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Cognitive Control Dysfunction in Workers Exposed to Manganese-Containing Welding Fume

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Abstract

Background—Chronic exposure to manganese (Mn) is a health concern in occupations such as welding because of well-established motor effects due to basal ganglia dysfunction. We hypothesized that cognitive control (the ability to monitor, manipulate, and regulate ongoing cognitive demands) would also be affected by chronic Mn exposure.

Methods—We examined the relationship between Mn exposure and cognitive control performance in 95 workers with varying intensity and duration (median 15.5 years) of exposure to welding fume. We performed linear regression to assess the association between exposure to Mn-containing welding fume and cognitive control tasks.

Results—Overall performance was inversely related to intensity of welding exposure ($p=0.009$) and was driven by the Two-Back and Letter Number Sequencing tests that assess working memory (both $p=0.02$).

Conclusions—Occupational exposure to Mn-containing welding fume may be associated with poorer working memory performance, and workers may benefit from practices that reduce exposure intensity.

Keywords

Manganese; Welding; Caudate nucleus; Cognitive control

Introduction

Chronic low-level exposure to manganese (Mn) is a health concern in selected communities and occupations such as welding because, in addition to well-established motor effects of

Mn overexposure, Mn has been associated with impaired cognition. Motor deficits are well documented in Mn-exposed workers, largely encompassing the cardinal features of parkinsonism: tremor, bradykinesia, and rigidity.[Racette, et al. 2012] Cognitive impairment has also been shown to occur at the earliest stages of Mn toxicity and affects multiple abilities, including reduced attention, poorer performance on working memory tasks, increased difficulty in learning new material, and slower reaction speed.[Bowler, et al. 2003, Bowler, et al. 2006, Zou, et al. 2014] Several studies have demonstrated dose-dependent relationships between Mn exposure and impaired cognitive performance on attention, concentration, working memory, cognitive flexibility, visuospatial skills, digit span, and symbol tasks.[Bowler, et al. 2007, Ellingsen, et al. 2008, Lucchini, et al. 1999] [Bowler, et al. 2015]

Neuroimaging provides an opportunity to investigate the neuroanatomic correlates of cognitive dysfunction in Mn-exposed workers. Functional MRI or PET studies have demonstrated differences in brain connections that underlie the cognitive dysfunction associated with Mn neurotoxicity.[Criswell, et al. 2011] We previously found that Mn-exposed workers had dopaminergic dysfunction in the caudate nucleus as compared to non-exposed control subjects.[Criswell, et al. 2015, Criswell, et al. 2011] Through caudate-cortical projections, the caudate nucleus is involved in higher order cognitive abilities [van Schouwenburg, et al. 2010] and is summarized under the term cognitive control. Cognitive control encompasses the goal-oriented ability to manipulate information, to distinguish relevant data from the extraneous, to be flexible, and to self-regulate in order to achieve high order objectives such as adaptation, prioritization, and organization.[Botvinick and Braver 2015, Rabinovici, et al. 2015]

The primary aim of this study was to determine if performance on cognitive control tasks is impaired in a dose-dependent manner by Mn exposure. We anticipated that Mn-exposed workers with chronic airborne Mn exposure would demonstrate impaired performance on cognitive control tasks. To test this hypothesis, we assessed Mn-exposed workers from welding worksites and comparable low Mn-exposed workers from other worksites with a targeted battery of cognitive control tasks. This guided and focused approach was designed to help further the understanding of Mn-induced cognitive impairment.

Materials and Methods

Study Participants

This study was approved by the appropriate institutional review board, and all study subjects proved written informed consent prior to study conduct. We included 95 adults from the US Midwest: 82 Mn-exposed workers who work or have worked at one of three welding sites and 13 comparable low Mn-exposed workers (to provide a greater range of Mn exposures overall). Mn-exposed workers were participants in a larger welding worksite based cohort study detailed previously.[Racette, et al. 2012] The comparison workers included Midwestern carpenters, brick layers, and construction workers who had never been welders or welder helpers, and had < 500 hours of welding fume exposure. There were no other exclusions relating to exposure in either group, as our primary analysis was based on estimated exposure, regardless of group. Exclusion criteria included Non-English speakers,

use of dopamine receptor blocking medications, stroke, or presence of neurologic or psychiatric conditions unlikely related to Mn exposure.

Welding Exposure Assessment

In order to assess dose-response associations, we used three exposure welding metrics [Racette, et al. 2012] that reflect total duration, mean intensity, and total cumulative exposure (intensity-weighted welding years). The cumulative exposure metric combines the intensity and duration of welding exposure components, and is a surrogate for cumulative Mn exposure ($\text{mg Mn/m}^3 - \text{years}$). We calculated this as detailed previously, [Racette, et al. 2012] using complete work history data. We obtained work history data from a validated structured questionnaire [Hobson, et al. 2009] that subjects completed in person. The questionnaire also inquired about other occupational exposures, age, sex, race, ethnicity, medical history, history of head injury resulting in hospitalization, occupational exposure to solvents or pesticides, consumption of alcohol in the past year, and current and past use of tobacco (ever/never cigarettes, pipe, cigars, or chewing tobacco).

Neuropsychological Testing

Trained test administrators conducted all cognitive assessments. Five tasks were administered that assess cognitive control in one or more of its subdomains (e.g. response inhibition, working memory, fluency). The z-scores for the main outcome variable of each task, the number of standard deviations above or below the mean for the respective task, were first aligned such that a negative z-score indicated worse performance for each of the five tests. We then averaged these five z-scores to create the composite score, deemed the “cognitive control summary score.” These five tasks, described below, are sensitive, specific, and validated measures that are frequently used in the cognitive neuroscience literature.

1. Verbal Fluency (VF): To assess letter fluency, the participant lists as many words as possible that fit a criterion in one minute. The age- and sex-adjusted total scaled score was used in the composite score.[McDowd, et al. 2011, Mikos, et al. 2011]
2. Letter Number Sequencing (LNS): The participant must use working memory to repeat and rearrange randomly assorted letters and numbers into numerical and letter order. The age- and sex-adjusted total scaled score was used in the composite score.[Gabrieli, et al. 1996]
3. Two-Back Letter Task (2B): The participant quickly decides if a stimulus matches the one that appeared two trials earlier, testing both working memory and response inhibition. Discriminability (mean accuracy rate minus the false positive response rate) was used in the composite score.[Braver, et al. 2001, Braver, et al. 2001, Costa, et al. 2008]
4. Go-No-Go (GNG): The participant must exercise response inhibition to one of four stimuli as each stimulus appears in random order at fast intervals. Discriminability was used in the composite score.[Braver, et al. 2001, Gauggel, et al. 2004]

5. Simon Task (SM): This task is based on the Simon Effect in which an impertinent spatial stimulus will slow down reaction time to a target stimulus when the correct response button is spatially discordant with the impertinent, distracting stimulus.[Wylie, et al. 2010] The difference between the reaction time for congruent and incongruent reaction time was used in the composite score.

VF was available for all 95 subjects, LNS was available for 94, 2B for 86, GNG for 90, SM for 82, and all five tests for 74 workers. We calculated the cognitive control summary score only for those workers who successfully completed all five tasks.

Vocabulary and Matrix Reasoning (Wechsler Adult Intelligence Scale-Third Edition, WAIS-III) were used to assess verbal and nonverbal intelligence, respectively. Age- and sex-adjusted scaled scores were averaged to estimate IQ. This estimate was used to determine whether IQ may confound the association between Mn exposure and cognitive control.

Clinical Assessment

To assess associations between cognitive and motor performance, all subjects were examined by a movement disorder specialist by using the Unified Parkinson Disease Rating Scale (UPDRS), motor subsection part 3 (UPDRS3).[Fahn, et al. 1987]

Statistical Analysis

We performed all statistical analyses using Stata 11.0 (College Station, Texas). We assessed the association between welding exposure and the cognitive control summary score using linear regression. In addition, we also considered z-scores for each of the five individual tasks as they may differ in their sensitivity to Mn exposure. We retained our exposure variables, as a continuous measure in the models, and then used locally weighted scatterplot smoothing (LOWESS) to verify the appropriateness of linear modeling of exposure. We adjusted all models of the association between welding and cognitive control *a priori* for age and sex. We also examined the effect of adjusting for IQ, years of education, consumption of tobacco and alcohol, history of head injury, and occupational exposure to solvents or pesticides. Finally, we verified that results were unchanged by excluding the three subjects who were Hispanic or non-white and one low Mn-exposed subject who reported occupational exposure to mercury.

Results

Characteristics of Subjects

Most subjects were non-Hispanic Caucasian men (Table I). Subjects were 23 to 66 years of age, with a median age of 53. They represented a wide range of welding fume exposure, ranging from no exposure to 46.2 years of exposure (median 15.5 years). UPDRS3 scores ranged substantially as well, from zero to 25 (median 10). As in the full welder cohort, [Racette, et al. 2012] UPDRS3 scores were markedly higher (worse) among the workers from the welding worksites than in the other workers (Table I). Among the Mn-exposed workers, UPDRS3 was positively associated with intensity-weighted welding years but not duration of welding fume exposure after accounting for age, sex, and examiner (data not shown in tables).

Welding Fume Exposure and Cognitive Control

Workers from the welding worksites had lower IQ and cognitive control test scores than workers from other (non-welding) worksites, specifically for 2B, GNG, and LNS (Table I, respective unadjusted t-test p-values were 0.02, 0.09, and 0.14). The cognitive control summary score (i.e. mean z-score) was strongly inversely associated with intensity of welding exposure, after adjusting for age, sex, and duration of exposure ($p=0.009$), whereby welders performed 0.53 (95% CI 0.14, 0.93) standard deviations worse than workers not exposed to welding fume (i.e. per unit change in the intensity score, with welder helpers and workers around welding demonstrating intermediate test performance) (Table II). Secondary analyses indicated that the association between welding intensity and cognitive control was driven by performance on the LNS and 2B cognitive tests (both p-values 0.02; Table II). However, there was no evidence that total duration of welding fume exposure was inversely associated with the summary score or any individual test scores. Accordingly, there was only a modest inverse association between the cognitive control summary score and intensity-weighted welding years ($p=0.14$; Table III). Although confidence intervals widened, these age- and sex-adjusted associations were otherwise fairly similar when we simultaneously also accounted for other occupational exposures, head injury, tobacco, alcohol, educational attainment, race, and ethnicity (Table III).

Discussion

This study identified significantly poorer performance on cognitive control tasks in relation to intensity of welding fume exposure. This association was linear, dose-dependent, and driven primarily by the two working memory tasks within our battery. Consequently, these findings may have relevance to occupational exposure standards for Mn and other components of welding fume. The association was more modest when considering intensity-weighted welding years which combines both intensity and duration of welding fume exposure, as we saw no evidence that total years of exposure were inversely associated with test performance after accounting for intensity of exposure. Our study findings are consistent with other studies of Mn-exposed subjects in whom working memory was shown to be impaired in a dose-dependent manner, using a set of different tasks. [Bowler, et al. 2015, Bowler, et al. 2007] Overall, these findings add to the existing literature on basal ganglia-mediated cognitive dysfunction in Mn-exposed workers.

This study has multiple strengths, including use of a relatively larger sample size than most previous studies, use of non-litigant workers, application of a rigorous hypothesis-driven approach to minimize the number of comparisons, and the ability to adjust for numerous potential confounders including other occupational exposures and alcohol consumption. Equally importantly, our welding-exposed subjects came from a well-defined work force from one of three Midwestern welding worksites, [Racette, et al. 2012] and the reference workers geographically similar tradeworkers, selected to be comparable to these welding-exposed workers. This rigorous approach adds confidence to the associations we observed. However, our results are somewhat weaker than in previous studies that have demonstrated robust results in domains other than just working memory, [Bowler, et al. 2007, Bowler, et al. 2007] possibly explained by differences in study populations.

There are a few limitations to the study design that may have affected our results. The exposure metrics were estimated from work histories and previously published intensity weights, [Racette, et al. 2012] since systematic exposure air monitoring data were not available. Biomarkers of exposure, such as blood, only reflect recent exposures and are not reliable to quantify long-term exposures.[Baker, et al. 2014, Wongwit, et al. 2004] The healthy worker survivor effect may also limit our ability to detect a dose-response relationship with cognitive control dysfunction. While we believe that motor dysfunction would impact workers' ability to perform their job duties more than cognitive dysfunction, we may be underestimating the importance of executive functions in welding occupations. It is possible that all of the results were biased upward (away from the hypothesized direction) by the healthy worker survivor effect. This might occur if workers with better cognitive control performance are more able to retain their jobs at the welding worksites. Of particular note, if ability to weld depends on response inhibition, then this could explain the lack of an inverse association between intensity-weighted welding years and GNG test performance, contrasting with a strong suggestion that GNG performance was worse in workers from the welding worksites in comparison to the other workers. Finally, it is also possible that our sample size was too small, although this study was larger than many previous studies including welders.

In conclusion, these results contribute to the evolving literature on basal ganglia-mediated cognitive dysfunction. Our findings are slightly different than previous literature in that they suggest that there is more modest evidence of cognitive control dysfunction associated with Mn exposure, and that working memory is particularly influenced. Our results also build on past research by suggesting the intensity of exposure may be more important than total duration of exposure for these outcomes. Thus, workers may particularly benefit from practices that reduce exposure intensity.

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Table I

Characteristics of Subjects and Performance on Cognitive Testing, Overall and by Worksite Type

	All Workers	Welding Worksite	Other Worksite
	N = 95	N = 82	N = 13
	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>
Non-Hispanic Caucasian	92 (97)	80 (98)	12 (92)
Male	88 (93)	76 (93)	12 (92)
	<u>Mean (SD)</u>	<u>Mean (SD)</u>	<u>Mean (SD)</u>
Age, years	49.7 (11.8)	51.2 (11.5)	40.2 (9.1)
Minimum	23	25	23
Median	53	55	40
Maximum	66	66	53
Duration in a job with any welding exposure, years	18.2 (13.5)	20.6 (12.9)	3.2 (5.4)
Minimum	0	0	0
Median	15.5	17.7	0
Maximum	46.2	46.2	17.6
Intensity-weighted welding years ^a	7.8 (9.6)	8.9 (9.8)	0.4 (0.7)
Minimum	0	0	0
Median	3.7	4.6	0
Maximum	37.9	37.9	2.2
Education, years	12.7 (1.2)	12.6 (1.1)	12.9 (1.6)
Minimum	9	12	9
Median	12	12	13
Maximum	16	16	15
IQ ^b	9.9 (2.6)	9.8 (2.6)	10.9 (2.3)
Minimum	4	4	7
Median	10	10	11
Maximum	15	15	15
Letter Number Sequencing ^c	9.8 (2.6)	9.6 (2.7)	10.8 (1.6)
Minimum	4	4	7
Median	10	10	11
Maximum	17	17	13
Verbal Fluency ^d	8.7 (2.9)	8.6 (2.8)	9.5 (2.8)
Minimum	2	2	4
Median	9	9	9
Maximum	16	16	15
Go No Go Discriminability ^e	0.84 (0.13)	0.83 (0.14)	0.89 (0.07)
Minimum	0.21	0.21	0.76
Median	0.88	0.87	0.90
Maximum	0.99	0.99	0.97
Two Back Discriminability ^f	0.59 (0.17)	0.57 (0.17)	0.69 (0.17)

	All Workers	Welding Worksite	Other Worksite
	N = 95	N = 82	N = 13
	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>
Minimum	0.16	0.16	0.27
Median	0.61	0.58	0.76
Maximum	0.93	0.93	0.91
Simon (Reaction Time) ^g	55 (33.7)	55.9 (34.4)	50.1 (30.4)
Minimum	-35.75	-35.75	-6.75
Median	55.5	55.5	47.5
Maximum	140	140	93.75
UPDRS3	11.1 (7.2)	12.5 (6.6)	1.9 (1.6)
Minimum	0	1	0
Median	10	12.25	2
Maximum	25	25	6

^aCalculated according to Racette et al. 2012.

^b Average of age- and sex-adjusted total scaled scores for vocabulary and matrix reasoning (Wechsler Adult Intelligence Scale – Third Edition, WAIS-III), excludes two workers from a welding worksite without these data.

^c Age- and sex-adjusted total scaled score, excludes one worker from a welding worksite who was unable to complete the test due to time constraints.

^d Age- and sex-adjusted total scaled score.

^e Excludes 5 workers from a welding worksite.

^f Excludes 9 workers from a welding worksite.

^g Excludes 13 workers from a welding worksite.

Abbreviations: UPDRS3 Unified Parkinson Disease Rating Scale, motor subsection 3.

Cognitive Control Task Performance in Relation to Duration and Intensity of Welding Fume Exposure

Table II

Outcome (z-score) ^b	Mutually Adjusted and Adjusted for Age and Sex						
	Duration of Welding Exposure (per Year)			Intensity of Welding Exposure ^a			
	N	Beta Coefficient ^c	95% CI	p-value	Beta Coefficient ^d	95% CI	p-value
Cognitive Control Summary Score	74	0.011	-0.004, 0.025	0.14	-0.53	-0.93, -0.14	0.009
LNS Scaled Score	94	0.018	-0.004, 0.039	0.11	-0.74	-1.35, -0.13	0.02
VF Scaled Score	95	0.006	-0.015, 0.027	0.56	-0.15	-0.76, 0.45	0.62
GNG Discriminability	90	0.019	-0.003, 0.040	0.09	-0.19	-0.81, 0.43	0.54
2B Discriminability	86	0.011	-0.011, 0.033	0.33	-0.71	-1.32, -0.11	0.02
SM, Reaction Time Interference Effect ^e	82	0.012	-0.012, 0.037	0.33	-0.19	-0.92, 0.53	0.59
IQ (z-score)^b							
Total Scaled IQ (Verbal and Matrix Combined)	93	0.009	-0.012, 0.030	0.41	-0.64	-1.25, -0.03	0.04
Scaled Verbal	93	0.008	-0.014, 0.030	0.45	-0.52	-1.14, 0.10	0.10
Scaled Matrix Reasoning	95	0.009	-0.013, 0.030	0.42	-0.58	-1.19, 0.030	0.06

^aIntensity-weighted welding years divided by total duration (years) of welding fume exposure, resulting in a continuous variable between 0 and 1 assigned according to the intensity weighting as detailed in Racette et al. 2012.

^bLower cognitive control summary score (mean of all five tasks' z-scores) or lower individual cognitive control task z-score indicates poorer performance.

^cChange in z-score (standard deviations from the mean) per year of welding fume exposure.

^dChange in z-score (standard deviations from the mean) per one unit change in intensity of exposure, where 0 = no exposure and 1 = maximum intensity.

^eMultiplied by negative one so that a lower score indicates poorer performance.

Abbreviations: CI, Confidence Interval; LNS, Letter Number Sequencing; VF, Verbal Fluency; GNG, Go-No-Go; 2B, Two-Back Letter Task; SM, Simon Task

Table III
Cognitive Control Task Performance in Relation to Intensity-weighted Welding Years

Outcome (z-score) ^b	N	Adjusted for Age and Sex			Fully Adjusted ^a		
		Beta Coefficient ^c	95% CI	p-value	Beta Coefficient ^c	95% CI	p-value
Cognitive Control Summary Score	74	-0.011	-0.025, 0.004	0.14	-0.011	-0.029, 0.007	0.22
LNS Total Scaled Score	94	-0.016	-0.039, 0.007	0.16	-0.018	-0.045, 0.008	0.17
VF Total Scaled Score	95	-0.007	-0.029, 0.015	0.51	-0.006	-0.031, 0.019	0.66
GNNG Discriminability	90	0.008	-0.015, 0.03	0.48	0.010	-0.017, 0.037	0.46
2B Discriminability	86	-0.022	-0.044, -0.00002	0.05	-0.020	-0.046, 0.006	0.12
SM, Reaction Time Interference Effect ^d	82	0.006	-0.0196, 0.031	0.66	0.008	-0.020, 0.036	0.57

^a Adjusted for age (continuous), sex, tobacco use (ever/never smoking cigarettes, cigar or pipe; ever/never use of chewing tobacco), alcohol consumption (frequency of drinking in past year, drinks per day when drinking in the past year, history of alcoholism), ever head injury requiring hospitalization, occupational exposure to pesticides, occupational exposure to solvents; and excludes one Hispanic subject, two non-white subjects, and one subject with reported occupational exposure to mercury.

^b Lower cognitive control summary score (mean of all five tasks' z-scores) or lower individual cognitive control task z-score indicates poorer performance.

^c Change in cognitive control summary score or individual test z-score (standard deviations from the mean for that task) for each intensity-weighted welding year of exposure (Racette et al. 2012).

^d Multiplied by negative one so that a lower score indicates poorer performance.

Abbreviations: CI, Confidence Interval; LNS, Letter Number Sequencing; VF, Verbal Fluency; GNNG, Go-No-Go; 2B, Two-Back Letter Task; SM, Simon Task