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# Longitudinal T1 relaxation rate (R1) captures changes in short-term Mn exposure in welders

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## Abstract

**Objectives—**We demonstrated recently that the T1 relaxation rate (R1) captured short-term Mn exposure in welders with chronic, relatively low exposure levels in a cross-sectional study. In the current study, we used a longitudinal design to examine whether R1 values reflect the short-term dynamics of Mn exposure.

**Methods—**Twenty-nine welders were evaluated at baseline and 12 months. Occupational questionnaires estimated short-term welding exposure using welding hours in the 90 days prior to each study visit ($HrsW_{90}$). In addition, blood Mn levels, the pallidal index (PI; globus pallidus T1-weighted intensity (T1WI)/frontal white matter T1WI), and R1 values in brain regions of interest (ROIs) were determined as Mn biomarkers at each visit. Associations between changes in

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estimated welding exposure and changes in purported Mn biomarkers were assessed by Spearman's correlations with adjustment for age and baseline R1, $HrsW_{90}$, and blood Mn values.

**Results—**Changes in welding hours ($HrsW_{90}$: the short-term welding exposure estimate), was associated significantly with changes in R1 values in the putamen (r=0.541, p=0.005), caudate (R=0.453, p=0.023), globus pallidus (R=0.430, p=0.032), amygdala (R=0.461, p=0.020), and hippocampus (R=0.447, p=0.025), but not with changes in blood Mn levels or the PI.

**Discussion—**Changes in R1 values correlated with changes in the short-term welding exposure estimate, but not with more traditional measures of Mn exposure (blood Mn levels or PI). These results suggest that R1 may serve as a useful marker to capture the short-term dynamics in Mn brain accumulation related to welding exposure.

### Keywords

Welders; manganese; MRI; R1; longitudinal

## Introduction

Manganese (Mn) is an essential nutrient that can be toxic at high doses, causing neurological effects such as parkinsonism and dystonia (Racette et al., 2005, Cersosimo and Koller, 2006), as well as cognitive and behavioral deficits (Dobson et al., 2004, Bowler et al., 2006, Flynn and Susi, 2009). There is uncertainty, however, regarding the occupational and public health consequences of Mn exposure, especially at low exposure levels. This is due partly to the lack of an objective and sensitive *in vivo* marker of Mn concentration in human brain, and partly because of insufficient data about the dynamic relationships between proposed biomarkers and exposure. In addition, the toxicokinetics of Mn accumulation in brain is complex and not well understood.

Mn blood levels are increased in welders (Lu et al., 2005) and have been suggested as markers for exposure. The relationship between Mn blood levels and exposure, however, is weak and often non-significant (Lu et al., 2005, Baker et al., 2014). Mn has paramagnetic properties and can shorten the MRI longitudinal relaxation time (T1) and increase T1-weighted intensity (T1WI). Thus, T1WI imaging has been used to determine the pallidal index [PI (T1WI in globus pallidus/T1WI in orbitofrontal white matter)] as an estimate of Mn accumulation in the globus pallidus (GP) (Pal et al., 1999, Sen et al., 2011, Baker et al., 2015a). Although useful, it has been hypothesized that the PI may not capture Mn brain accumulation sensitively when the exposure level is low because Mn deposition in frontal white matter regions (Dorman et al., 2006, Lee et al., 2015) will affect the "calibration" critical for the PI.

T1 relaxation rate (R1), a quantitative estimate of Mn, may overcome the need to use such a "calibration." We recently studied the relationship between R1 (1/T1) values and welding, using the welding hours in the 90 days prior to imaging ($HrsW_{90}$) as an estimate of short-term welding exposure. We found an association between R1 and $HrsW_{90}$ in all basal ganglia areas, as well as in regions outside the basal ganglia (amygdala, hippocampus, and frontal cortex). In contrast, the correlations between R1 values and long-term exposure measures were limited to the caudate and putamen regions of the basal ganglia (Lee et al., 2015). The current study is a follow-up of this cohort assessing blood metal levels, exposure estimates, and imaging longitudinally. We tested the hypothesis that changes in R1 values, but not blood metal levels or the PI, would be associated with changes in short-term welding exposure (estimated by $HrsW_{90}$), thus providing R1 as a marker of short-term dynamics of brain Mn exposure.

## Methods

### Subjects

Originally (Lee et al., 2015), 35 welders were recruited from regional unions in Philadelphia and Harrisburg, PA, USA, and from the community around the Penn State Milton S. Hershey Medical Center. Twenty-nine welders returned for this longitudinal cohort study and had full blood, exposure, and imaging data both at the baseline and follow-up (12 months later) visits. A detailed questionnaire at each visit confirmed that welders were welding actively and that controls had no history of welding. All subjects were male and denied past diagnosis of Parkinson's disease or related disorders. Welders represented several different trades and industry groups (e.g., boilermakers, pipefitters, pile drivers, railroad welders, and a variety of different manufacturing jobs).

Detailed demographic information was collected at baseline and updated at the follow-up visit, including age, education, history of smoking, and history of current and/or past major medical/neurological disorders. All subjects were examined and ascertained to be free of any obvious neurological and movement deficits using the Unified Parkinson's Disease Rating Scale-motor scores (UPDRS-III) with a threshold score of <15 (Racette et al., 2012). Blood samples were collected from all subjects on the day of the study visit (thus, not directly after welding exposure occurred). All subjects had normal liver function, blood calcium and magnesium levels, and no Fe deficiency. All welders underwent an orbital radiograph to rule out any metal fragments around the orbit. Written informed consent was obtained in accordance with guidelines approved by the Internal Review Board/Human Subjects Protection Office of the Penn State Milton S. Hershey Medical Center.

The mean time between study visits was 12.9 ± 0.9 months for welders. The subjects included in the current study (i.e., with both baseline and follow-up visits) did not differ significantly from those excluded (due to loss at follow-up) in terms of age, education, welding exposure, blood metal levels, or imaging measures at baseline (p's>0.06).

### Exposure Assessment

A supplementary exposure questionnaire SEQ (Lee et al., 2015) focused on the 90-day period prior to the MRI and determined the time spent welding, type of metal welded, and various types of welding performed. The exposure metrics derived from the SEQ were: hours spent welding, brazing, or soldering in the 90-day period preceding the MRI. That is, $HrsW_{90}$ = (weeks worked) * (h/week) * (fraction of time worked related directly to welding) (Lee et al., 2015). The E90 also was used to provide an estimate of the 90-day time-weighted cumulative exposure for each subject in the 90 days prior to their study visit (baseline or follow-up). This estimate is designed to account for both work exposure (based on the Mn exposure data for welders from OHSA) and ambient (non-work) exposure (Lee et al., 2015). A detailed description and the calculations used have been published (Lee et al., 2015), and are included in the Supplementary Data.

## Blood Analysis

Whole blood was analyzed for metal levels by Inductively Coupled Plasma Mass Spectrometry [ICP-MS; (Lee et al., 2015)]. Digestion was performed by microwave methods using the Discovery SPD digestion unit (CEM, Matthews, NC). After digestion, the samples were analyzed for trace minerals using the Thermo (Bremen, Germany) Element 2 SF-ICP-MS equipped with a concentric glass nebulizer and Peltier-cooled glass cyclonic spray chamber. Bulk mineral concentrations were determined by ICP-OES (Optical Emission Spectrometry) analysis on the Thermo iCAP equipped with a polypropylene cyclonic spray chamber.

## MRI Image acquisition and analysis

Images were acquired using a Siemens 3 T scanner (Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany) with an 8-channel head coil using the same parameters at both the baseline and 12-month follow-up visits. Namely, high-resolution T1-weighted and T2-weighted images were acquired for anatomical segmentation. T1W images were collected using an MPRAGE sequence with Repetition Time (TR)=1540 ms, Echo Time (TE)=2.3 ms, FoV=256 × 256 mm, matrix=256 × 256 mm, slice thickness=1 mm, slice number=176 (with no gap), and voxel spacing 1 × 1 × 1 mm. T2-weighted images were collected using a fast-spin-echo sequence with TR/TE=2500/316, and the same spatial resolution as the T1W images.

For whole brain fast T1 mapping, images were acquired using a spoiled gradient recalled echo (SPGR) with two flip angles and transmit field (B1) correction. Image acquisition parameters for T1 mapping were as follows: TR=15 ms, TE=1.45 ms, flip angles=4/25, FoV=250 × 250 mm, matrix=160 x160, slice thickness=1 mm, slice number=192 50% overlap, and voxel spacing=1.56 × 1.56 × 1 mm; and for the B1 field mapping: TR=1000 ms, TE=14 ms, flip angles=45/60/90/120/135, FoV=250 × 250 mm, matrix=32 x32, slice thickness=5 mm, and slice number=22.

## Defining brain regions of interest

Bilateral basal ganglia structures [GP, putamen, caudate nucleus], amygdala, and hippocampus were selected as ROIs based on literature reporting the effects of Mn exposure on movement, mood, and cognitive function mediated by these ROIs (Dorman et al., 2006, Chang et al., 2009, Criswell et al., 2012). These regions also showed significant correlations with exposure measurements in the prior cross-sectional study (Lee, 2015). The target ROIs were defined for each subject using automatic segmentation software (AutoSeg) (Joshi et al., 2004, Gouttard et al., 2007). The ROIs then were eroded by 1 voxel using a morphological operation in order to ensure that the segmented ROIs were within the anatomical ROIs based on the T1W image (Lee et al., 2015).

### Estimation of R1 values

First, whole brain T1 time images were generated by the scanner using a published method (Venkatesan et al., 1998). ROIs were co-registered onto the T1 maps using an affine registration implemented in 3D Slicer (www.slicer.org; Rueckert et al., 1999). R1 values were calculated as 1/T1 in each voxel and averaged over the entire ROI using a trimmed mean 5–95 percentile (Lee et al., 2015).

### Statistical analysis

SAS 9.4 (SAS Institute, Inc., Cary NC) was used to perform all statistical analyses. Right and left hemisphere MRI data were averaged (Lee et al., 2015). Since our previous study indicated that R1 primarily is associated with short-term exposure metrics (Lee et al., 2015), we focused our correlational analyses on the $HrsW_{90}$ and E90 exposure measures. Because this was a longitudinal study, in many analyses we used the change for an individual subject's parameters in the analyses. When this was done, we used the notation "Δ", e.g., as in "Δ $HrsW_{90}$." First, we used Spearman correlations to determine whether the association we found previously at baseline between R1 and $HrsW_{90}$/E90 was replicated at the follow-up visit. To investigate the associations between changes in blood metal levels, the PI, and R1 values and changes in short-term welding exposure estimated by $HrsW_{90}$ or E90, Spearman correlation analyses were conducted within welders with adjustment for age and baseline $HrsW_{90}$, blood metal levels, the PI, and R1 values to control for any lingering long-term Mn exposure on those measures. In addition, we ran the correlation analyses without the baseline covariates to determine whether they affected the associations. Because we had a focused hypothesis (see Introduction), no adjustment for multiple comparisons was used when we examined the associations. Statistical significance was set at $\alpha$=0.05.

## Results

### Demographics and exposure metrics

Each welder performed multiple types of welding, but overall shield metal arc welding (SMAW), gas metal arc welding (GMAW), and gas tungsten arc welding (GTAW) accounted for most of the welding done by subjects in this study. The most frequent base metal reported was mild steel, followed by stainless steel. E6010 (rutile) and E7018 (basic) electrodes were the most commonly used SMAW electrodes. Demographic information and exposure metrics, baseline blood levels of Mn and Fe, and brain imaging measures for welders included in the study are reported in Table 1.

### Correlation of R1 and HrsW90 at the follow-up visit

Our previous study indicated that at baseline, R1 was associated with $HrsW_{90}$ in several brain regions (Lee et al., 2015). In the current study, however, Spearman correlation analyses indicated only a trend between R1 and $HrsW_{90}$ in the putamen (R=0.329, p=0.087) at the follow-up time-point, and no association in other structures (p's>0.161). Although there was a somewhat smaller sample size in the current study (N=29 versus N=35 at baseline), this alone would not account for the difference between the current data and our prior work. The possible reason driving the weaker correlation may be that high-exposure welders showed stronger correlations at baseline, and per chance, more of the high-exposure welders dropped out.

### Change in short-term welding exposure estimated by $HrsW_{90}$ was associated with changes in R1 values

The changes in the estimates of short-term welding exposure ($\Delta HrsW_{90}$ or ΔE90) were not associated with $\Delta Mn_{blood}$, $\Delta Fe_{blood}$, or $\Delta Cu_{blood}$, or the PI (Table 2). Using Spearman correlation analysis, $\Delta HrsW_{90}$ (the simpler estimate of short-term welding exposure) was correlated significantly with ΔR1 in the GP (r=0.430, p=0.032), putamen (r=0.541, p=0.005), caudate (r=0.453, p=0.023), amygdala (r=0.461; p=0.020), and hippocampus (r=0.447, p=0.025; Table 2) but not the OFWM (r=0.183, p=0.382) or OFGM (r=0.033, p=0.874) after controlling for age and baseline R1, $HrsW_{90}$, and blood Mn values. These associations held for all regions except the caudate (R=0.305, p=0.114) when the correlations were run without baseline R1 as a covariate (data not shown). A similar pattern of results was obtained when the data were analyzed using linear regression (Supplemental Table 1). Interestingly, ΔE90, the more sophisticated estimate of short-term welding exposure, was not correlated significantly with ΔR1 (ps>0.10; Table 2). In addition, neither $\Delta Mn_{blood}$, $\Delta Fe_{blood}$, nor $\Delta Cu_{blood}$ were correlated with ΔR1 levels in any ROI (p's>0.12; data not shown).

## Discussion

This study extended our recent report on cross-sectional R1 findings in asymptomatic welders with chronic, relatively low levels of estimated welding exposure (Lee et al., 2015) by including follow-up analyses of the same cohort. Consistent with our previous report (Lee et al., 2015), the current results are supportive of the hypothesis that changes in R1 values, but not blood metal levels or the PI, are associated with changes in short-term welding exposure estimates—namely, the $HrsW_{90}$. In addition, the associations were observed in ROIs both within and outside the basal ganglia. These results provide further support that R1 may serve as a useful marker to capture the short-term dynamics of Mn brain accumulation related to welding exposure.

### Exposure level within the cohort

The mean blood Mn level for our welders was 10.5 ± 5.3 ng/mL, a value similar to that reported from a large European study of welders (i.e., 10.3 ng/mL) (Pesch et al., 2012). The average blood Mn level, however, was considerably lower compared to other studies (e.g., blood Mn>14.2 ng/mL, (Choi et al., 2007), but this may have been due to blood collection on the day of the study visit rather than directly after welding. In addition, the PI in our welders (mean PI =109) also was lower compared to several other studies (PI> 112) (Choi et al., 2007, Chang et al., 2009), suggesting that the welders in this study probably had overall lower Mn exposure. Many welders in our study worked only intermittently during the 90-day exposure period (data not shown), and this likely was a factor in keeping blood Mn levels and MRI indices (PI and R1 values) low relative to other studies (Dorman et al., 2006, Chang et al., 2009). Moreover, our welders reported an average of ~300 HrsW in the 90-day period prior to the study visit, which is approximately equivalent to what a half-time welder completely engaged in welding would report. Several of our welders also reported some (protective) respirator usage that also may have attenuated blood Mn levels and PI values.

## Traditional blood and MRI measures do not capture short-term exposure changes in welders with lower exposure levels

Gauging welding-related exposure and its consequences is hampered by the lack of an objective, sensitive, *in vivo* marker of Mn concentration in humans. Blood metal levels and the PI have been reported previously to correlate with Mn exposure (Chang et al., 2010). These traditional measurements, however, are not sensitive to lower-level exposures (reviewed by Baker et al., 2014). Consistent with this, a recent study in welding trainees suggested that exposure to Mn over a longer period (90 days) and at higher levels (1 mg-days/$m^3$) is needed to produce significant changes in blood Mn levels (Baker et al., 2015b). Other studies have suggested that blood Mn levels reflect exposure over very recent time periods (hours to days; Aschner and Dorman, 2006). In the current study, changes in blood metal levels did not capture changes in welding exposure. This may have occurred because our welders had relatively low exposure levels to which traditional measures are not sensitive, the blood samples were collected on the day of the study visit and not directly after welding exposure, or a combination of these factors. In addition, the PI did not capture changes in estimated welding exposure. The current results confirm that blood Mn levels and the PI are not sensitive to detect short-term (reflecting the 90 day time window prior to study visit) changes in lower-level welding exposures.

## R1 captured changes in short-term welding exposure

We previously demonstrated that R1, even at low Mn exposure levels, captures exposure in the basal ganglia related to welding (Lee et al., 2015). In the current study, we demonstrated for the first time that the changes in R1 values in all brain ROIs correlated with changes in the short-term welding exposure estimated by $HrsW_{90}$. These data extend our previous results showing R1 values are associated with short-term exposure metrics (Lee et al., 2015) and suggest further that R1 may capture the short-term dynamics of changes in Mn exposure.

Several previous studies have investigated the effects of high-level Mn exposure and demonstrated the presence of neurological symptoms (Mergler and Baldwin, 1997, Harris et al., 2005, Antonini et al., 2006). In addition, past studies (Dietz et al., 2001, Choi et al., 2007, Chang et al., 2010, Baker et al., 2015a, Lee et al., 2015) have interrogated the effects of low-level Mn exposure that typically does not correspond to a clinical phenotype. Previous longitudinal studies in welders found preserved motor function (i.e., using the grooved pegboard and UPDRS-III scores) in welders over short time-frames (90 days; Baker et al., 2015b) but decreased targeted functional outcomes over long time periods (~6 years; Ellingsen et al., 2015). In the current study, our subjects were welding on average part-time (300 hrs in the 90 days prior to each study visit compared to ~600 hrs for the number of hours full-time welders would weld), with lower mean Mn levels. The study is the first to demonstrate that the changes in R1 values correlate significantly with changes in short-term welding exposure estimates ($HrsW_{90}$) in lower-level Mn exposure welders, a finding that is novel and supports further that R1 values may serve as a marker to capture the dynamic changes in brain Mn exposure.

## R1 changes outside basal ganglia regions

The current study also extended the previous longitudinal results in Mn-exposed welders to include not only basal ganglia regions, but also additional brain regions outside the basal ganglia (amgydala, hippocampus, and OF). The results are consistent with previous studies reporting significant Mn accumulation in white matter and cortical structures in non-human primates (Guilarte et al., 2006) and increased T1 intensities in the thalamus and hippocampus in welders (Long et al., 2014). Importantly, R1 changes in these regions also correlated with changes in $HrsW_{90}$, supporting that Mn may have effects outside of basal ganglia areas that traditionally were implicated in Mn exposure. Since the hippocampus and OF (Lee et al., 2015) areas demonstrate increased Mn accumulation, it is possible that this may lead to impaired memory and/or frontal capacity since these structures are intimately involved in these functions (see Duncan and Owen, 2000, Burgess et al., 2002 for reviews). These results are consistent with our previous findings in welders (Lee et al., 2015) and the hypothesis proposed by Dorman et al. (2006) that the PI is confounded by Mn entering not only the GP, but also other brain areas including the orbitofrontal white matter.

## Strengths and limitations of the study

The study took advantage of a longitudinal design because between-subject variability is much greater than within-subject variability. For example, it has been demonstrated that the majority of variance in blood Mn levels was between individuals (94%) and only ~6% was within individuals (Baker et al., 2015b). In addition, the same group demonstrated that Mn blood levels seem to be regulated tightly under relatively normal conditions and in new welders who were within 7 days of exposure. The tight Mn regulation, however, is perturbed when longer or higher exposure and blood accumulation occurs. We suspect a similar situation may occur in brain Mn accumulation. Consistent with this notion, in our subjects with chronic welding exposure, the changes in R1 values were correlated with changes in short-term welding exposure estimated by $HrsW_{90}$ even after controlling for a number of potential confounders including baseline exposure values. Our study, however, is limited by not including new welders. A future study with new welders may test the hypothesis of whether brain Mn accumulation will occur only after perturbation of metal homeostatic mechanisms.

It is worthwhile to note that the major limitation of our study with active welders is the inability to measure the exact air Mn content in welding fumes for each subject. We assigned weights to different types of welding and exposure factors (e.g., confined space, use of local exhaust ventilator) to provide a more sophisticated estimate of the degree of Mn exposure for each subject. The potential for misclassification, however, becomes greater for the E90 measure as more uncertain information is incorporated [see Supplemental information in (Lee et al., 2015). These limitations may be responsible for the lack of significant correlations between R1 and the E90. Also, our welders had lower-level Mn exposure (as measured by blood metal levels) compared to other studies (Ellingsen et al., 2006, Ellingsen et al., 2008, Chang et al., 2009).

## Conclusion

Changes in R1 values captured the changes in a short-term welding exposure estimate (three-month time-frame) better than a traditional measure of Mn exposure [blood metal levels (best to reflect acute exposure)] or the PI (best reflecting short-term and chronic exposure). Coupled with our recent report (Lee et al., 2015), this follow-up study of asymptomatic welders with relatively lower-level Mn exposure is consistent with the notion that R1 may serve as a marker of Mn accumulation, and capture changes in brain better than the traditional PI or direct blood measurement. As such, it may be useful in monitoring Mn brain tissue exposure for occupational health studies, especially in an era when public health guidelines for Mn exposure are lower and protective gear is better.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## List of Abbreviations

| | |
|---|---|
| **GP** | Globus pallidus |
| **HrsW** | Hours spent welding, brazing, or soldering in the 90 day period preceding MRI |
| **MRI** | Magnetic resonance imaging |
| **R1** | T1 relaxation rate |
| **ROIs** | regions-of-interest |
| **T1** | MRI longitudinal relaxation time |
| **T1WI** | T1-weighted intensity |
| **TE** | Echo Time |
| **TR** | Repetition Time |
| **UPDRS** | Unified Parkinson’s Disease Rating Scale |
| **YrsW** | cumulative lifetime years welding |

## References

Antonini JM, Santamaria AB, Jenkins NT, Albini E, Lucchini R. Fate of manganese associated with the inhalation of welding fumes: potential neurological effects. Neurotoxicology. 2006; 27:304–310. [PubMed: 16219356]

Aschner M, Dorman DC. Manganese: pharmacokinetics and molecular mechanisms of brain uptake. Toxicol Rev. 2006; 25:147–154. [PubMed: 17192121]

Baker MG, Criswell SR, Racette BA, Simpson CD, Sheppard L, Checkoway H, Seixas NS. Neurological outcomes associated with low-level manganese exposure in an inception cohort of asymptomatic welding trainees. Scand J Work Environ Health. 2015a; 41:94–101. [PubMed: 25380186]

Baker MG, Simpson CD, Stover B, Sheppard L, Checkoway H, Racette BA, Seixas NS. Blood manganese as an exposure biomarker: state of the evidence. Journal of occupational and environmental hygiene. 2014; 11:210–217. [PubMed: 24579750]

Baker MG, Stover B, Simpson CD, Sheppard L, Seixas NS. Using exposure windows to explore an elusive biomarker: blood manganese. Int Arch Occup Environ Health. 2015b

Bowler RM, Gysens S, Diamond E, Nakagawa S, Drezgic M, Roels HA. Manganese exposure: neuropsychological and neurological symptoms and effects in welders. Neurotoxicology. 2006; 27:315–326. [PubMed: 16343629]

Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. Neuron. 2002; 35:625–641. [PubMed: 12194864]

Cersosimo MG, Koller WC. The diagnosis of manganese-induced parkinsonism. Neurotoxicology. 2006; 27:340–346. [PubMed: 16325915]

Chang Y, Kim Y, Woo ST, Song HJ, Kim SH, Lee H, Kwon YJ, Ahn JH, Park SJ, Chung IS, Jeong KS. High signal intensity on magnetic resonance imaging is a better predictor of neurobehavioral performances than blood manganese in asymptomatic welders. Neurotoxicology. 2009; 30:555–563. [PubMed: 19376157]

Chang Y, Woo ST, Kim Y, Lee JJ, Song HJ, Lee HJ, Kim SH, Lee H, Kwon YJ, Ahn JH, Park SJ, Chung IS, Jeong KS. Pallidal index measured with three-dimensional T1-weighted gradient echo sequence is a good predictor of manganese exposure in welders. J Magn Reson Imaging. 2010; 31:1020–1026. [PubMed: 20373449]

Choi DS, Kim EA, Cheong HK, Khang HS, Ryoo JW, Cho JM, Sakong J, Park I. Evaluation of MR signal index for the assessment of occupational manganese exposure of welders by measurement of local proton T1 relaxation time. Neurotoxicology. 2007; 28:284–289. [PubMed: 16828869]

Criswell SR, Perlmutter JS, Huang JL, Golchin N, Flores HP, Hobson A, Aschner M, Erikson KM, Checkoway H, Racette BA. Basal ganglia intensity indices and diffusion weighted imaging in manganese-exposed welders. Occupational and environmental medicine oemed-2011-100119. 2012

Dietz MC, Ihrig A, Wrazidlo W, Bader M, Jansen O, Triebig G. Results of magnetic resonance imaging in long-term manganese dioxide-exposed workers. Environ Res. 2001; 85:37–40. [PubMed: 11161650]

Dobson AW, Erikson KM, Aschner M. Manganese neurotoxicity. Annals of the New York Academy of Sciences. 2004; 1012:115–128. [PubMed: 15105259]

Dorman DC, Struve MF, Wong BA, Dye JA, Robertson ID. Correlation of brain magnetic resonance imaging changes with pallidal manganese concentrations in rhesus monkeys following subchronic manganese inhalation. Toxicol Sci. 2006; 92:219–227. [PubMed: 16638924]

Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci. 2000; 23:475–483. [PubMed: 11006464]

Ellingsen DG, Chashchin M, Bast-Pettersen R, Zibarev E, Thomassen Y, Chashchin V. A follow-up study of neurobehavioral functions in welders exposed to manganese. Neurotoxicology. 2015; 47:8–16. [PubMed: 25579701]

Ellingsen DG, Dubeikovskaya L, Dahl K, Chashchin M, Chashchin V, Zibarev E, Thomassen Y. Air exposure assessment and biological monitoring of manganese and other major welding fume components in welders. Journal of Environmental Monitoring. 2006; 8:1078–1086. [PubMed: 17240914]

Ellingsen DG, Konstantinov R, Bast-Pettersen R, Merkurjeva L, Chashchin M, Thomassen Y, Chashchin V. A neurobehavioral study of current and former welders exposed to manganese. Neurotoxicology. 2008; 29:48–59. [PubMed: 17942157]

Flynn MR, Susi P. Manganese, iron, and total particulate exposures to welders. Journal of occupational and environmental hygiene. 2009; 7:115–126.

Gouttard, S.; Styner, M.; Joshi, S.; Smith, RG.; Hazlett, HC.; Gerig, G. Medical Imaging. International Society for Optics and Photonics; 2007. Subcortical structure segmentation using probabilistic atlas priors; p. 65122J-65122J-65111.

Guilarte TR, McGlothan JL, Degaonkar M, Chen MK, Barker PB, Syversen T, Schneider JS. Evidence for cortical dysfunction and widespread manganese accumulation in the nonhuman primate brain following chronic manganese exposure: a 1H-MRS and MRI study. Toxicol Sci. 2006; 94:351–358. [PubMed: 16968886]

Harris MK, Ewing WM, Longo W, DePasquale C, Mount MD, Hatfield R, Stapleton R. Manganese exposures during shielded metal arc welding (SMAW) in an enclosed space. J Occup Environ Hyg. 2005; 2:375–382. [PubMed: 16080259]

Joshi S, Davis B, Jomier M, Gerig G. Unbiased diffeomorphic atlas construction for computational anatomy. NeuroImage. 2004; 23:S151–S160. [PubMed: 15501084]

Lee EY, Flynn MR, Du G, Lewis MM, Fry R, Herring AH, Van Buren E, Van Buren S, Smeester L, Kong L, Yang Q, Mailman RB, Huang X. T1 Relaxation Rate (R1) Indicates Nonlinear Mn Accumulation in Brain Tissue of Welders With Low-Level Exposure. Toxicol Sci. 2015; 146:281–289. [PubMed: 25953701]

Lee EY, Flynn MR, Du G, Li Y, Lewis MM, Herring AH, Van Buren E, Van Buren S, Kong L, Fry RC, Snyder AM, Connor JR, Yang QX, Mailman RB, Huang X. Increased R2* in the caudate nucleus of asymptomatic welders. Toxicol Sci. 2016

Long Z, Jiang Y-M, Li X-R, Fadel W, Xu J, Yeh C-L, Long L-L, Luo H-L, Harezlak J, Murdoch JB. Vulnerability of welders to manganese exposure–A neuroimaging study. Neurotoxicology. 2014; 45:285–292. [PubMed: 24680838]

Lu L, Zhang L-l, Li GJ, Guo W, Liang W, Zheng W. Alteration of serum concentrations of manganese, iron, ferritin, and transferrin receptor following exposure to welding fumes among career welders. Neurotoxicology. 2005; 26:257–265. [PubMed: 15713346]

Mergler D, Baldwin M. Early manifestations of manganese neurotoxicity in humans: an update. Environ Res. 1997; 73:92–100. [PubMed: 9311535]

Milne DB, Sims RL, Ralston NV. Manganese content of the cellular components of blood. Clin Chem. 1990; 36:450–452. [PubMed: 2311212]

Pal PK, Samii A, Calne DB. Manganese neurotoxicity: a review of clinical features, imaging and pathology. Neurotoxicology. 1999; 20:227–238. [PubMed: 10385886]

Pesch B, Weiss T, Kendzia B, Henry J, Lehnert M, Lotz A, Heinze E, Käfferlein HU, Van Gelder R, Berges M. Levels and predictors of airborne and internal exposure to manganese and iron among welders. Journal of Exposure Science and Environmental Epidemiology. 2012; 22:291–298. [PubMed: 22377681]

Racette B, Tabbal S, Jennings D, Good L, Perlmutter J, Evanoff B. Prevalence of parkinsonism and relationship to exposure in a large sample of Alabama welders. Neurology. 2005; 64:230–235. [PubMed: 15668418]

Racette BA, Criswell SR, Lundin JI, Hobson A, Seixas N, Kotzbauer PT, Evanoff BA, Perlmutter JS, Zhang J, Sheppard L. Increased risk of parkinsonism associated with welding exposure. Neurotoxicology. 2012; 33:1356–1361. [PubMed: 22975422]

Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. Medical Imaging, IEEE Transactions on. 1999; 18:712–721.

Sen S, Flynn MR, Du G, Tröster AI, An H, Huang X. Manganese accumulation in the olfactory bulbs and other brain regions of “asymptomatic” welders. Toxicological Sciences. 2011; 121:160–167. [PubMed: 21307282]

Venkatesan R, Lin W, Haacke EM. Accurate determination of spin-density and T1 in the presence of RF-field inhomogeneities and flip-angle miscalibration. Magnetic resonance in medicine. 1998; 40:592–602. [PubMed: 9771576]

Williams, M.; Todd, GD.; Roney, N.; Crawford, J.; Coles, C.; McClure, PR.; Garey, JD.; Zaccaria, K.; Citra, M. (ATSDR), A. f. T. S. a. D. R. Toxicological Profile for Managnese. Atlanta: U.S. Department of Health and Human Services, Public Health Service; 2012. p. 556

Zielhuis RL, del Castilho P, Herber RF, Wibowo AA. Levels of lead and other metals in human blood: suggestive relationships, determining factors. Environ Health Perspect. 1978; 25:103–109. [PubMed: 720295]

## Highlights

- A one-year follow-up study investigated associations between changes in estimated welding exposure and changes in purported Mn biomarkers in welders with chronic, low-level exposure.
- Traditional measures (blood Mn levels or the pallidal index) did not correlate with changes in estimated welding exposure levels (hours welding in the 90-day period prior to study visit).
- Changes in R1 values correlated significantly with changes in estimated welding exposure levels (hours welding in the prior 90-day period) in areas both within and outside basal ganglia regions.
- R1 may serve as a marker to capture short-term dynamics of Mn brain accumulation and clearance.

## Table 1

Demographic, exposure metrics, blood metals, and MRI measures in welders (N=29) at baseline and follow-up.

| | Baseline | Follow-up |
|---|---|---|
| **Age (y)** | 47.0 ± 11.2 | 48.6 ± 11.2 |
| **Education (y)** | 13.6 ± 2.4 | 13.6 ± 2.4 |
| **BMI** | 29.0 ± 5.8 | 29.6 ± 5.7 |
| **Hemoglobin** | 15.4 ± 1.0 | 15.1 ± 1.0 |
| **AST (IU/L)** | 36.1 ± 8.0 | 38.6 ± 10.3 |
| **ALT (IU/L)** | 39.9 ± 19.4 | 43.5 ± 12.8 |
| **UPDRS-III** | 2.0 ± 2.6 | 3.6 ± 3.9 |
| **HrsW (h)** | 297 ± 171 | 321 ± 194 |
| **YrsW (y)** | 26.1 ± 11.0 | 27.1 ± 11.0 |
| **Mn (ng/mL)** | 10.2 ± 2.5 | 10.7 ± 4.5 |
| **Fe (μg/mL)** | 560± 54 | 509 ± 71 |
| **Cu (ng/mL)** | 875 ± 126 | 731 ± 139 |
| **GP R1** | 0.870 ± 0.059 | 0.887 ± 0.041 |
| **PUT R1** | 0.705 ± 0.057 | 0.711 ± 0.037 |
| **CN R1** | 0.669 ± 0.083 | 0.661 ± 0.032 |
| **AMY R1** | 0.548 ± 0.071 | 0.536 ± 0.024 |
| **HIP R1** | 0.517 ± 0.049 | 0.515 ± 0.035 |
| **PI** | 109 ± 2.5 | 108 ± 1.7 |
| **OFWM** | 0.920 ± 0.066 | 0.963 ± 0.047 |
| **OFGM** | 0.638 ± 0.035 | 0.627 ± 0.025 |

Data represent the mean ± standard deviation.

### Table 2

Spearman correlations in welders of changes in blood and imaging measures with changes in HrsW and the E90.

| | ΔHrsW | | ΔE90 | |
|---|---|---|---|---|
| | **R** | **P value** | **R** | **P value** |
| **ΔBlood Mn** | 0.253 | 0.212 | 0.352 | 0.092 |
| **ΔBlood Fe** | −0.047 | 0.818 | 0.292 | 0.167 |
| **ΔBlood Cu** | 0.198 | 0.332 | 0.113 | 0.601 |
| **ΔPI** | 0.153 | 0.465 | −0.218 | 0.318 |
| **ΔGlobus pallidus R1** | **0.430** | **0.032** | −0.003 | 0.988 |
| **ΔPutamen R1** | **0.541** | **0.005** | 0.223 | 0.306 |
| **ΔCaudate Nucleus R1** | **0.453** | **0.023** | 0.284 | 0.190 |
| **ΔAmygdala R1** | **0.461** | **0.020** | 0.026 | 0.905 |
| **ΔHippocampus R1** | **0.447** | **0.025** | 0.200 | 0.361 |
| **ΔOFWM R1** | 0.183 | 0.382 | −0.105 | 0.634 |
| **ΔOFGM R1** | 0.033 | 0.874 | −0.285 | 0.187 |

Spearman correlations in welders of changes in blood and imaging measures with changes in HrsW and the E90 after adjustment for age, baseline R1, baseline $HrsW_{90}$ or E90 appropriately, and baseline Mn blood levels from each ROI. Significant correlations are indicated in bold text.