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Prospective study on neurotoxic effects in manganese-exposed bridge construction welders

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A B S T R A C T

Background: In a group of 43 confined space welders dose–effect relationships had been identified for adverse neurological/neuropsychological functional effects in relation to manganese (Mn) in blood or air (cumulative exposure index). The welders' exposure to Mn was unprotected and with poor ventilation, lasting on average 16.5 months. A follow-up examination 3.5 years later, after cessation of confined space welding, was carried out to re-assess the status of mood, movement/neuromotor and cognitive functions, and olfaction.
Methods: In 2008, 26 welders (70% response rate) were retested using a similar methodology as at baseline (Bowler et al., 2007). A general linear model was used to estimate individual-specific endpoint differences over time. Mean age was 47 years, mean years of education 12.4, and mean total years of welding 16.9 years. Thirteen participants no longer welded.
Results: At follow-up, mean blood Mn concentration had decreased from 10.0 to 8.4 μg/L ($p = 0.002$). Those still welding had higher blood Mn than those no longer welding (9.9 μg/L vs. 6.8 μg/L, $p = 0.002$). Several domains of cognitive functioning improved substantially as shown by large effect sizes. Emotional disturbance improved only slightly clinically, but complaints of depression and anxiety persisted. Motor dexterity/tactile function and graphomotor tremor improved significantly, while psychomotor speed remained unchanged. The findings of the neurological examination (UPDRS) did not change compared to baseline, whereas rigidity, dominant postural hand tremor and body sway worsened. Olfactory test scores remained depressed.
Conclusion: After 3.5 years of cessation of confined space welding, only cognitive function improved significantly, while olfactory, extrapyramidal, and mood disturbances remained constant or were exacerbated. This suggests differential intrinsic vulnerabilities of the brain loci involved with Mn exposure. As the Mn exposure of the Bay Bridge welders frequently exceeded the Cal-OSHA TLV of 0.2 mg Mn/m^3 at baseline, a more stringent preventive measure is recommended for confined space welding.

1. Introduction

Manganese (Mn) is of vital importance for humans in small amounts, but neurotoxicity occurs at higher doses. The first clinical description of a neurological syndrome – postural instability, frequent hallucinations, emotional lability – associated with inhalation exposure to Mn dust was made by Couper (1837) in a series of five pyrolusite ore (MnO_2) crushers. In the occupational setting, the syndrome became known as manganism and has been reported in miners, chemical industry and dry-cell battery workers, steel production and Mn alloy workers, and welders (Feldman, 1999; World Health Organization – International Programme on Chemical Safety, 1981). This neurotoxic condition, often described as Mn-induced parkinsonism, presents features similar to idiopathic Parkinson's Disease (IPD). However, it differs

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from IPD by younger age of onset, a normal [^{18}F]L-DOPA PET scan, lack of response to L-DOPA treatment, postural tremor, and Mn deposits (MRI scan) in the corpus striatum and globus pallidus during the chronic exposure phase (Feldman, 1999).

At present, the incidence of clinical cases of manganism is rather low; however, numerous articles report on mild neurotoxic effects associated with workplace inhalation exposure to Mn. Some of these effects have been termed ‘‘subclinical’’, implying that they can occur in otherwise asymptomatic individuals and may represent early indicators of manganism. The nature of these effects, the Mn exposure levels at which they occur and their potential for progression or reversibility are therefore of particular clinical and regulatory interest (MRC-IEH/IOM: Institute for Environment and Health/Institute of Occupational Medicine, 2004). Subclinical neurotoxic effects include basal ganglia-related perturbations (motor inefficiency), cognitive deficits (e.g. working and delayed memory problems), and mood disturbances.

Health compensation claims or law suits involving welders are not uncommon in the USA and concern is growing about the potential neurologic effects associated with Mn exposure from welding fumes (NIOSH, 2009). In particular, welders working in confined spaces (e.g. pipefitters, boiler makers, shipyard and construction workers) may experience elevated Mn exposures (Harris et al., 2005; Meeker et al., 2007). In the welding setting, there is a risk of being overexposed to readily bio-available Mn of respirable particulate through fumes from using Mn-containing rods, wires, fluxes and base metal (steel and alloys), especially when welding occurs without appropriate ventilation and/or personal protection equipment. Significant inverse dose–effect relationships were found for ambient air-Mn (cumulative exposure) and/or blood-Mn with performance on motor and/or cognitive tests in confined space bridge welders (Bowler et al., 2007) or shipyard and heavy machinery welders (Ellingsen et al., 2008). The former study also showed dose–effect with mood changes using the Symptom Checklist-90-Revised (SCL-90-R), whereas the latter did not when using the Q-16 symptom questionnaire – a less discriminative measure developed for solvent exposure.

In January 2005, we examined a cohort of confined space welders engaged in the construction of a new span of the San Francisco-Oakland Bay Bridge. Some time before this study, the welders had suffered from subacute Mn exposure episodes (with signs of *locura manganica*) during the active phase of the bridge reconstruction, as documented by industrial hygiene surveys from January 2003 to June 2004 conducted for Cal-OSHA compliance (Park et al., 2006, 2009). This baseline study revealed neurological, neuropsychological, and neurophysiological (sensory/autonomic) adverse effects significantly associated with the Mn concentration in whole blood and/or a cumulative Mn exposure index (CEI) (Bowler et al., 2007). This paper describes a follow-up health survey in this cohort of welders we conducted in August 2008. They were re-tested and neurological, neuropsychological, and olfactory functions were evaluated. The goal of this follow-up was to determine the potential reversibility of Mn-related health findings in the Bay Bridge cohort after 3.5 years reduction or cessation of Mn exposure through welding. We hypothesized that welders who had short-term subacute Mn exposure, once removed from over-exposure to Mn, will exhibit improved health outcomes.

2. Methods

2.1. Study population

At the 2005-baseline study, the initial welders' cohort of 43 males was on average 43.8 years old, had 12.6 years of education, welded on average 16.5 months on the bridge, and was exposed to Mn-containing welding fumes with little or no personal protection. Mean time-weighted average (TWA) of Mn-air ranged from 0.11 to 0.46 mg/m^3 [frequency above Cal-OSHA TLV of 0.20 mg/m^3 was 55% (88 samples out of 159 total non-short-term samples)] (Bowler et al., 2007). Of the 43 participants in the 2005-baseline examination, 26 were recruited for the 2008-follow-up study, of whom 13 were still occupied in welding operations. A minimum language proficiency was required to work on the Bay Bridge construction project, and therefore it was considered valid to use data from welders for whom English is a second language.

The majority of the Bay Bridge welder cohort had previously been involved in workers' compensation proceedings (all of the proceedings were completed prior to the follow-up study). In the consent form, participants were asked to take part in the study, in order to update information regarding their mental and physical health, as well as their work history since their earlier visit. The data collected in the present study were not used for purposes other than scientific research and were not provided or used in the welders' previously concluded workers' compensation proceedings. The researchers were not compensated by the workers' compensation legal team.

2.2. Procedures and study design

Approval for the follow-up study was obtained from the Institutional Review Boards (IRB) at San Francisco State University and the U.S. Department of Defense. From the original group of 43 welders, 6 had relocated out of the state of California, leaving 37 eligible for recruitment and testing. Among them, 6 were unreachable or did not return telephone calls and one person declined. For the remaining total of 30, follow-up appointments were scheduled for August 2008. Four did not appear for their appointments, resulting in a response rate of 26/37 (70.3%).

The study employed a prospective longitudinal design. The methodology used at follow-up was similar to baseline. Participants were introduced to the intent and methodology of the study with recruitment letters and telephone calls. On the testing day, each participant first signed the IRB consent forms outlining confidentiality procedures and was then assigned to a neuropsychological tester who was, whenever possible, the same person as at baseline. In the consent form, participants were asked to take part in the study in order to update information regarding their mental and physical health, as well as their work history since their earlier visit.

The neuropsychological tests were administered in the same order to all participants. Trained graduate students administered the motor, olfactory, and CATSYS (Danish Product Development, 1996) tests. A board-certified neurologist (JW), skilled and experienced in movement disorder assessments, re-administered the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987). Work and health histories related to the period after the baseline study were collected. The participants were briefly interviewed by the P.I. (RMB), followed by the neuropsychological testing and a neurological examination. Self-report measures of health symptoms and standardized mood scales (SCL-90-R), and BRFSS (Behavioral Risk Factor Surveillance System) were completed by the participants and reviewed for completeness. Blood samples were collected by a certified phlebotomist and analyzed for trace levels of Mn and Pb by the same Microbiology and Environmental Toxicology Laboratory at the University of California at Santa Cruz (Smith et al., 2007). Appropriate quality assurance procedures were followed throughout the course of the study. All test protocols were scored and double-scored using the respective test manuals and any differences in scoring were reviewed and resolved by the P.I. Double data-entry procedures were utilized. The data were entered into an SPSS 16 file and converted to a SAS v9.1 dataset.

2.3. Exposure assessment

Exposure characteristics at follow-up were collected via interview by an expert on occupational exposures (RP). The work histories included total number of years of career welding, current employment status and type of employment with respect to welding, total number of months engaged in welding since January 2005, and the percentage of time spent performing automated or manual welding. Personal monitoring for air-Mn was no longer feasible after the baseline study.

2.4. Blood sampling

At follow-up, 24 out of 26 participants provided a 4-mL venous blood sample, one had a needle phobia and another was examined on a later day, when the phlebotomist was no longer available. The refrigerated blood samples were hand-carried in an appropriate cooler to the laboratory facility where they were analyzed for Mn and Pb using the same methodology as at baseline (Smith et al., 2007).

2.5. Olfactory test

Olfactory function was re-assessed with the University of Pennsylvania Smell Identification Test (UPSIT) (Doty, 1995). The administration and scoring of this 'scratch and sniff' test followed the standardized procedures described in the test manual. Qualitative diagnostic ratings of olfaction (normosmia, mild microsmia, microsmia, anosmia) were assigned to each welder's test scores based on normative data (similar on demographics) from the University of Pennsylvania Smell and Taste Center.

2.6. Neurological assessment

The neurologist (JW) administered and rated the Motor scale and the Activities of Daily Living (ADL) scale of the UPDRS for 25 of the participants. Postural sway and postural hand tremor were measured with the same CATSYS system as at baseline following standardized procedures (Després et al., 2000).

2.7. Neuropsychological testing

The same battery of domain-tailored sensitive neuropsychological tests used at baseline was included at follow-up with the exception of those tests which did not show impairment at baseline, in order to conserve time and resources. Tests at follow-up included: the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997), Rey–Osterrieth Complex Figure (Lezak et al., 2004; Strauss et al., 2006), Stroop Color/Word (Golden, 1978; Strauss et al., 2006), Delis–Kaplan Executive Function System Design Fluency (Delis et al., 2001), and Auditory Consonant Trigrams (Boone et al., 1990; Lezak et al., 2004). The complete neuropsychological test battery is presented in Table 1 and shows the specific cognitive tests used for each functional domain, the cognitive function(s) assessed, and the type of score used for each test. Mood was assessed with the Symptom Checklist-90-Revised (SCL-90-R) (Derogatis, 1992) and the Behavioral Risk Factor Surveillance System (BRFSS) (Hennessy et al., 1994). Motor dexterity, grip strength, and graphomotor tremor of the hands were re-assessed using Grooved Pegboard, Fingertapping, Dynamometer, and Parallel Lines test respectively (Lezak et al., 2004).

Re-administering a test of cognitive effort such as the Tomm, given at baseline, would increase its transparency as a test of

Table 1
Neuropsychological cognitive test battery.

Domains of function and cognitive tests	Cognitive function(s) assessed	Type of score
Intelligence Quotient (IQ) (WAIS-III)		
Full IQ	General cognitive and intellectual function (Performance & Verbal quotients)	Composite Index Score[a]
Performance IQ	Nonverbal cognitive functions (non-verbal scaled subtest scores)	Composite Index Score[a]
Verbal IQ	Verbal intellectual ability (verbal scaled subtest scores)	Composite Index Score[a]
Cognitive flexibility and executive functioning		
Stroop Color/Word	Inhibiting automatic response of reading color words printed in incongruent colors	*T* Score[b]
Design Fluency – Total Correct	Nonverbal analog of verbal fluency	Scaled Score[c]
Information processing speed		
Stroop Color *T* Score	Speeded naming of color hues	*T* Score[b]
Stroop Word *T* Score	Speeded reading of color words	*T* Score[b]
Working memory/attention and concentration/learning		
WAIS-III Working Memory Index (WMI)	Manipulation of information in short term memory	Composite Index Score[a]
WAIS-III Digit Span – longest digits (forward)	Repetition of digits	Raw Score
WAIS-III Digit Span – longest digits (backward)	Mental tracking of digits requiring working memory	Raw Score
WAIS-III Letter-Number Sequencing Scaled Score	Measure of attention and sustaining concentration and set shifting	*z* Score[a]
Auditory Consonant Trigrams 18″ *z* Score	Measure of frontal lobe function, memory with 18 s distraction	*z* Score[d]
Visuospatial memory		
Rey–Osterrieth Immediate Recall *T* Score	Visuo-spatial constructional ability and immediate (3 min) recall	*T* Score[b]
Rey–Osterrieth Delayed Recall *T* Score	Visuo-spatial constructional ability and delayed (30 min) recall	*T* Score[b]
Visuomotor tracking speed (WAIS-III)		
Processing Speed Index (PSI)	Performance & speed on 2 non-verbal WAIS-III tests	Composite Index Score[a]
Digit Symbol Coding	Fine visual-motor speed and accuracy of non-verbal learning	Scaled Score[a]
Verbal skills (WAIS-III)		
Verbal Comprehension Index (VCI)	Verbal abstraction, knowledge, conceptualization, and oral expression	Composite Index Score[a]
Comprehension	Measure of common sense, practical knowledge, social judgment	Scaled Score[a]
Similarities	Capacity for verbal concept formation, abstract thinking	Scaled Score[a]
Vocabulary	Word knowledge – expressive vocabulary	Scaled Score[a]
Information	Fund of general information and knowledge about the world	Scaled Score[a]

Composite Index Score: $M = 100$, $SD = 15$; *T* Score: $M = 50$, $SD = 10$; Scaled Score: $M = 10$, $SD = 3$; *z* Score: $M = 0$, $SD = 1$.
[a] Age-corrected (Wechsler, 1997).
[b] Age-corrected (Strauss et al., 2006).
[c] Age-corrected (Delis et al., 2001).
[d] Age-corrected (Boone et al., 1990).

malingering (Guilmette et al., 1993) and thus invalidate the results. For this reason, the Victoria Symptom Validity Test (VSVT) (Slick et al., 2005) was chosen as an additional test of effort to confirm or disconfirm the validity of a welder's cognitive and mood impairments. Participants are presented a total of forty-eight 5-digit items and asked to make a delayed forced-choice identification of the preceding item. Scores are rated as questionable, valid (at or above chance), or invalid (below chance). The entire set of 48 items had excellent internal consistency reliability, with a coefficient alpha of 0.89, and showed excellent predictive validity (Slick et al., 2005).

2.8. Missing data

A WAIS-III Full-Scale Intelligence Quotient (FSIQ) and a Verbal Comprehension Index (VCI) could not be computed for 7 non-native English speakers who did not complete all subtests of the WAIS-III. These 7 participants did, however, understand the instructions to the non-verbal tests. One participant, who re-scheduled too late, did not complete the entire test battery, resulting in missing data for the neurological and CATSYS tests. Two participants were excluded on the dynamometer test due to abnormally low scores (>3 SDs below the mean). One participant had missing data for the olfactory test. The reduced paired sample size for the SCL-90-R analyses was due to 2 participants at follow-up not completing the battery for personal scheduling reasons and 1 participant not completing it at baseline.

2.9. Statistical analysis

The descriptive statistics for continuous variables were means, standard deviations, and ranges. Percentages were reported for categorical variables. For the neuropsychological tests, age-adjusted scores for 21 variables were used. The primary analysis for these variables was the general linear model with the dependent measure the individual-specific differences between follow-up and baseline. The independent variable was ethnicity. It should be pointed out that the original 2005-baseline cohort of 43 welders comprised 22 white and 21 non-white males. This balanced proportion was no longer present in the group of 26 participants who returned for follow-up, i.e. 7 white and 19 nonwhite. Reports by the welders led us to assume that white welders were more reluctant to accept the poor working conditions on the bridge. This intrinsic selection bias contributed to test scores and therefore ethnicity was included in all statistical analyses of these test scores. The ethnicity-adjusted estimated mean difference between 2008 and 2005 was the estimated value of the coefficient of the intercept in the linear model. The t-statistic was applied and the corresponding p-value reported. A default α level of 0.05 was used for most statistical tests. For comparing groups on neuropsychological tests within a domain, adjustments [False Discovery Rate (FDR); Benjamini and Hochberg, 1995] for multiple comparisons were used. The technique proposed by Benjamini and Hochberg is a sequential approach to controlling the False Discovery Rate in multiple comparisons. It yields much greater power than the Bonferroni technique and has been used in reporting results in several research applications (Williams et al., 1999). In addition, effect size was calculated according to Cohen's d statistic (Cohen, 1992), where the input parameters were the estimated mean difference obtained from the linear model, the Pearson correlation coefficient estimated, and the standard deviation calculated as the pooled standard deviation. The standard deviation was computed by using the product of the standard error of the estimated intercept of the linear model and the square root of the sample size of the specific neuropsychological test variable, where only non-missing data were used.

Multivariate analysis of covariance and nonparametric tests (Wilcoxon Rank Sum) were also used. These analyses were carried out using SAS/STAT software (SAS Institute Inc., 2003).

3. Results

3.1. Study population and exposure characteristics

The demographics, work and exposure characteristics, and biomarkers of exposure for the 26 participants of the follow-up study were compared with those of the baseline study (Table 2). At follow-up, mean age was 47.0 years, mean education was 12.3 years, and 73.1% (n = 19) of the cohort were non-white (14 Hispanic, 4 African American, 1 Asian). Chi-square analysis on ethnic differences between baseline and follow-up showed that proportionally more Hispanics than non-Hispanics returned for

Table 2
Bay Bridge welder cohort: demographics, work and exposure characteristics of subjects with both baseline and follow-up participation.

	Baseline (2005)				Follow-up (2008)			
	n	Mean (%)	SD	Range	n	Mean (%)	SD	Range
Demographics								
Age	26	43.4	9.2	28–62	26	47	9.2	32–65
Years of education	26	12.3	2	7–17	26	12.3	2	7–17
Ethnicity								
White	7	(26.9)			7	(26.9)		
Non-white	19	(73.1)			19	(73.1)		
Smoking								
Current smokers	4	(15.4)			2	(7.7)		
Ex-smokers	11	(42.3)			13	(50)		
Work and exposure								
Total years welding	26	15	10.9	1.1–32	26	16.9	10.9	1.1–34
Currently welding	17	(65.4)			13	(50.0)		
Disabled	4	(15.4)			7	(26.9)		
Doing other work	0				3	(11.6)		
Injured	0				2	(7.7)		
Laid off	5	(19.2)			1	(3.8)		
Type of welding (% of time)								
Automatic	25	71.8	23.1	10–100	20	21.7	36.6	0–100
Manual	25	25.6	19.3	0–65	20	62.8	44.4	0–100
Biomarkers of exposure								
Blood Pb (μg/dL)	23	2.5	0.7	1.2–4.2	24	1.9	1.1	0.7–5.2
Blood Mn (μg/L)	23	10.0	2.5	5.8–15.3	24	8.4	2.6	5.1–13.4

follow-up, χ^2 (1, n = 43) = 15.465, $p < 0.001$. When adjusting for ethnicity, welders who did not return at follow-up had significantly better scores on Digit Span (p = 0.045) and Auditory Consonant Trigrams 18 s delay (p = 0.017) on the baseline testing, but they did not differ from returnees on other demographic or outcome (neuropsychological, motor, and neurologic) variables. The number of still active bridge welders decreased from baseline to follow-up, while the overall number of disabled participants increased. Two of the 4 disabled in 2005 remained disabled at follow-up while the other 2 resumed work at other non-welding jobs. Of those not disabled in 2005, 1 welder became injured and 3 disabled at follow-up. Of the 5 laid-off at baseline 2 became disabled, 1 was injured, 1 found other non-welding work, and 1 restarted welding but was newly laid off at follow-up. There were 13 participants who had stopped welding at follow-up (among them 7 were disabled, 2 injured, and 1 laid-off). Non-welders did not differ significantly from those currently welding in 2008 on ethnicity or years of education, but had a higher mean age (non-welders M = 51.62; welders M = 42.31; p = 0.007). The 7 welders disabled at follow-up became disabled due to either a back injury at work, a fall, or other physical or mental injuries. The disabled welders did not differ significantly from non-disabled welders on CATSYS Postural Sway, Condition Eyes Open (p = 0.920) or Condition Foam-Eyes Closed (p = 0.544), although their injuries still may be secondary effects of Mn-related weakness or dizziness causing falls. The total number of years of career welding increased on average from 15.0 to 16.9 years at follow-up.

Blood Mn concentration (MnB) decreased significantly from 10.0 μg/L at baseline to 8.4 μg/L at follow-up (p = 0.002). Further analyses showed a significant (p = 0.002) difference in MnB at follow-up between the 13 current welders (mean = 9.9 μg/L, SD = 2.38) and the 13 non-welders (mean = 6.8 μg/L, SD = 1.72). The non-welders had a significantly lower mean MnB at follow-up than at baseline (n = 10, mean difference = −1.8 μg/L; p = 0.001), whereas for the current welders MnB at follow-up was also lower than at baseline but not statistically significant (n = 12, mean difference = −0.85 μg/L; p = 0.183). The mean MnB for the 7 welders who were disabled at follow-up was 7.2 μg/L (SD = 1.15). Apart from Mn, there was also relative low Pb exposure, but in view of the measured blood Pb concentrations, Pb exposure had decreased further, as shown by the mean PbB which was at baseline 2.5 μg/dL (SD = 0.7) vs. 1.9 μg/dL (SD = 1.1) at follow-up. Between baseline and follow-up, the overall nature of the welding operations dropped from 71.8% automated welding to 21.7%, while manual welding increased from 25.6% to 62.8% (paired data).

3.2. Cognitive effort

On the Victoria Symptom Validity Test, participants had an average score of 44.52 (SD = 4.13) total correct items. All participants obtained qualitative ratings of "valid" for the total number of correct items, indicating performance significantly above chance.

3.3. Olfaction

The UPSIT showed 17 out of 25 (68%) participants with normal sense of smell or mild microsmia at follow-up compared to 14 (56%) at baseline, whereas participants with microsmia or anosmia changed from 11 (44%) at baseline to 8 (32%) at follow-up. However the change in frequencies for these categories over time was not significant. An ANOVA comparison between the paired continuous UPSIT scores of the participants in the baseline (mean = 29.72, SD = 5.24) and follow-up (mean = 29.76, SD = 5.05) studies did not show a statistical difference. Those currently welding in 2008 did not differ from non-welders on total UPSIT scores, adjusting for age (p = 0.280).

3.4. Mood: SCL-90-R and BRFSS

Fig. 1 shows the mean scores and standard errors of the SCL-90-R scales for the baseline and follow-up studies. Compared to the 2005-baseline study, the participants at follow-up obtained clinically lower (but statistically non-significant) mean scores on all individual and global scales. At both time points, however, participants had elevated scores on scales of somatization, obsessive–compulsiveness, interpersonal sensitivity, depression, anxiety, psychoticism, the global severity index, and the positive symptom total. There was no differential effect of ethnicity on SCL-90-R scores.

No significant differences in proportions of clinical caseness (T-score greater than 63 on SCL-90-R global severity index, or on 2 or more SCL-90-R subscales) were found between 2005 and 2008. Additionally, caseness did not differ by ethnicity or welding status.

A MANOVA revealed that the SCL-90-R subscale scores differed between welders and non-welders at follow-up, Pillai's

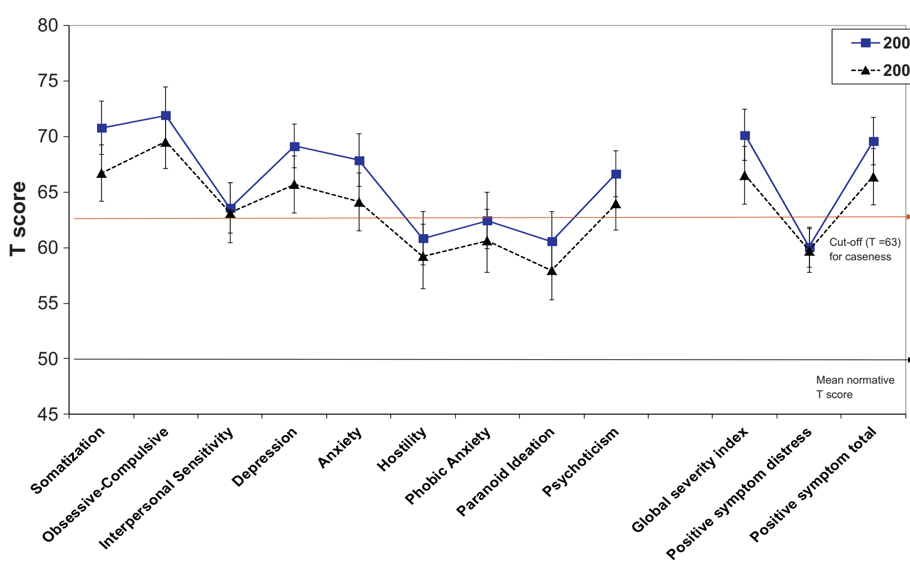

Fig. 1. SCL-90-R mean T scores for the baseline (2005) and follow-up (2008) studies in the Bay Bridge welder cohort.

Trace = 0.760, $F(12,11) = 2.90$, $p = 0.044$, $\eta^2 = 0.76$. Post hoc ANOVAs did not reveal univariate effects, although non-welders had slightly higher mean scores on each scale. Similar analyses compared the 7 participants who were disabled at follow-up to the 19 not disabled and no significant differences were found on the SCL-90-R scales. Additionally, SCL-90 scores were examined separately for non-disabled welders and no difference between 2005 and 2008 was found.

Based on the BRFSS, the average reported days of poor physical health (out of 30) decreased from 14 at baseline to 12 at follow-up. This difference was significant in a repeated-measures analysis of covariance (ANCOVA) adjusting for participants' age, Wilks' $\Lambda = 0.691$, $F(1,23) = 10.275$, $p = 0.004$, $\eta^2 = 0.309$. The average reported days of poor mental health were 15 at baseline and 9 at follow-up. This difference was non-significant, adjusting for age. Non-welders had significantly more days of poor physical health (mean = 17.46, $SD = 11.39$) than those currently welding (mean = 6.42, $SD = 10.03$), $t(23) = 2.65$, $p = 0.017$. Likewise, the number of poor mental health days was higher for non-welders (mean = 14.0, $SD = 11.39$) compared to welders (mean = 3.83, $SD = 4.73$), $t(16,28) = 2.95$, $p = 0.009$.

3.5. Neurological examination: UPDRS, CATSYS, and motor tests

At follow-up, participants had a lower mean score on the UPDRS Activities of Daily Living and total motor scales (Table 3). A UPDRS bradykinesia score was computed by summing scores of Fingertapping, hand movements, rapid alternating movements of hands, leg agility, arising from a chair, gait and body bradykinesia/hypokinesia. Changes in the scores of ADL, total motor, and bradykinesia did not reach statistical significance. However, resting tremor and rigidity increased at follow-up. The difference in rigidity, although significant ($z = -3.235$, $p = 0.001$), was small, suggesting a slight worsening in muscular rigidity. Paired analyses of the CATSYS results (Table 3) revealed a significant worsening at follow-up for dominant hand tremor, as reflected by center frequency ($p = 0.024$) and standard deviation ($p = 0.005$). Tremor intensity and the harmonic index increased but the changes were of borderline significance ($0.05 \leq p < 0.1$). Sway intensity (eyes open) increased significantly ($p = 0.048$). At follow-up a statistically significant increase for Grooved Pegboard (dominant) *T* Score ($p = 0.003$) and a decrease for Parallel Lines (graphomotor hand tremor) score ($p = 0.027$) were observed, while Fingertapping and dynamometer performances did not change significantly (Table 3).

Those currently welding in 2008 did not differ from non-welders on the UPDRS or motor tests, but had significantly higher CATSYS tremor intensity, adjusting for age ($p = 0.050$).

3.6. Neuropsychological performance

Neuropsychological test scores at baseline and follow-up were analyzed using a linear model where the dependent variable is the individual-specific difference between 2008 and 2005 adjusted for ethnicity. Table 4 shows the estimated means and standard deviations. Statistically significant changes were observed for several neuropsychological tests. Effects sizes were computed using Cohen's *d*, taking paired correlations and ethnicity into account. The effect sizes of the significant results (after correction for False Discovery Rate) ranged from 0.36 to 2.42 which, according to Cohen's guidelines (1988), are considered small (>0.20 to <0.50), medium (>0.50 to <0.80) or large (>0.80). The effect sizes (*d*) indicated that differences between the scores at baseline and follow-up, when controlling for ethnicity, were greatest for WAIS-III Vocabulary ($d = 2.42$) and WAIS-III VCI ($d = 2.07$). Differences were also large for Rey–Osterrieth Delayed Recall ($d = 1.11$) and Immediate Recall ($d = 0.91$), WAIS-III Verbal IQ ($d = 1.42$) and Comprehension ($d = 0.81$). The other 3 test differences (Stroop Color/Word, Processing Speed Index, Digit Symbol Coding) were of small or medium effect size (0.36–0.76). Since no air monitoring data were available at follow-up, total years of career welding was used for the study of exposure–effect relationships. No significant effects were found using career years of welding.

Additional analyses were conducted comparing the 13 participants still welding at follow-up to the 13 no longer welding. Independent samples *t* tests indicated that the two groups did not differ significantly on any of the neuropsychological or motor outcome variables at follow-up ($p > 0.05$). Similar analyses compared the 7 participants who were disabled at follow-up to the 19 not disabled. Student's *t* tests were not significant for any of the neuropsychological outcome variables. Further analyses were performed to investigate whether those disabled at follow-up had scored worse on neuropsychological outcomes at baseline than

Table 3
Bay Bridge welder cohort: neurological and motor test results.

	Baseline (2005)			Follow-up (2008)			*p* value (*t* statistic)	Effect size[a,b]
	n	Mean	SD	*n*	Mean	SD		
CATSYS Hand Tremor (dominant hand)/Postural Sway								
Tremor: intensity	23	0.14	0.07	23	0.17	0.07	0.077†	−0.241
Tremor: center frequency	23	7.72	1.49	23	7.16	1.56	0.024*	**−0.419**
Tremor: standard deviation	23	3.33	0.96	23	2.76	0.92	0.005**	**−0.247**
Tremor: harmonic index	23	2.39	0.40	23	2.56	0.41	0.063†	0.226
Sway 1: sway intensity (eyes open)	23	4.19	1.49	23	5.48	2.22	0.048*	**0.518**
Sway 4: sway intensity (eyes closed + foam)	23	9.60	5.95	23	12.33	6.93	0.115	0.121
UPDRS								
Activities of Daily Living	24	6.83	4.98	24	5.13	3.51	0.243 NS	NA
Motor	24	6.38	7.91	24	5.33	4.73	0.889 NS	NA
Bradykinesia	24	4.42	6.61	24	2.63	2.79	0.513 NS	NA
Motor dexterity and strength (dominant hand)								
Dynamometer *T* Score	23	32.52	7.33	23	29.83	8.95	0.050†	−0.724
Gooved Pegboard *T* Score	26	49.54	8.99	26	57.81	12.51	0.003**	**0.689**
Fingertapping *T* Score	26	43.62	12.35	26	45.12	11.28	0.283	0.284
Parallel Lines test	26	1.96	1.28	26	1.46	1.56	0.027*	**−0.347**

NS: nonsignificant (Wilcoxon test); NA: effect size not available.
[a] Effect size measured using Cohen's *d*.
[b] Bolded values shown for effect sizes of significant test differences.
* $p < 0.05$.
** $p < 0.01$.
† $0.05 \leq p < 0.1$.

Table 4
Bay Bridge welder cohort: neuropsychological test results by domain of cognitive function.

	Baseline (2005)			Follow-up (2008)			*p* value (*t*-statistics)	Effect size[a,b]
	n	Mean	SD	*n*	Mean	SD		
Intelligence Quotient (IQ) (WAIS-III)								
Full IQ	19	92.47	12.83	19	94.68	14.99	0.177	0.512
Performance IQ	25	90.28	13.61	25	95.00	12.91	0.065	0.609
Verbal IQ	19	90.74	13.86	19	94.32	16.30	0.016*	**1.423**
Cognitive flexibility and executive functioning								
Stroop Color/Word *T* Score	26	37.35	13.30	26	43.65	10.32	0.016*	**0.364**
Design Fluency – Total Correct Scaled Score	24	9.83	3.19	24	10.25	3.49	0.810	0.063
Information processing speed								
Stroop Color *T* Score	26	37.27	10.03	26	38.77	8.94	0.386	0.229
Stroop Word *T* Score	26	39.12	12.27	26	42.08	8.90	0.459	0.189
Working memory/attention and concentration/learning								
WAIS-III Working Memory Index (WMI)	24	86.67	10.82	24	88.50	11.46	0.197	0.337
WAIS-III Digit Span – longest digits (forward)	25	8.12	2.07	25	8.56	2.42	0.042	0.457
WAIS-III Digit Span – longest digits (backward)	25	4.92	1.58	25	5.56	1.83	0.055	0.470
WAIS-III Letter-Number Sequencing Scaled Score	24	7.83	2.33	24	7.79	2.52	0.577	0.104
Auditory Consonant Trigrams 18″ *z* Score	25	−1.53	0.94	25	−0.86	0.82	0.027	0.407
Visuospatial memory								
Rey–Osterrieth Immediate Recall *T* Score	26	35.50	12.88	26	47.23	15.39	0.001*	**0.905**
Rey–Osterrieth Delayed Recall *T* Score	25	36.16	11.53	25	47.96	19.15	0.001*	**1.113**
Visuomotor tracking speed (WAIS-III)								
Processing Speed Index (PSI)	26	86.31	12.68	26	90.69	10.73	0.039*	**0.640**
Digit Symbol Coding Scaled Score	26	7.23	2.46	26	8.00	2.67	0.008*	**0.761**
Verbal skills (WAIS-III)								
Verbal Comprehension Index (VCI)	19	92.68	16.14	19	95.58	17.57	0.012*	**2.068**
Comprehension Scaled Score	25	8.60	3.08	25	9.72	3.90	0.013*	**0.811**
Similarities Scaled Score	19	8.26	3.98	19	8.89	3.23	0.191	0.812
Vocabulary Scaled Score	21	8.19	3.22	21	9.10	3.75	0.001*	**2.416**
Information Scaled Score	19	9.42	2.50	19	9.58	2.93	0.350	0.511

[a] Effect size measured using Cohen's *d*.
[b] Bolded values shown for effect sizes of significant test differences after Benjamini and Hochberg (1995) False Discovery Rate Adjustment.
* Significant after Benjamini and Hochberg (1995) False Discovery Rate Adjustment.

those who did not become disabled. Results did not indicate a statistically significant difference in baseline scores ($p > 0.05$) between these two groups.

4. Discussion

This is the first follow-up study to be conducted in Mn-exposed welders. Moreover, only two longitudinally designed prospective studies dealing with the outcome of early neurotoxic effects in occupational Mn exposure settings where exposure decreased or ceased over time could be found. An 8-year longitudinal study (Roels et al., 1999) in a Belgian dry-alkaline battery plant showed that the extent of improvement of hand-eye coordination was inversely proportional to the magnitude of the cumulative air-Mn exposure of the past. The results suggest that, beyond a certain level of exposure to Mn in air, the impact of the neurotoxic action of Mn in the brain has reached a point of no return rendering complete reversibility of early neurotoxic effects no longer possible. A follow-up study (Bouchard et al., 2007) in Canadian ferromanganese smelter workers 14 years after cessation of exposure suggested, similar to the present study, persistent deficits for certain neuromotor functions, cognitive flexibility, and adverse mood states, while recovery occurred for other functions. Two other investigations, initially not designed as prospective studies, did not show significant changes of early neurotoxic effects in longitudinal scenarios with decreasing Mn exposure. Lucchini et al. (1999) did not find any difference in the results of four selected computerized tests (Addition, Digit Span, Finger Tapping, Symbol Digit) of the Swedish Performance Evaluation System in a cohort of 30 Italian ferroalloy workers examined in 1990–1991 and 1995. Using the CATSYS system (Danish Product Development, 1996), Blond and Netterström (2007) measured postural hand tremor in 92 Danish Mn-exposed electro-steel workers in 1995 and 2003, but over this time span changes in tremor intensity did not differ significantly from changes observed in controls. The Danish study found also that in the presence of concomitant Pb exposure, Mn-associated neurotoxic effects should be cautiously interpreted by taking into account the potential effect modifying impact of Pb exposure on early neurotoxic endpoints (Blond and Netterström, 2007; Blond et al., 2007). Given the individual PbB concentrations measured at baseline and follow-up [overall PbB range: 5.1–15.3 μg/dL; all below the BEI of 30 μg/dL (ACGIH, 2009)], one may infer that Pb exposure was low at the welding stations during the Bay Bridge reconstruction or at other workplaces after the baseline study and, hence, of no concern for the CNS endpoints studied. This conclusion is corroborated by multiple regression models in which PbB did not appear as significant independent or effect-modifying variable.

The main objective of this prospective study was to evaluate to what extent early Mn-associated neurotoxic effects detected in the 2005-baseline study (Bowler et al., 2007) were reversed 3.5 years later. We postulated an overall decrease of Mn exposure on the basis of changes in work practices and health status reported during the follow-up inquiry. Among the 26 participants in the follow-up study the number of those still welding decreased from 17 to 13 while the number of disabled increased from 4 to 7. Between baseline and follow-up, the overall nature of the welding operations dropped from 71.8% automated welding to 21.7%, while manual welding increased from 25.6% to 62.8% (paired data). The Cal-OSHA compliance survey in the period 2003–2004 of the Bay Bridge reconstruction showed that manual stick welding generated lower ambient air levels of Mn than automated welding (Bowler et al., 2007). As shown by the difference in neurological, motor, and neuropsychological test results between baseline and follow-up, some improvement in function was found following removal of exposure to primarily automated welding. Despite MnB being a poor biomarker of Mn exposure on individual basis, the significant decrease of MnB on a group basis at follow-up (% decrease for paired data: total group 16%; ex-welders 20.1%; still welders 7.9%) seems to confirm a substantial overall reduction of external Mn exposure 3.5 years after the baseline study. It is of note that the 13 welders still welding continued to have higher levels of Mn in blood than the nonwelders (mean = 9.9 μg/L vs. 6.8 μg/L) and showed higher tremor intensity on the CATSYS despite the significant decrease in confined space welding. This suggests that welding continues to be a health hazard for Mn exposure.

The Bay Bridge welder follow-up study focused in particular on four neurological functions, which continued to be adversely affected after 3.5 years as a consequence of subacute Mn exposure from inhalation of welding fumes. The affected endpoints suggested neurotoxic disruptions in neurological functions which apart from dedicated cortical regions also involve specific brain structures, such as the limbic system (olfaction and mood), the basal ganglia (movement/neuromotor), the frontal cortex and the hippocampus (cognitive/neuropsychological function) (Carter et al., 2009).

As to olfaction, only a few occupational studies involving inhalation exposure to Mn addressed the potential effect of Mn on the olfactory function (Antunes et al., 2007; Mergler et al., 1994). This study is the first prospective investigation of olfactory effects associated with Mn exposure. Results of the qualitative diagnostic ratings of the UPSIT did not reveal a significant improvement of the welder's olfactory sense at follow-up, suggesting that functional sequelae remain 3.5 years after subacute Mn exposure from welding fumes. It remains to be elucidated whether this olfactory deficit is linked to irreversible disruptions caused by translocation of Mn from the olfactory bulb to more distal brain structures. It is interesting to note that in rats, only 6 days of inhalation of ultrafine Mn-oxide aerosols (~0.5 mg/m^3, particle size 0.03 μm) were sufficient to cause significantly increased Mn in tissue of the olfactory bulb, striatum, frontal cortex, and cerebellum with concomitant inflammatory changes (TNF-α) in these brain regions (Elder et al., 2006). Another potential cause of lack of smell improvement may be local inflammation of the olfactory mucosa (olfactory epithelium with receptor cells) due to respiratory irritants in welding fumes other than Mn. The latter possibility cannot be ruled out in view of the compromised lung function at baseline (Bowler et al., 2007), which tended to exacerbate 3.5 years later (results not-published).

Mood disturbances are one of the first classic effects associated with Mn overexposure (Bowler et al., 1999). In pre-employment health screenings for work on the Bay Bridge, mood disturbance would have resulted in non-hiring. Indeed, the 26 welders did not report having had emotional disturbance prior to their hiring for the Bay Bridge reconstruction work. On a group basis, follow-up SCL-90-R scores had improved slightly compared to baseline, although not statistically significant. Clinical elevations (score >63) were noticed in 6 out of 9 symptom domains. The number of participants who met the criteria for being a 'clinical case' dropped from 19 at baseline to 17 at follow-up and did not reach statistical significance. The highest elevation in the SCL-90-R scores was found on the obsessive–compulsive scale, which signifies less of a personality characteristic (Lezak et al., 2004) than a reflection of the extent to which the participants were distressed by their attention and memory problems.

On a group basis, the participants reported experiencing more days of poor mental and physical health per month than the general population of California (3.2 and 2.6 respectively). They reported a mean of 14 days of poor physical health at baseline, compared to 12 at follow-up. When comparing participants who were still welding with those who were no longer involved in welding operations, a likely healthy worker effect was observed in that the remaining active welders had fewer days of poor physical and mental health than the ex-welders. The 13 participants who had stopped welding at follow-up (among them 7 were disabled, 2 injured, and 1 laid-off) also scored higher on the SCL-90-R scales than those still welding, revealing greater mood disturbance.

Roels et al. (1999) reported evidence of reversibility in Mn-associated neuromotor disruption. In the present study, slight improvement at the group level was noticed at follow-up for the UPDRS scores for Activities of Daily Living (e.g. speech, handwriting, and cutting food), motor movement, and bradykinesia. Of the motor tests, motor speed (Fingertapping) did not significantly improve, whereas motor dexterity/tactile function (Grooved Pegboard test) and graphomotor hand tremor, distinct from postural hand tremor, significantly improved at follow-up. Postural hand tremor as measured by the CATSYS, worsened at follow-up as suggested by significantly decreased center frequency of the tremor and its standard deviation, while tremor intensity and harmonic index tended to increase. Abnormal postural hand tremor is characterized by less irregularity (lower standard deviation) and a spectral power in a narrow frequency band (lower center frequency) (Beuter et al., 1999). There is only one other follow-up study of hand tremor using the CATSYS test system (Blond and Netterström, 2007), but this study did not show significant differences in postural hand tremor of electro-steel smelter workers tested in 1995 and 2003. The hand tremor findings of the Danish study are possibly compromised by selection bias. Indeed, only 60 out of the original 92 participants at baseline were considered for follow-up. The drop-outs had most likely been subjected to worse occupational Mn exposure conditions than the participants selected for follow-up, as shown by the median MnB which amounted to 10.7 μg/L in the drop-outs against 8.2 μg/L in the follow-up participants.

Postural balance is a complex task that is controlled by both the central and peripheral nervous systems. Maintaining upright posture requires integration of brain sensory inputs and motor outputs controlling the body musculature to achieve appropriate coordination. Visual, proprioceptive, and vestibular pathways yield sensory information relevant to maintain postural balance (Carter et al., 2009). The CATSYS sway test in the Bay Bridge welders showed for the Eyes Open condition a significant increase of 31% in postural balance (worsening) from baseline to follow-up, and a statistically non-significant increase of 28% for the Foam-Eyes Closed condition. This follow-up study is the first to show a persistent effect of Mn exposure on postural balance. Two cross-sectional studies on postural balance of Mn-exposed workers showed results in line with our findings. Chia et al. (1993) reported poorer postural stability in the Eyes Closed condition, and Myers et al. (2003) found significantly increased sway values under Eyes Open conditions in smelter workers compared to controls, but not under Eyes Closed conditions.

Cognitive functions such as language, reading, writing, memory, and intelligence (IQ) are to a large extent associated with activities in the cerebral cortex and hippocampus (Carter et al., 2009). Cognitive deficits in short-term memory have been reported in numerous studies with Mn-exposed workers (Bast-Pettersen et al., 2004; Bowler et al., 2006; Lucchini et al., 1999; Mergler et al., 1994; Roels et al., 1987, 1992, 1999). A most remarkable finding of this prospective study of the Bay Bridge welders is that many neuropsychological test results, which showed dose–effect associations with MnB and/or CEI at baseline, had significantly improved at follow-up. Tests of cognitive effort at baseline and follow-up support the validity of these findings. The largest effect sizes (improvement) were observed for tests in the verbal skill domain, including word knowledge, higher level verbal abstraction, and fund of information. These verbal scores reflect both crystallized and fluid intelligence, as described by Horn and Cattell (1966). Visuospatial memory was the domain with the next highest improvement at follow-up, followed by visuo-motor processing and tracking speed.

The reduced sample size ($n = 26$) available for re-testing 3.5 years after the baseline study may have limited power to obtain statistically significant findings for score differences. Nevertheless, a number of medium to large effect sizes reflected substantial changes between baseline and follow-up, indicating worsening (postural hand tremor and body sway) or improvement (motor dexterity, and 9 out of 21 cognitive tests).

This is the first study which shows different patterns of long-term outcome of CNS changes in Mn-exposed workers. It suggests that toxicodynamic processes underlying Mn-induced adverse CNS effects and subsequent recovery/reversibility may be brain-site specific. Over a time span of 3.5 years, disruptions linked to the frontal cortex (cognitive functions) appeared to improve at a faster rate than adverse effects on functions involving the basal ganglia (motor and coordination functions) or the limbic system (olfaction and mood), which suggests differential intrinsic vulnerabilities of these brain loci with regard to Mn exposure. This interpretation is supported by results from $MnSO_4$ inhalation studies in nonhuman primates (Dorman et al., 2006). The rate and extent of Mn accumulation in the basal ganglia are much higher than in the frontal cortex, while the clearance rate of Mn after cessation of exposure is much more rapid in the primates' frontal cortex than in the basal ganglia. This implies that brain loci may differ in their critical Mn concentrations, which may determine whether a particular site-specific neuronal disruption in the CNS remains permanently damaged, recovers partially, or normalizes. No interaction with age was obtained, suggesting that not age, but the Mn concentration in the different brain regions, was responsible for the observed longitudinal changes.

5. Conclusion

This follow-up study of Mn-exposed welders showed mixed results as to the reversibility of adverse CNS findings. After 3.5 years of decrease or cessation of Mn exposure, improvement in several domains of cognitive functions and motor dexterity was evidenced. Mood improved only to a limited extent, while olfaction, postural hand tremor, and body sway did not improve or worsen. Despite the relative young age of the welders (mean 47 years), both current and ex-welders continued to present with features of Mn-induced parkinsonism. Our findings are in line with the conclusions based on nonhuman primate studies, in that structural and functional disruption of the basal ganglia alone cannot explain the continuum of dysfunctions from psychiatric to cognitive to motor abnormalities associated with Mn exposure (Burton and Guilarte, 2008). Accumulation of Mn in the frontal cortex of nonhuman primates promotes inflammation and cell death and accelerates neurodegenerative changes in that part of the brain, which is postulated to trigger early signs of cognitive deficits (Guilarte et al., 2008).

This Bay Bridge welder study highlights a historical lack of compliance with Cal-OSHA's TLV-TWA for exposure to airborne Mn (0.2 mg/m^3) and insufficient surveillance of confined space welding. After 3.5 years decrease or cessation of Mn exposure long-term sequelae are detected. These results, coupled with the fact that more than 90% of Mn particulate in welding fume is of respirable size (aerodynamic diameter $<10\ \mu$m), highlight the need for stringent prevention strategies.

Conflict of interest statement

The authors' freedom to design, conduct, interpret, and publish research is not compromised by any controlling sponsor as a condition of review and publication. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. None of the authors have any competing financial interests. The P.I. author (RMB) has not served as an expert witness on health effects of manganese within the last 3 years. The only funding for the study was from the DOD as stated in the acknowledgement. R.L. Doty is President and major shareholder in Sensonics, Inc., the manufacturer of the olfactory test used in this study.

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