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San Francisco/Oakland Bay Bridge Welder Study

Olfactory function

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ABSTRACT

Background: The sense of smell can be damaged by airborne xenobiotics, including aerosolized heavy metals, reflecting the direct exposure of its receptors to the outside environment.

Objectives: To determine whether professional welders working in confined spaces exhibit olfactory dysfunction. To determine whether such dysfunction, if present, is related to indices of metal exposure associated with welding, as well as measures of neurologic and neuropsychological function.

Methods: The University of Pennsylvania Smell Identification Test (UPSIT) and a battery of neurologic and neuropsychological tests were administered to 43 welders who worked for 1 to 2 years on the San Francisco/Oakland Bay Bridge. Blood levels of Mn, Fe, Cu, and Pb were obtained.

Results: Relative to matched controls, the welders had significantly lower UPSIT scores, with a mean (SEM) of 29.51 (0.90) for welders and 36.55 (0.88) for controls. Eighty-eight percent scored below their individually matched controls. As in idiopathic Parkinson disease, the welders' olfactory test scores were unrelated to a broad spectrum of neurologic and neuropsychological test measures, as determined by principal components analysis. Although blood levels of Mn were associated with the time spent working on the bridge, workers with the highest Mn blood levels exhibited better olfactory function than those with the lowest Mn blood levels. The basis of this paradox, which has been observed previously, is unknown.

Conclusions: Professional welders may be at risk for loss of smell function, although such loss seems to be unrelated to neurologic and neuropsychological test performance.

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GLOSSARY

ANOVA = analysis of variance; **UPDRS** = United Parkinson's Disease Rating Scale; **UPSIT** = University of Pennsylvania Smell Identification Test; **WAIS-III** = Wechsler Adult Intelligence Scale III.

Welders, particularly those who work in confined spaces with no airway protection and inadequate ventilation, are commonly exposed to hazardous fumes and toxins. The majority of the toxic fumes come from vaporized metals during the welding process.¹ Such metals react with the air and become oxides that can form respirable particles that can be deposited in the nasal cavity and lungs.² Inhalation exposure varies as a function of the type of welding and the materials used. The typical constituents of welding fumes are a mixture mainly of iron (Fe), chromium (Cr), manganese (Mn), aluminum (Al), nickel (Ni), and cadmium (Cd).²

Most studies addressing associations between welding and respiratory tract toxicology

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focus on the lung and neglect the upper airways. However, there is evidence that a disproportionate number of welders have disorders of the naso-oral cavity, including sore throats,³ flu-like symptoms,³ septal ulcerations and perforations,^{4,5} and nasal cancers.^{5,6} Moreover, there are reports that industrial exposure to Cd, Mn, and Cr can alter the sense of smell, with prevalence rates as high as 67%.^{5,7,8} In a recent study of 351 welders, more than half had “taste” problems, although no chemosensory testing was performed and no distinction was made between flavor sensations dependent on the sense of smell and those dependent on the sense of taste.³

In the present study, a component of the San Francisco/Oakland Bay Bridge Welder Study,^{9,10,11} we quantitatively evaluated the olfactory function of professional welders who worked in confined spaces on the Bay Bridge, and compared their test scores with those of matched normal controls. These scores were also correlated with those from a number of neurologic, neuropsychological, and physiologic (e.g., blood levels of Mn, Fe, Cu, and Pb) measures. Principal components analysis was used to determine whether the olfactory test scores were largely independent of neurologic and neuropsychological test measures, as was previously shown for patients with idiopathic Parkinson disease (PD).¹²

METHODS **Subjects.** The 43 professional welders were assessed on behalf of their employer as part of a State and Federal Workers’ Compensation administrative mandate. They ranged in age from 23 to 66 years [mean (SD) = 43.8 (10.0) years]. On average, they had 12.6 (2.0) years of education. They were selected from a larger group of 45 male welders, 2 of whom were excluded because of scores on the Test of Memory Malingering (TOMM) indicated low effort.¹³ Eight of the 43 were current cigarette smokers (18.6%). All were employed as workers on the northeastern arm of the San Francisco/Oakland Bay Bridge for durations ranging from 6 to 28 months [mean (SD) duration = 16.5 (6.0) months] and represented approximately 90% of all welders working on the bridge during this period. At the time of testing, 51.2% of the welders were still working on the bridge, 20.9% were welding at another location, and 28.9% were no longer welding. 51.2% were white Americans, 32.6% were Hispanic Americans, 11.6% were African-Americans, 2.3% were Asian, and 2.3% were other.

The olfactory function of 43 healthy controls, matched to the welders on the basis of age, sex, education, and smok-

ing habits, was also tested. These individuals were selected from a control subject database maintained at the University of Pennsylvania Smell and Taste Center. When more than one match was available for a given patient, a random numbers table was used to determine which individual was included as the match. In four cases, the closest available age match was off by 2 years, in two cases by 3 years, and in another by 4 years. The ages of the two groups did not differ significantly [welders and controls mean (SD) ages = 43.8 (10.0) and 43.0 (10.5) years].

Olfactory testing. The University of Pennsylvania Smell Identification Test (UPSIT; Sensonics, Inc., Haddon Heights, NJ) was used in this study.¹⁴ This self-administered standardized test incorporates 40 microencapsulated odorants and a forced-choice multiple alternative format to establish both absolute (e.g., normosmia, anosmia, or mild, moderate, or severe hyposmia) and relative (percentile ranks) indices of function.¹⁵ The UPSIT is highly reliable (test–retest $r > 0.90$) and has been administered to hundreds of thousands of subjects throughout the world, including workers exposed to workplace chemicals.¹⁶ It is sensitive to idiopathic PD¹⁷ and differentiates between patients with PD and patients with either progressive supranuclear palsy¹⁸ or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–induced parkinsonism.¹⁹

Blood assays. Blood samples were obtained from the antecubital vein using standard procedures²⁰ for 37 of the subjects. The plasma was transferred to polystyrene tubes containing EDTA-NA₂ and frozen at -10°C until analysis. Blood levels of Mn and Pb and plasma levels of Fe and Cu were determined using atomic absorption spectroscopy.²¹

Neurologic and neuropsychological tests. As part of the neurologic examination by a board certified neurologist, the motor and the activities of daily living scales of the United Parkinson’s Disease Rating Scale (UPDRS) were administered.^{22,23} The welders had mean UPDRS scores of 6.79 (SD = 5.08; range = 0 to 19) on the activities of daily living scale and 6.62 (SD = 8.16; range = 0 to 24) on the motor scale.^{22,23}

A large neuropsychological test battery was also administered. This battery included a number of tests that overlapped the domains previously evaluated in the assessment of associations between olfactory and psychological measures in idiopathic PD.¹² The neuropsychological test measures used in the principal components analysis of the present study were the verbal and performance subscales of the Wechsler Adult Intelligence Scale III,²⁴ the word list I and II and logical memory I and II subscales of the Wechsler Memory Scale (verbal learning and memory in a contextualized prose, intellectual functioning—verbal learning and recall),²⁴ the Rey–Osterrieth Complex Figure Test—copy, immediate recall, and delayed recall (visuospatial processing and visual learning and memory),²⁵ Finger Tapping Test (psychomotor speed and strength),²⁶ Verbal Paired Associates (verbal learning and memory),²⁷ Cancellation (executive functions—forced choice extension to the Wisconsin Card Sorting Test),²⁸ and Visual Attention Test (reaction time to visual stimuli).²⁹ The results of these and the other neuropsychological tests are presented in detail elsewhere.¹⁰

Statistical analyses. Analysis of variance (ANOVA) was used to compare means (e.g., UPSIT scores of welders and controls). Pearson product–moment correlations were used

to assess relationships between selected variables. Principal component analysis, with varimax rotation, was used to better define associations among variables, as well as to allow for a comparison of component structures to previous ones obtained from patients with PD.³⁰ Such analysis, in effect, identifies clusters of interrelated variables that measure an underlying common trait or principal component, and statistically establishes clusters that are relatively unrelated to one another but account for reasonable amounts of variance.

RESULTS The mean UPSIT scores of the welders were lower than that of their matched controls [means (SEMs) = 29.62 (0.98) and 36.90 (0.26); one-way ANOVA $F(1,46) = 23.06, p < 0.001$], with the average deficit reflecting moderate microsmia. Thirty-eight (88%) performed more poorly than their controls, although only 3 (7%) were anosmic. Seventeen (39.5%) fell below the 10th percentile of a large normative sample of subjects of the same age and sex.¹⁵ The percentages of those with mild, moderate, or severe microsmia were 30.2, 18.6, and 16.3%. Interestingly, of the 42 subjects who provided information regarding their chemosensory function before being tested, more than half (52.4%) were unaware of a problem.

Fifteen of the 37 welders for whom blood level data were available had elevated levels of Mn at the time of testing [mean (SD) = 12.17 (0.41) $\mu\text{g/L}$; range = 10.2 to 15.3; reference range = 4 to 10 $\mu\text{g/L}$]. Two had elevated Fe levels [mean (SD) = 1,872 (203.64) $\mu\text{g/L}$; range = 1,728 to 2,016; reference range = 600 to 1,700 $\mu\text{g/L}$]. None had abnormal elevated levels of Pb [mean (SD) = 2.8(1.1) $\mu\text{g/dL}$; range = 1.24 to 6.59; reference < 20 $\mu\text{g/dL}$] or Cu [mean (SD) = 807 (119.71) $\mu\text{g/L}$; range = 601 to 1,114; reference range = 700 to 1,500 $\mu\text{g/L}$]. No meaningful correlations were present between UPSIT scores and the levels of Fe, Cu, Pb, or Mn (Pearson r values = $-0.13, 0.02, -0.13,$ and 0.20 ; all p values > 0.20). However, in the case of Mn, the UPSIT scores of welders with blood Mn levels in the top and bottom tertiles differed [$F^{1,24} = 4.80, p = 0.038$]. This effect was in the direction opposite as to what one might expect; i.e., those with higher Mn blood levels had higher UPSIT scores [mean (SEM) = 31.92 (1.79)] than those with lower Mn blood levels [mean (SEM) = 22 (1.79)]. No significant correlations were present between UPSIT scores and the number of years of professional welding or the time the workers had spent on the Bay Bridge (r values = -0.19 and $0.01, p$ values = 0.23 and 0.91), although Mn blood levels tended to be higher in welders who worked for longer periods on the bridge ($r = 0.35, p =$

0.02). The UPSIT scores of those welders who reported having a smell problem, a taste problem, or both a taste and smell problem, did not differ from those welders who did not report having such problems (all p values ≥ 0.29).

The Pearson correlations among the olfactory, neuropsychological, and neurologic measures revealed clear clusters of interrelated variables. Those between the olfactory and the neuropsychological and neurologic measures were small and not significant. The principal components analysis revealed a factor structure among the variables similar to that observed previously for patients with PD, with the primary factor being a cognitive/memory factor (table).¹² As in PD, the additional factors of tremor, gross motor, fine motor, and olfactory function were observed. The cancellation task fell on a separate factor. The six factors with eigenvalues > 1.00 accounted for 77% of the explained variance. The factor solution was generally stable. Thus, a 20-trial jackknife procedure found similar groupings on all 20 trials, including a separate olfactory factor in every case.

DISCUSSION The present study suggests that professional welders who work in enclosed spaces with poor ventilation are at risk for decreased smell function. Thus, nearly three-quarters of the welders evaluated in this study exhibited marked deficits in the ability to smell, as measured by a well-validated standardized test of olfactory function. Although anosmia was not the norm, the UPSIT scores of the welders were, on average, seven points lower than those of age-, sex-, education-, and smoking habit-matched controls. Nearly a third exhibited mild microsmia, and approximately a quarter exhibited severe microsmia. The fact that approximately a quarter of the welders were unaware of their chemosensory deficit before testing is in accord with what is seen in other disorders, including Alzheimer disease and idiopathic PD, where even higher percentages of unawareness have been reported.^{17,31}

An important observation of this study is that the degree of olfactory dysfunction in the welders was not meaningfully related to the magnitude of a broad range of neurologic ratings and neuropsychological measures. Thus, as in the case of idiopathic PD, the olfactory deficits seem to be largely independent of the other cognitive, memory, perceptual-motor, and neurologic manifestations of the disorder. The principal components analysis factor structure was remarkably similar to that observed in several studies of PD, sharing major

Measure	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
WAIS-III Verbal IQ	0.821	0.129	0.094	0.121	0.099	-0.199
Wechsler Memory Scale III	0.818	-0.197	0.004	0.072	0.077	0.206
Logical Memory	0.793	0.042	-0.202	-0.042	-0.132	0.055
WAIS-III Performance IQ	0.780	0.338	-0.130	-0.017	0.059	-0.136
Verbal Paired Associates	0.762	-0.146	-0.137	-0.282	0.096	0.272
Rey-Osterrieth Complex Figure Test	0.670	-0.104	0.001	-0.248	0.075	0.399
Tremor R	0.066	0.892	-0.060	0.000	0.218	-0.014
Tremor L	0.015	0.880	-0.185	-0.039	0.091	-0.120
Swallow	-0.060	0.744	0.139	-0.047	-0.203	0.314
Alternating Movements L	-0.211	-0.109	0.838	-0.097	-0.018	-0.272
Alternating Movements R	-0.070	-0.210	0.822	-0.133	0.045	-0.295
Masked Facies	-0.003	0.307	0.704	0.229	-0.082	0.254
Gait	0.037	-0.063	0.624	0.323	-0.454	0.033
Finger Tapping Test (dominant hand)	-0.108	-0.197	0.001	0.936	0.045	-0.002
Finger Tapping Test (nondominant hand)	-0.121	0.016	0.103	0.928	-0.117	-0.134
UPSIT	0.115	0.080	-0.099	0.051	0.921	0.048
Cancellation	-0.152	-0.088	0.189	0.081	-0.071	-0.791
Speech	-0.029	0.461	0.460	-0.128	0.434	0.229
Visual attention (reaction time)	0.216	0.211	-0.364	0.466	0.264	0.027
% Variance accounted for	19.901	14.684	14.770	12.261	7.842	7.242

Only factors with eigenvalues > 1.00 are depicted; numbers in boldface type reflect loading > 0.60. WAIS-III = Wechsler Adult Intelligence Scale III; UPSIT = University of Pennsylvania Smell Identification Test.

factors that can be described as reflecting cognitive/memory, tremor, fine motor, and olfaction.^{12,31,32} Unlike PD patients, however, the cancellation test did not load meaningfully on any of the extracted factors, and some elements of the factor structure were less well defined. This may be a reflection of the smaller sample size of the present study and the fact that older PD patients likely have a broader range of motor disabilities than younger welders exposed to toxic fumes.

Although taste perception, per se, was not studied in this work, a number of the welders complained of taste loss before being tested. In most cases, reports of taste loss reflect decreased flavor sensations derived from stimulation of the olfactory receptors retronasally during mastication and deglutition.³³ Thus, with the exception of sweet, sour, bitter, salty, and perhaps metallic and monosodium glutamate-related sensations, the majority of flavor sensations commonly considered as tastes (e.g., chocolate, onion, banana, raspberry, steak sauce, pizza, cherry, licorice) are dependent on an intact sense of smell. Although more research is needed to determine whether welders exhibit true taste deficits, the gustatory system is much more robust to insult than the olfactory system,³⁴ in part because of the redun-

dancy of taste bud innervation by a number of paired nerves (i.e., CN VII, IX, and X).³⁵

The basis of the smell loss of the welders in this study is not entirely clear. Although the data demonstrate that the welders had smell dysfunction, both in relation to matched controls and in relation to well-validated normative data, additional control groups, such as ones consisting of industrial workers who are not involved in welding operations, might be of value in better defining causality. Industrial workers in general are more prone to head trauma, for example, which can alter olfaction,³⁶ as well as to nanoparticles that have been associated with neurodegenerative diseases.^{37,38,39} The most likely hypothesis, however, is that the olfactory epithelium of the welders was damaged by exposures to airborne metals, possibly in a cumulative fashion. Heavy metals, when inhaled or otherwise introduced into the nasal cavity, can damage the olfactory epithelia of rodents (e.g., Ni),⁴⁰ and olfactory loss can occur in humans as a result of exposure to industrial dusts containing Cd, Cr, Pb, Mn, Ni, and Hg.^{7,8,42,43} For example, heightened odor thresholds to phenol were observed in 106 Cd- and Ni-dust-exposed alkaline battery workers relative to 84 matched controls.⁴¹ Twenty-seven percent of the exposed

workers were anosmic, compared with 5% of the controls.

In addition to damaging the olfactory epithelium directly, metals may also damage more central olfactory structures as a result of their uptake into the brain via the olfactory mucosa and receptors or, more generally, the circulatory system. It is well established that metal particles, including Mn, can deposit themselves within the olfactory cleft, where they are poorly cleared by mucociliary clearance.⁴⁴ This enhances absorption by the epithelium and the formation of complexes with mucus polysaccharides. From the mucosa, they gain access to the olfactory bulbs and other CNS structures via endocytotic uptake by apical processes of the olfactory receptor cells, which serve as both the receptor cell and the first order neuron. Once inside the receptor cell, the metal is transported, likely in combination with an endogenous substance, down the axon to the first synapse within the olfactory bulb.⁴⁵ Depending on its concentration, the agent can enter other cells through tight junctions or transsynaptically. Movement from the olfactory bulb to the cortex can occur within hours, because transport occurs at velocities up to approximately 3.0 mm per hour.⁴⁶

In the present study, 40.5% of the welders had abnormally elevated blood levels of Mn, whereas Fe, Cu, and Pb were within normal limits in nearly all cases. Elevated Mn has been previously noted in welders.⁴⁷ Although this observation suggests that the exposure in the present subjects was mainly to Mn, it is not entirely clear whether Mn, per se, is the basis of their smell problem. Indeed, those workers with the highest blood Mn levels tended to have relatively less olfactory dysfunction, implying the lack of a 1:1 relationship between Mn levels and such function. This suggests that the blood-brain barrier may be effective in protecting, at least to some degree, against loss of olfaction arising from elevated blood Mn. The regulation of excretion of Mn from liver to bile, along with its competition with iron for transport across the blood-brain barrier,^{48,49} likely mitigates the effectiveness of this route of movement of Mn into the brain.

The paradoxical association between elevated blood levels of Mn and olfactory function has been reported by others in different settings. For example, one study found that high urinary Mn levels were associated with low odor detection thresholds to phenyl-ethyl-methyl-ethyl-carbinol in 34 Mn-exposed workers of a ferroalloy production plant ($r = -0.31, p = 0.06$).⁵⁰ Another study,

using the same odorant, reported lower odor detection thresholds among 68 Mn alloy workers exposed to similarly moderate levels of Mn.²⁰ These investigators suggested that this effect could be due to an excitatory component of Mn intoxication. It is also conceivable that workers who breathe mostly through their mouth have less olfactory insult than those who breathe through their nose and, in turn, absorb more Mn into the blood. Mn may also influence olfaction by altering the effectiveness of inhibitory neurotransmitters such as γ -aminobutyric acid and glycine. Thus, olfactory bulb glycine content is markedly decreased in mice after intraperitoneal administration of Mn for 9 weeks (5 mg MnCl_2/kg body weight).⁵¹

It should be noted that the olfactory system has protective mechanisms to minimize the uptake of xenobiotic agents into the brain. Thus, olfactory receptor cells die off and are replaced periodically with new cells from progenitor cells within the basement membrane.⁵² Factors associated with the cell turnover are complex, but it is entirely conceivable that heavy metal poisoning of the receptor cells could induce apoptosis and subsequent cell replacement, mitigating the amount of toxin that ultimately becomes transported to the bulb. Additionally, numerous systems within the olfactory mucosa are known to metabolize foreign agents,⁵³ and metal-binding molecules such as carnosine are highly concentrated within the olfactory receptor cells and bulb. Carnosine is exceptionally abundant in the bulb (10 to 50 times more concentrated than in the rest of the brain) and is known to combine with metals such as Ni, Cd, and Zinc to form water-soluble stable complexes.⁵⁴ Thus, it may serve as an endogenous protective agent.

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REFERENCES

1. Bancroft K. Safety and the professional welder. *Occup Health Safety* 2002;71:84–86.
2. Antonini JM, Lewis AB, Roberts JR, et al. Pulmonary effects of welding fumes: review of worker and experimental animal studies. *Am J Industr Med* 2003;43:350–360.
3. El-Zein M, Malo JL, Infante-Rivard C, Gauthrin D. Prevalence and association of welding related systemic and respiratory symptoms in welders. *Occup Environ Med* 2003;60:655–661.
4. Lee CR, Yoo CI, Lee JH, Kang SK. Nasal septum perforation in welders. *Industrial Health* 2002;40:286–289.
5. Sunderman FW Jr. Nasal toxicity, carcinogenicity, and olfactory uptake of metals. *Ann Clin Lab Sci* 2001;31:3–24.
6. Teschke K, Morgan MS, Checkoway H, et al. Surveillance of nasal and bladder cancer to locate sources of exposure to occupational carcinogens. *Occup Environ Med* 1997;54:443–51.
7. Doty RL, Hastings L. Neurotoxic exposure and olfactory impairment. *Clin Occup Environ Med* 2001;1:547–575.
8. Mascagni P, Consonni D, Bregante G, Chiappino G, Toffoletto F. Olfactory function in workers exposed to moderate airborne cadmium levels. *Neurotoxicology* 2003;24:717–724.
9. Park RM, Bowler RM, Eggerth DE, et al. Issues in neurological risk assessment for occupational exposures: the Bay Bridge welders. *Neurotoxicology* 2006;27:373–384.
10. Bowler RM, Roels HA, Nakagawa S, et al. Dose-effect relations between manganese exposure and neurological, neuropsychological, and pulmonary function in confined space bridge welders. *Int J Occup Environ Med* 2007;64:167–177.
11. Bowler RM, Gysens S, Diamond E, Nakagawa S, Drezgic M, Roels HA. Manganese exposure: neuropsychological and neurological symptoms & effects in welders. *Neurotoxicology* 2006;27:315–326.
12. Doty RL, Riklan M, Deems DA, Reynolds C, Stellar S. The olfactory and cognitive deficits of Parkinson's disease: evidence for independence. *Ann Neurol* 1989;25:166–171.
13. Teichner G, Wagner MT. The Test of Memory Malingering (TOMM): normative data from cognitively intact, cognitively impaired and elderly patients with dementia. *Arch Clin Neuropsychol* 2004;19:455–464.
14. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav* 1984;32:489–502.
15. Doty RL. The Smell Identification Test administration manual. Haddon Heights, NJ: Sensonics, 1995.
16. Schwartz B, Doty RL, Monroe C, Frye RE, Barker S. Olfactory function in chemical workers exposed to acrylate and methacrylate vapors. *Am J Public Health* 1989;79:613–618.
17. Doty RL, Deems DA, Stellar S. Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology* 1988;38:1237–1244.
18. Doty RL, Golbe LI, McKeown DA, Stern MB, Lehrach CM, Crawford D. Olfactory testing differentiates between progressive supranuclear palsy and idiopathic Parkinson's disease. *Neurology* 1993;43:962–965.
19. Doty RL, Singh A, Tetrud J, Langston JW. Lack of major olfactory dysfunction in MPTP-induced parkinsonism. *Ann Neurol* 1992;32:97–100.
20. Mergler D, Huel G, Bowler R, et al. Nervous system dysfunction among workers with long-term exposure to manganese. *Environ Res* 1994;64:151–180.
21. Peblan PA, Pearson KH. Determination of manganese in whole blood and serum. *Clin Chem* 1979;25:1915–1918.
22. Fahn S, Elton RL. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB. Recent developments in Parkinson's disease. Flatham Park, NJ: Macmillan Healthcare Information, 1987: 153–163.
23. Goetz CG, LeWitt PA, Weindenman M. Standardized training tools for the UPDRS activities of daily living scale: newly available teaching program. *Mov Disord* 2003;18:1455–1458.
24. Wechsler D. WAIS-III and WMS-III technical manual. San Antonio: The Psychological Corp, 1997.
25. Spreen O, Strauss E. A compendium of neuropsychological tests. 2nd ed. New York: Oxford University Press, Inc, 1998.
26. Halstead WC. Brain and intelligence. Chicago: University of Chicago Press, 1947.
27. Wippich W. Priming on verbal perceptual tests: roles of lexical, surface, and conceptual processes. *Psychol Res* 1995;57:250–259.
28. Della Sala S, Laiacona M, Spinnler H, Ubezio C. A cancellation test: its reliability in assessing attentional deficits in Alzheimer's disease. *Psychol Med* 1992;22:885–901.
29. Smith MJ, Brebion G, Banquet JP, Cohen L. Retardation of mentation in depressives: Posner's covert orientation of visual attention test. *J Affect Disord* 1995;35:107–115.
30. Wilkinson L. Systat 9. Chicago: Systat, Inc, 1999.
31. Doty RL, Reyes P, Gregor T. Presence of both odor identification and detection deficits in Alzheimer's disease. *Brain Res Bull* 1987;18:597–600.
32. Petrinovich L, Hardyck C. Behavioral changes in Parkinson patients following surgery: a factor analytic study. *J Chronic Dis* 1964;17:225–233.
33. Burdach KJ, Doty RL. The effects of mouth movements, swallowing, and spitting on retronasal odor perception. *Physiol Behav* 1987;41:353–356.
34. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg* 1991;117:519–528.
35. Witt M, Reutter K, Miller IJ Jr. Morphology of the peripheral taste system. In: Doty RL. Handbook of olfaction and gustation. 2nd ed. New York: Marcel Dekker, 2003.
36. Doty RL, Yousem DM, Pham LT, Kreshak AA, Lee WW. Olfactory dysfunction in patients with head trauma. *Arch Neurol* 1997;54:1131–1140.

37. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect* 2005; 113:823–839.
38. Dobson J. Nanoscale biogenic iron oxides and neurodegenerative disease. *FEBS Lett* 2001;496:1–5.
39. Hautot D, Pankhurst QA, Khan N, Dobson J. Preliminary evaluation of nanoscale biogenic magnetite in Alzheimer's disease brain tissue. *Proc R Soc Lon B* 2003;270 (suppl 1):S62–S64.
40. Evans JE, Miller ML, Andringa A, Hastings L. Behavioral, histological, and neurochemical effects of nickel (II) on the rat olfactory system. *Toxicol Appl Pharmacol* 1995;130:209–220.
41. Adams RG, Crabtree N. Anosmia in alkaline battery workers. *Br J Ind Med* 1961;18:216–221.
42. Watanabe S, Fukuchi Y. Occupational impairment of the olfactory sense of chromate producing workers. *Jpn J Indust Health* 2000;23:606–611.
43. Bolla KI, Schwartz BS, Stewart W, Rignari J, Agnew J, Ford DP. Comparison of neurobehavioral function in workers exposed to a mixture of organic and inorganic lead and in workers exposed to solvents. *Am J Ind Med* 1995;27:231–246.
44. Tjalve H, Henriksson J. Uptake of metals in the brain via olfactory pathways *Neurotoxicology* 1999;20:181–195.
45. Shipley MT. Transport of molecules from nose to brain: transneuronal anterograde and retrograde labeling in the rat olfactory system by wheat germ agglutinin-horseradish peroxidase applied to nasal epithelium. *Brain Res Bull* 1985;15:129–142.
46. Tjalve H, Mejare C, Borg-Neczak K, et al. Uptake and transport of manganese in primary and secondary olfactory neurones in pike. *Pharmacol Toxicol* 1995;77:23–31.
47. Josephs KA, Ahlskog JE, Klos KJ, et al. Neurologic manifestations in welders with pallidal MRI T1 hypersensitivity. *Neurology* 2005;64:2033–2039.
48. Jankovic J. Searching for a relationship between manganese and welding and Parkinson's disease. *Neurology* 2005;64:2021–2028.
49. Takeda A. Manganese action in brain function. *Brain Res Rev* 2003;41:79–87.
50. Lucchini R, Bergamaschi E, Smargiassi A, Festa D, Apostoli P. Motor function, olfactory threshold, and hematological indices in manganese-exposed ferroalloy workers. *Environ Res* 1997;73:175–180.
51. Bonilla E, Arrieta A, Castro F, Davila JO, Quiroz I. Manganese toxicity: Free amino acids in the striatum and olfactory bulb of the mouse. *Invest Clin* 1994;35: 175–181.
52. Mackay-Sim A. Neurogenesis in the olfactory neuroepithelium. In: Doty RL. *Handbook of olfaction and gustation*. 2nd ed. New York: Marcel Dekker, 2003:93–114.
53. Ding X, Dahl AR. Olfactory mucosa: composition, enzymatic localization and metabolism. In: Doty RL. *Handbook of olfaction and gustation*. 2nd ed. New York: Marcel Dekker, 2003:51–73.
54. Baran J. Metal complexes of carnosine. *Biochemistry (Mosc)* 2000;65:789–797.

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