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Welding-related brain and functional changes in welders with chronic and low-level exposure

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ABSTRACT

Although an essential nutrient, manganese (Mn) can be toxic at high doses. There is, however, uncertainty regarding the effects of chronic low-level Mn-exposure. This review provides an overview of Mn-related brain and functional changes based on studies of a cohort of asymptomatic welders who had lower Mn-exposure than in most previous work. In welders with low-level Mn-exposure, we found: 1) Mn may accumulate in the brain in a non-linear fashion: MRI R1 (1/T1) signals significantly increased only after a critical level of exposure was reached (e.g., ≥300 welding hours in the past 90 days prior to MRI). Moreover, R1 may be a more sensitive marker to capture short-term dynamic changes in Mn accumulation than the pallidal index [T1-weighted intensity ratio of the globus pallidus vs. frontal white matter], a traditional marker for Mn accumulation; 2) Chronic Mn-exposure may lead to microstructural changes as indicated by lower diffusion tensor fractional anisotropy values in the basal ganglia (BG), especially when welding years exceeded more than 30 years; 3) Mn-related subtle motor dysfunctions can be captured sensitively by synergy metrics (indices for movement stability), whereas traditional fine motor tasks failed to detect any significant differences; and 4) Iron (Fe) also may play a role in welding-related neurotoxicity, especially at low-level Mn-exposure, evidenced by higher R2* values (an estimate for brain Fe accumulation) in the BG. Moreover, higher R2* values were associated with lower phonemic fluency performance. These findings may guide future studies and the development of occupation- and public health-related polices involving Mn-exposure.

1. Effects of occupational manganese exposure on the central nervous system

Manganese (Mn) is an essential nutrient but can be neurotoxic to the central nervous system (CNS) at high doses, and has been associated with neurobehavioral disorders such as manganese-induced parkinsonism (Cersosimo and Koller, 2006; Colosimo and Guidi, 2009; Guilarte and Gonzales, 2015). Mn toxicity is of great public health importance because *"hundreds of thousands of workers in the United States and millions of workers worldwide are exposed to [Mn-rich] welding aerosols on a daily basis"* (Antonini et al., 2009). The neurological symptoms from extremely high level Mn-exposure consist initially of reduced response speed, irritability, intellectual deficits, mood changes, and compulsive behaviors, and progress to more prominent, irreversible neurological dysfunction upon protracted exposure (Guilarte, 2013; Hauser et al., 1996; Huang et al., 1993; Mergler and Baldwin, 1997; Pal et al., 1999). Neuronal degeneration and/or dysfunctional dopamine release also have been reported in basal ganglia (BG) areas including the globus pallidus, striatum, and substantia nigra pars reticulata (Colosimo and Guidi, 2009; Criswell et al., 2012; Guilarte, 2010, 2013; Guilarte et al., 2008; Khalid et al., 2011; Perl and Olanow, 2007). Recently, Racette et al. (2012) reported that Mn-exposed workers had a higher prevalence of parkinsonian features compared to unexposed workers, and the parkinsonian

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symptoms assessed by UPDRS (Unified Parkinson's Disease Rating Scale)-III motor scores increased with cumulative long-term Mn-exposure (Racette et al., 2016).

Establishing reliable, quantitative *in vivo* biomarkers for Mn brain accumulation, particularly tissue dosage to the brain, has been challenging (Bader et al., 1999), and significant effort has been expended to discover surrogate biomarkers of Mn-related neurotoxicity. Several cellular and neurochemical studies using animal models have been conducted to understand possible mechanisms of Mn toxicity (Aschner and Dorman, 2006; Benedetto et al., 2009; Dobson et al., 2004; Erikson et al., 2006; Iavicoli et al., 2009; Jones and Miller, 2008; Levy and Nassetta, 2003; Norenberg and Rao, 2007; O'Neal and Zheng, 2015; Sidoryk-Wegrzynowicz and Aschner, 2013a,b; Takeda, 2003; Wright and Baccarelli, 2007; Yokel, 2006). It is known that influx of Mn into the brain is carrier-mediated, e.g., through divalent metal transporter-1 (DMT-1), transferrin, or ZIP8 (O'Neal and Zheng, 2015) that are located at the interface of the blood-brain-barrier (BBB). The major route for transport of Mn into the brain is via the BBB, but inhaled Mn can enter the brain via the olfactory pathway or through the blood-cerebrospinal fluid (CSF) barrier (Schmitt et al., 2011; Zoni et al., 2012). Efflux of Mn from the brain is by slow diffusion (Yokel, 2009), and the average half-life in brain has been estimated to be between 52 and 74 days (Crossgrove and Zheng, 2004; Newland et al., 1987), leading to potential accumulation. Excessive Mn brain accumulation following acute and/or chronic exposure to Mn, and problems with adequate Mn clearance from brain (e.g., mutations in the SLC30A10 gene), likely cause neurotoxic effects in the CNS (Leyva-Illades et al., 2014). For example, disruptions in several neurotransmitter systems, including dysfunctional dopaminergic activity, have been reported (Guilarte et al., 2008; Perl and Olanow, 2007), and disrupted glutamate and γ-aminobutyric acid (GABA) systems have been suggested (Burton et al., 2009; Sidoryk-Wegrzynowicz and Aschner, 2013a).

In humans, welders have been among the most studied occupational groups since Mn is one of the major elements in many types of welding fumes (Burgess, 1995). Prior studies of welders have documented subclinical motor and non-motor symptoms that do not meet criteria for occupational manganism (Bowler et al., 2006a,b, 2007a,b; Chang et al., 2009; Cowan et al., 2009a,b; Ellingsen et al., 2008; Simon-Sanchez et al., 2009), with several reporting significant associations between Mn-exposure and subclinical symptoms (Chang et al., 2009; Meyer-Baron et al., 2013; Simon-Sanchez et al., 2009).

Recently, magnetic resonance imaging (MRI) markers have been used to examine Mn-related brain and functional changes. For example, Mn brain accumulation has been linked to higher MRI T1-weighted (T1W) intensity and/or T1 relaxation rate (R1: 1/T1) that was greatest in the globus pallidus (GP; Dorman et al., 2006b; Kim et al., 1999). These changes have been associated with slower motor function (Chang et al., 2009; Dion et al., 2016; Shin et al., 2007) and/or with poorer performance in working memory and executive function (Chang et al., 2009). Mn-induced volume decrease also was reported in the GP and cerebellum, and these correlated with reduced performance in fine motor and executive function tasks in full-time welders (Chang et al., 2013).

There is, however, uncertainty regarding the effects of the chronic low-level Mn-exposure that probably is most relevant to occupational and public health. This is due partly to the lack of an objective and sensitive *in vivo* marker of low-level Mn accumulation in brain. In the present review, we provide an overview of Mn-related brain and functional changes based on studies of a cohort of asymptomatic welders with welding exposures lower than most previous studies.

2. Establishment of a Pennsylvania-based welder cohort with chronic, low Mn exposure

2.1. Subjects

We recruited both our welders and controls locally from the community around the Penn State Milton S. Hershey Medical Center and nearby Harrisburg, PA, as well as from the Philadelphia, PA area (Lee et al., 2015). In contrast to many of prior studies (Chang et al., 2009; Choi et al., 2007; Long et al., 2014) that purposefully recruited subjects from high exposure, full-time professionals (e.g., boilermakers and shipyard workers) who may or may not reside locally, we recruited both full- and half-time welders only locally. A total of 80 subjects were recruited at baseline, 48 with and 32 without a history of welding exposure. Of these, 43 welders and 31 controls completed the MRI acquisition with good quality images. Welders, defined as subjects who had welded at any point in their lifetime, represented several different trade groups (e.g., boilermakers, pipefitters, and a variety of different manufacturing jobs). Out of 43 welders, 35 were active welders and 7 welders did not weld during the 90 days prior to study participation. For the 35 active welders, the duration between the last time they welded and study participation varied between ~1-5 days. For the 7 welders without welding during the 90 days prior to study participation, the duration between welding cessation and data collection varied between 5 and 180 months. Controls were volunteers from the same regional community with various occupations that did not have any lifetime history of welding. All subjects were male and answered negatively for past diagnosis of Parkinson's or other neurological disorders. All subjects were ascertained to be free of any obvious neurological and movement deficits using the UPDRS-III (Goetz et al., 2008) with a threshold score of <15 (Lee et al., 2015). Subjective symptoms were evaluated by UPDRS-I and −II that assess non-motor (I) and motor (II) experiences of daily living (Goetz et al., 2008).

2.2. Assessment of the cohort

Exposure and behavioral function assessment: We estimated welding exposure using the following measures: recent hours welding, brazing, or soldering [$HrsW_{90}$ = (weeks worked) * (h/week) * (fraction of time worked related directly to welding)]; the E_{90} (an estimate of the cumulative 90 day exposure to Mn, past 90 days); lifetime exposure [cumulative lifetime welding years (YrsW = years spent welding during the subjects' life)]; and the ELT (an estimate of cumulative exposure to inhaled Mn over the individual's life, lifetime) (Lee et al., 2015). In addition, whole blood metal (Fe and Mn) levels were obtained. To assess behavioral functions, UPDRS-III and Grooved Pegboard test (traditional motor and fine motor tasks), single- and multi-finger pressing tasks (for synergy metrics), and standardized neuropsychological tests were administered (Lee et al., 2017; Lewis et al., 2016b). All blood, MRI, and behavioral measurements were collected on the same day.

Estimations of brain MRI measurements: We used state-of-the-art MRI techniques on a Siemens 3 T scanner (Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany) with an 8-channel head coil to acquire high-resolution T1-weighted (T1W), T2-weighted (T2W), rapid T1 mapping (to assess R1), a multigradient-echo sequence [to estimate the apparent transverse relaxation rate: R2* (1/T2*)], and diffusion tensor images (DTI). Bilateral basal ganglia (BG) structures [GP, putamen (PUT), and caudate nucleus (CN)] were selected as regions of interest (ROI) (Chang et al., 2009; Criswell et al., 2012; Dorman et al., 2006b).

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