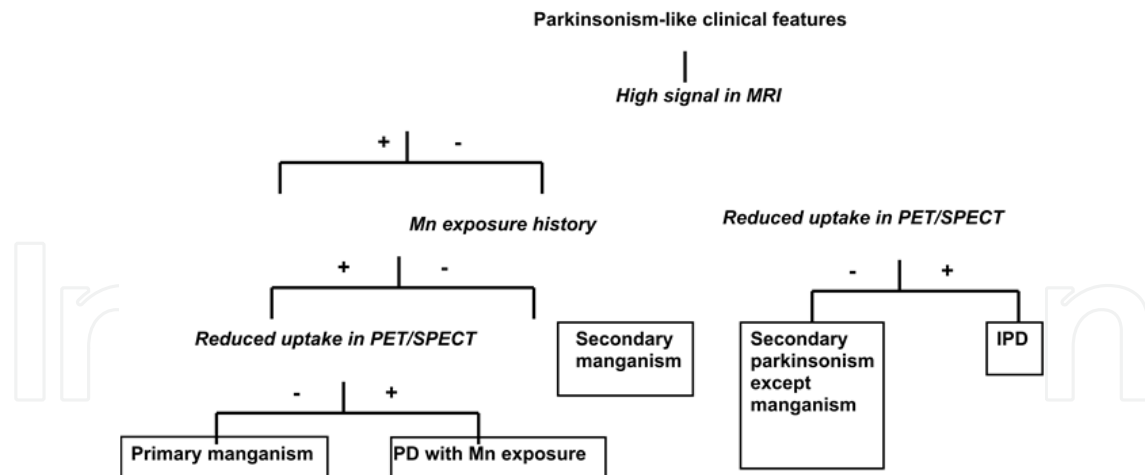


Fig. 2. Differential diagnosis of manganese from parkinson's disease (Kim, 2006)

When a patient exhibits parkinsonian features, MRI is recommended. Observation of bilateral symmetrical increases in signal intensities, mainly confined to the globus pallidus on T1-weighted MRI, in a patient confirms recent CNS exposure to Mn. It should be noted that a negative MRI signal can occur when worker exposure to Mn ceased more than 6–12 months prior to testing. When a patient with a high T1 signal and an Mn exposure history also shows normal uptake by PET/SPECT, primary manganese should be highly suspected. If a patient who has a high T1 signal and an Mn exposure history also shows reduced uptake upon PET/SPECT, the patient should be categorized as suffering from IPD with coincidental Mn exposure. When a patient yielding a high T1 signal upon MRI does not have an Mn exposure history, but shows normal uptake upon PET/SPECT, he/she may be diagnosed with secondary manganese attributable to liver cirrhosis or TPN. If a patient without a high T1 signal shows reduced uptake on PET/SPECT, he/she could possibly have IPD. When a patient without a high T1 signal on MRI shows normal uptake on PET/SPECT, he/she would be under suspicion of a form of secondary parkinsonism other than manganese (Kim 2006). However, neuroimaging should be combined with clinical evaluation for the differential diagnosis of parkinsonism (Ravina et al., 2005).

#### 4. Recent developments in functional neuroimaging in Mn-induced parkinsonism

##### 4.1 MRS

In vivo proton magnetic resonance spectroscopy ( $[^1\text{H}]\text{-MRS}$ ) is an image-guided, noninvasive method for monitoring of neurochemical metabolites in the brain (Rosen and Lenkinski, 2007). Currently,  $[^1\text{H}]\text{-MRS}$  is the biomedical technique that is most commonly employed to obtain metabolic information to aid in the diagnosis of many neurological diseases, and also allows disease progression to be followed and response to treatment to be evaluated (Ross et al., 2006). Although MRS permits noninvasive, in vivo measurement of brain metabolites, only a few MRS investigations have been performed to date in efforts to assess the neurological effects of heavy metals in the environmental or occupational health. Recently, a few reports have analyzed the impact of lead exposure on brain metabolism in vivo in adults and children (Meng et al., 2005; Trope et al., 2001; Weisskopf, 2007; Weisskopf et al., 2007). However, little is known about the effects of chronic Mn exposure on brain metabolites in vivo. Two reports employed MRS to investigate the potential neurotoxic effects of chronic Mn exposure on the

brain (Guilarte et al., 2006; Kim et al., 2007). Guilarte et al. (2006) assessed the toxic effects of chronic Mn exposure on the levels of brain metabolites in non-human primates. This [<sup>1</sup>H]-MRS study found a decrease in the N-acetylaspartate/creatine (NAA/Cr) ratio in the parietal cortex and frontal WM at the end of the period of exposure to Mn, relative to baseline, indicating ongoing neuronal degeneration or dysfunction. NAA is known to serve as a neuronal marker (Birken and Oldendorf, 1989). A reduction in NAA levels in the brain can be interpreted as indicating neuronal dysfunction or even neuronal loss (Vion-Dury et al., 1994). Kim et al. (2007) investigated the potential neurotoxic effects of chronic Mn exposure in welders. Using point-resolved spectroscopy (PRESS) at 1.5 T, the cited authors measured the NAA/Cr, choline/creatine (Cho/Cr), and NAA/Cho ratios in the basal ganglia, and found no significant differences between welders and control subjects.

In a recent study, Chang et al., (2009b) sought to determine whether metabolic differences existed between 35 welders chronically exposed to Mn and 20 healthy age-matched control individuals, by measuring brain metabolites using [<sup>1</sup>H]-MRS. MRI and *in vivo* single-voxel MRS were performed using the GE 3T MRI system (Signa Excite HD, General Electric Medical Systems, Milwaukee, WI) equipped with an eight-channel RF head coil. The MRS spectra of individual metabolites were analyzed using a Linear Combination Model (Provencher, 1993) running a Linux system. Five brain metabolites—NAA; the Glx complex, including both glutamine (Gln) and glutamate (Glu); total creatine (tCr); total choline (tCho); and myoinositol (mI)—were measured in the anterior cingulate cortex (ACC) and parietal WM. Further, the cited authors investigated correlations between neurochemical changes in the ACC of the brain and neurobehavioral alterations, to assess possible associations between chronic Mn exposure and cognitive deficits (Chang et al., 2009b). The means and standard deviations of blood Mn concentration in welders and controls were found to be  $1.53 \pm 0.42$  and  $1.06 \pm 0.29$   $\mu\text{g}/\text{dL}$ , respectively. The mean value of workplace Mn air concentrations was  $0.15 \text{ mg}/\text{m}^3$ . The welders had worked for  $21.3 \pm 7.2$  (mean  $\pm$  SD) years. All welders were shown to be devoid of clinical manganism, by neurological examination. This study on welders using proton-MRS showed that the NAA/tCr, Glx/tCr, and tCho/tCr ratios in both the ACC and parietal WM did not differ significantly between welders and controls. However, the mI levels in the ACC, but not in the parietal WM, were significantly lower in welders compared with control individuals. Further, in the frontal lobe of the brain, the mI/tCr ratio was significantly correlated with verbal memory scores as well as blood Mn concentrations. Kim et al. (2007) found no statistically significant differences in the levels of brain metabolites (NAA and Cho only were measured) between welders and controls. However, although the cited authors used a PRESS sequence with a short echo time, mI levels was not analyzed, unlike in the study of Chang et al. cited above. The results of the latter work agree with those of a previous study (Kim et al., 2007), but a direct comparison of mI levels is not possible. Guilarte et al. (2006) reported a decrease in NAA level in the parietal cortex and frontal WM of the brains of Mn-exposed monkeys. However, when the spectroscopic findings of the work of Chang (2009b) and that of Guilarte et al. (2006) are compared, it is important to consider methodological differences between a human and animal study. MI is known to serve as a cerebral osmoregulator (Strange et al., 1994), and hence may play a role as an intracellular osmolyte. Thus, mI depletion may reflect glial cell swelling associated with long-term exposure to Mn. Previous [<sup>1</sup>H]-MRS studies on the brains of cirrhotic patients with overt hepatic encephalopathy (HE) often found a large increase in Glx concentration, and depletion of mI, but no change in

NAA level, in the ACC and basal ganglia; these changes are considered to be typical metabolic abnormalities associated with HE (Geissler et al., 1997; Laubenberger et al., 1997; Weissenborn & Kolbe, 1998). In the early stages of HE, spectral alterations in mI and/or choline levels have been observed, but without corresponding increases in the Glx concentration (Kreis et al., 1992; Laubenberger et al., 1997; Miese et al., 2006; Naegele et al., 2000; Spahr et al., 2000). Compared with HE patients, welders did not show any abnormal change in Glx metabolism in a study by Chang et al. (2009b). The MRS results in welders are compatible with findings in patients in the early stages of HE. The cited study suggested that the depletion of mI in welders may reflect a possible glial cell effect rather than a neuronal effect, associated with long-term exposure to Mn. More recently, Dydak et al. (2011) used MRS to investigate brain metabolites in the globus pallidus, putamen, thalamus, and frontal cortex of 10 Mn-exposed smelters and 10 age- and gender-matched controls. Additionally, they used the MEGA-PRESS sequence to determine GABA levels in the thalamus. In addition to a significant decrease in the NAA/Cr ratio in the frontal cortex of exposed subjects, a significant increase in GABA level was observed in the thalamus, attributable to Mn exposure. The authors recommended that a combination of PI assessment and measurement of GABA level may provide a powerful, non-invasive biomarker of both Mn exposure and pre-symptomatic Mn neurotoxicity. Further studies using MRS are needed to identify brain metabolites in Mn-exposed workers.

#### 4.2 fMRI

The use of fMRI to study neurological diseases has become much more common over the last decade. However, employing fMRI to assess neurotoxicity in humans is a rather novel approach. Chang et al. (2010a) performed the first-ever fMRI experiment, using sequential finger-tapping, to investigate the behavioral significance of additionally recruited brain regions in welders who had experienced chronic Mn exposure. The study population consisted of 42 males, aged 40 years or older, who were current full-time welders, with more than 5 years of welding experience in a factory (Chang et al., 2010a). The control population consisted of 26 age- and gender-matched non-welding production workers from the same factory, who were not exposed to other hazardous materials such as paint. MRI examinations were performed using a 3.0 T whole-body scanner (Signa Excite HD), and blood oxygenation level-dependent (BOLD) contrast data were collected for each participant. T2\*-weighted echo planar imaging was used in fMRI acquisition. In the finger-tapping test, each participant was asked to place the thumb on the tip of the index finger, middle finger, ring finger, little finger, ring finger, middle finger, index finger and another finger, in that order, as quickly and precisely as possible. In the cited study, the mean and standard deviation of blood Mn concentrations in welders and control individuals were  $1.55 \pm 0.45$  and  $1.15 \pm 0.31$   $\mu\text{g}/\text{dL}$ , respectively. The mean workplace air Mn concentration was  $0.14 \text{ mg}/\text{m}^3$ . The welders had an average welding experience of 20.5 years. All welders were shown to be devoid of clinical manganism by neurological examination. Performance on the Grooved Pegboard and finger-tapping tests (right and left hand) were significantly lower among welders than controls. Maximum frequencies, as determined by evaluation of hand pronation/supination, and finger-tapping test results using CAT SYS 2000 (Danish Product Development), were significantly lower among welders than controls. No difference in the results of other rhythmic tests (slow/fast), again using CAT SYS 2000, was evident between the groups.



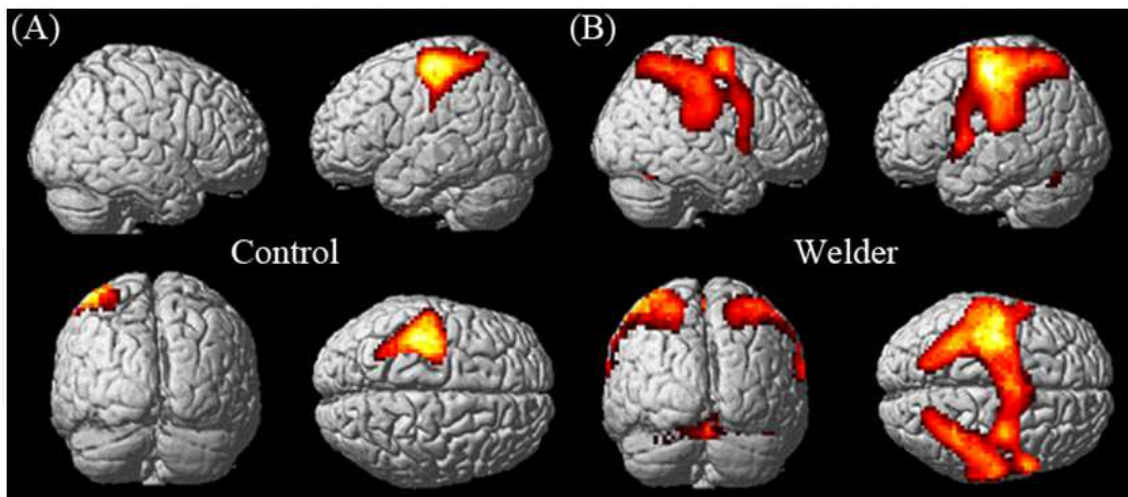


Fig. 3. Statistical parametric maps (SPM) of sequential finger tapping movement with right hand for control (A) and welder group (B) displayed on 3D SPM template brain. All activation voxels are significant at  $P < 0.00001$  FDR corrected for multiple comparison across whole brain. Chang et al. (2010a)

During finger-tapping tasks conducted on welders who were chronically exposed to Mn, significant activation foci were noted in the bilateral primary sensorimotor cortex (SM1), the bilateral supplementary motor area (SMA), the bilateral dorsolateral premotor cortex (dPMC), the bilateral superior parietal cortex, and the bilateral dentate nucleus, when data from movement and rest periods were compared. In contrast, control participants exhibited significant activation of the contralateral (left) SM1 (Fig. 3). Activation of the bilateral SM1, bilateral SMA, bilateral dPMC, bilateral superior parietal cortex, and ipsilateral dentate nucleus was higher in the welding group than in the control group. No region showed significantly more activation in controls compared to welders. PI correlated with activation observed in the contralateral SM1, in terms of finger-tapping test data from the left hand. The fMRI variables correlated with motor behavior. Grooved Pegboard performance (right hand) correlated with activation, as seen also in ipsilateral and contralateral SMA data obtained during finger-tapping with the right hand. Left-hand finger-tapping data collected during the first 10 sec of the task significantly correlated with activation of the ipsilateral and contralateral SMA when finger-tapping was evaluated on the left side. Bilateral SM1 hyperactivity may reflect motor re-organization in the brains of Mn-exposed welders, which might compensate for existing subclinical motor deficits. It seems likely that the mechanisms regulating sensorimotor control (i.e., systems operative from the basal ganglia output to the cortical sensorimotor regions, via the thalamus) may compensate for abnormalities in the basal ganglia and thereby prevent the appearance of symptoms in presymptomatic welders. In addition, hyperactivity of the SMA suggests that it is more difficult for welders (compared to controls) to perform a simple sequential finger-tapping task; thus, more SMA activity is recruited via the basal ganglia-thalamo-cortical loop, which allows for successful performance of the sequential finger-tapping task. However, these findings do not agree with those reported for patients with IPD. Functional neuroimaging of participants performing tasks requiring motor selection and initiation showed that the SMA was hypoactivated in patients with IPD, compared to normal participants (Sabatini et al., 2000). In summary, the collective findings suggest that, when relatively simple tasks are set, fMRI may uncover evidence of compromised brain functioning in patients with subclinical

manganism. The finding of excessive recruitment of the cortical motor network in chronically Mn-exposed group is in line with the emerging concept of use of adaptive neural mechanisms to compensate for latent dysfunction in the basal ganglia (Buhmann et al., 2005).

Chang et al. (2010b) also performed fMRI, combined with two-back memory tests, to assess the neural correlates of Mn-induced memory impairment in response to subclinical dysfunction in the working memory networks of welders exposed to Mn for extended periods of time. The study population consisted of 23 males, aged 40 years or older, who were current full-time welders with more than 5 years of welding experience in a factory. The control population consisted of 21 age- and gender-matched non-welding production workers from the same factory, who were not exposed to other hazardous materials such as paint. The MRI equipment and the fMRI protocol were identical to those used in the report on fMRI data obtained using the finger-tapping task (this work is summarized above). The working memory paradigm consisted of a two-back memory task combined with a “rest” control task. Stimuli were projected onto a viewing screen, attached within the bore of the scanner, and viewed at a distance of approximately 20 cm from the eyes of the participant, after reflection from two mirrors positioned on top of the head coil. In the cited study, Mn exposure status was similar to that of subjects recruited for the fMRI study that employed the finger-tapping task. All welders were shown to be devoid of clinical manganism, by neurological examination. Welders showed significantly lower performance on cognitive neurobehavioral tests, including the Korean Auditory Verbal Learning Test (K-AVLT) (i.e., delayed recall and recognition), the Korean Complex Figure Test (K-CFT) (i.e., copy,

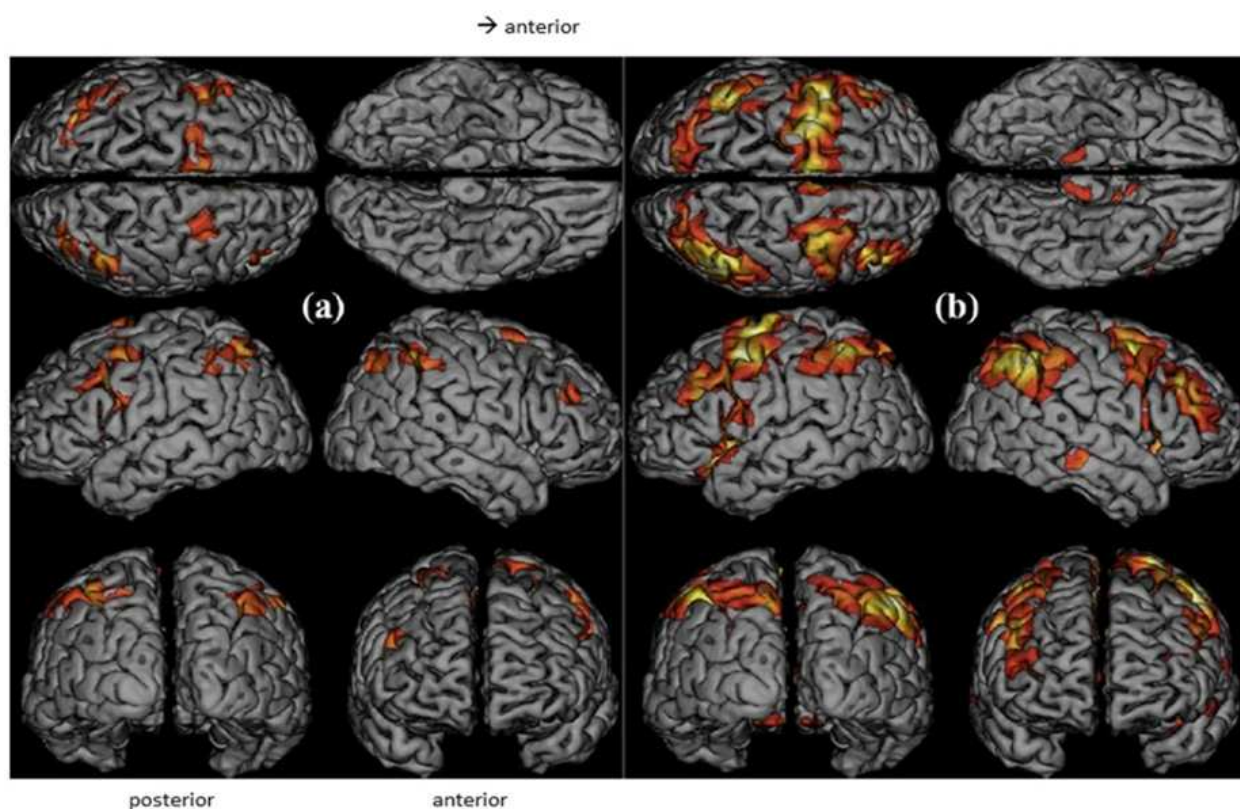


Fig. 4. The activations in fMRI with two-back memory tests from within group analysis in (a) controls and (b) welders ( $p < 0.05$ , FDR corrected for multiple comparison). Chang et al. (2010b)

immediate recall, and delayed recall), digit span tests (both forward and backward), and the Stroop tests, compared to controls. Chronic Mn exposure caused increased brain activity in working memory networks during the two-back verbal working memory task.

The cited authors observed activation of the inferior frontal cortex, the basal ganglia (including the putamen), and the bilateral cerebellum, as well as activation of the common memory-related network of frontal and parietal cortical areas including the premotor cortex, the middle frontal cortex, the inferior and superior frontal cortex, the inferior and superior parietal cortex, the precuneus, and the cuneus, in welders exposed to Mn (Fig. 4). Between-group analysis revealed increased brain activity in the left (contralateral) SM1, the right inferior parietal cortex, the anterior and posterior cingulate cortex, the bilateral inferior frontal cortex, and the basal ganglia of welders, compared to controls, during the memory task. No region was significantly more activated in controls compared to welders. After controlling for age and educational level, the percentage change in activation of the parietal cortex was associated with K-AVLT (i.e., delayed recall and recognition). The percentage change in activation of the inferior frontal cortex was significantly associated with scores on the Stroop color and error indices. The percentage change in activation of the ACC was significantly associated with K-AVLT (i.e., recognition) and digit span (i.e., forward) test results.

The basal ganglia-thalamo-cortical circuitry was originally viewed as almost exclusively involved in control of movement. However, these structures are now considered to be essential for non-motor function (DeLong & Wichmann, 2009). Considering that the basal ganglia are the brain regions that receive most Mn deposits, a speculative explanation of the higher basal ganglia activity in welders is that, if performance is to be matched to that of normal subjects, an increased recruitment of basal ganglia cells is required in welders to compensate for a diminished working memory capacity. Together, the fMRI findings indicate that welders might need to recruit more neural resources to the working memory network, to compensate for subtle working memory deficits and alterations in working memory processes, if they are to perform tasks at the same level as is possible by healthy control individuals.

#### 4.3 DTI

DTI is a unique method used to characterize WM micro-integrity, and relies on the principle that water diffusion is highly anisotropic in brain WM structures (Beaulieu, 2002). Thus, DTI reveals the orientation of WM tracts in vivo, and yields indices of microstructural integrity by quantification of the directionality of water diffusion (Le Bihan et al., 2001; Moseley et al., 1990). Although a few previous studies have explored the neurotoxicity associated with exposure to heavy metals such as Hg (Kinoshita et al., 1999) and Mn (McKinney et al., 2004) using diffusion-weighted image (DWI), no report on DTI-detected alteration of microscopic integrity within the WM of subjects experiencing chronic Mn exposure has appeared. Kim et al. (2011) used DTI to investigate whether welders exposed to Mn exhibited differences in WM integrity, compared to control subjects. MRI examinations were performed using a 3.0 T whole body scanner (Signa Excite HD). Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were measured on a voxel-wise basis in 30 male welders exposed to Mn and in 19 age- and gender-matched control subjects (Kim et al., 2011). In the cited study, the means and standard deviations of blood Mn concentration in welders and control individuals were  $1.52 \pm 0.47$   $\mu\text{g}/\text{dL}$  and  $1.17 \pm 0.33$   $\mu\text{g}/\text{dL}$ , respectively.

The mean workplace Mn air concentration was 0.15 mg/m<sup>3</sup>. The welders had an average welding experience of 20.6 years. All welders were shown to be devoid of clinical manganism by neurological examination. Welders showed significantly lower performances in all of the digit symbol, digit span, Stroop, Grooved Pegboard, and finger-tapping tests, compared to controls. Further, the results of the digit symbol, digit span, and Stroop tests were significantly associated with PI and blood Mn level after controlling for age, educational level, smoking status, and alcohol consumption. In addition, relationships between dependent measures and PI were stronger than those seen when blood Mn was used as an independent variable. Direct comparisons between welders and controls using investigator-independent Statistical Parametric Mapping (SPM) voxel-wise analysis of DTI metrics revealed a reduction in FA in the genu, body, and splenium of the corpus callosum (CC), and the frontal WM, in Mn-exposed welders. PI showed a statistically significant correlation with FA in the genu (left), body, and splenium of the CC. Blood Mn levels showed statistically significant correlations with FA in the genu (left) and body of the CC, and in the frontal WM. Further, marked increases in RD, but negligible changes in AD, were evident in the genu, body, and splenium of the CC, and the frontal WM. PI was significantly correlated with RD in the body of the CC. However, the blood Mn level did not show a statistically significant correlation with RD. All of these findings suggested that microstructural changes in the CC and the frontal WM result from a compromised radial directionality of fibers in such areas, primarily caused by demyelination. As the digit span (forward) test is more likely to measure attention and immediate recall, and the digit span (backward) test more specifically explores working memory, the statistically significant positive correlation between FA and digit span performance score (forward) suggests that the reduced FA in the frontal WM is in part responsible for the impaired attention of welders. The Stroop word and color/word tests are often used to measure executive function. Therefore, correlations between FA in the frontal WM, and the Stroop word and color/word test scores, suggest that poor performance on executive functioning, as measured using the Stroop word test (information processing) and the color/word test (executive function), are closely associated with lower FA values in the frontal WM.

In summary, correlation of DTI matrices with motor and cognitive neurobehavioral performance indices suggested that the observed microstructural abnormalities were associated with subtle motor and cognitive differences between welders and controls. This was the first study to use DTI to examine Mn-exposed workers (Kim et al., 2011). However, the functional significance of reduced frontal WM integrity evident in welders with chronic Mn exposure needs to be established in further work.

## 5. Conclusion

Neuroimaging is undergoing a shift from morphological to functional approaches as new technologies are gradually introduced. For morphological neuroimaging reflecting Mn exposure, PI on T1-weighted MRI data exploring target organ dosages of Mn reflects the cumulative Mn dose better than does assessment of blood Mn. For use in functional neuroimaging exploring Mn exposure, fluorodopa-PET/DAT SPECT serves as an index of the integrity of the dopaminergic nigrostriatal pathway, and is useful to differentiate between manganism and IPD. Recently, proton MRS has been used to identify brain metabolites in Mn-exposed workers. Chang et al. (1999b) suggested that subclinical neurologic effects attributable to long-term Mn exposure are associated with possible glial

cell effect rather than neuronal deficits. The use of fMRI, combined with motor tasks, has suggested that cortical hyperactivity may reflect motor re-organization in the brains of Mn-exposed welders, to compensate for subclinical motor deficits. When cognitive tasks are set, fMRI findings indicate that welders might need to recruit more neural resources to the working memory network to compensate for subtle subclinical working memory deficits. Therefore, fMRI is useful to detect subclinical cortical deficits in subjects who have experienced chronic exposure to Mn. DTI revealed microstructural deficits in WM integrity in welders exposed to Mn. Thus, functional neuroimaging can evaluate both subclinical WM integrity and cortical function in those exposed to Mn. Such neuroimaging combined with neurobehavioral performance evaluation shows promise in the elucidation of the pathophysiology of Mn neurotoxicity.

## 6. References

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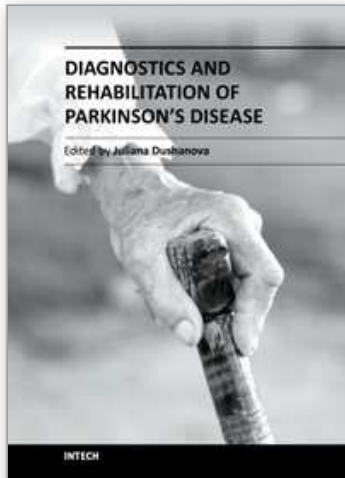


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## **Diagnostics and Rehabilitation of Parkinson's Disease**

Edited by Dr. Juliana Dushanova

ISBN 978-953-307-791-8

Hard cover, 528 pages

**Publisher** InTech

**Published online** 07, December, 2011

**Published in print edition** December, 2011

Diagnostics and Rehabilitation of Parkinson's Disease presents the most current information pertaining to news-making topics relating to this disease, including etiology, early biomarkers for the diagnostics, novel methods to evaluate symptoms, research, multidisciplinary rehabilitation, new applications of brain imaging and invasive methods to the study of Parkinson's disease. Researchers have only recently begun to focus on the non-motor symptoms of Parkinson's disease, which are poorly recognized and inadequately treated by clinicians. The non-motor symptoms of Parkinson's disease have a significant impact on patient quality of life and mortality and include cognitive impairments, autonomic, gastrointestinal, and sensory symptoms. In-depth discussion of the use of imaging tools to study disease mechanisms is also provided, with emphasis on the abnormal network organization in parkinsonism. Deep brain stimulation management is a paradigm-shifting therapy for Parkinson's disease, essential tremor, and dystonia. In the recent years, new approaches of early diagnostics, training programmes and treatments have vastly improved the lives of people with Parkinson's disease, substantially reducing symptoms and significantly delaying disability. Written by leading scientists on movement and neurological disorders, this comprehensive book should appeal to a multidisciplinary audience and help people cope with medical, emotional, and practical challenges.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Yangho Kim (2011). Neuroimaging in Manganese-Induced Parkinsonism, *Diagnostics and Rehabilitation of Parkinson's Disease*, Dr. Juliana Dushanova (Ed.), ISBN: 978-953-307-791-8, InTech, Available from: <http://www.intechopen.com/books/diagnostics-and-rehabilitation-of-parkinson-s-disease/neuroimaging-in-manganese-induced-parkinsonism>

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