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Chronic ambient hydrogen sulfide exposure and cognitive function

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ABSTRACT

Background: Exposures to hydrogen sulfide gas (H_2S) have been inconclusively linked to a variety of negative cognitive outcomes. We investigated possible effects on cognitive function in an urban population with chronic, low-level exposure to H_2S.

Methods: Participants were 1637 adults, aged 18–65 years from Rotorua city, New Zealand, exposed to ambient H_2S from geothermal sources. Exposures at homes and workplaces were estimated from data collected by summer and winter H_2S monitoring networks across Rotorua in 2010/11. Metrics for H_2S exposure at the time of participation and for exposure over the last 30 years were calculated. H_2S exposure was modeled both as continuous variables and as quartiles of exposure covering the range of 0–64 ppb (0–88 μg/m^3). Outcomes were neuropsychological tests measuring visual and verbal episodic memory, attention, fine motor skills, psychomotor speed and mood. Associations between cognition and measures of H_2S exposure were investigated with multiple regression, while covarying demographics and factors known to be associated with cognitive performance.

Results: The consistent finding was of no association between H_2S exposure and cognition. Quartiles of H_2S exposure had a small association with simple reaction time: higher exposures were associated with faster response times. Similarly, for digit symbol, higher H_2S exposures tended to be marginally associated with better performance.

Conclusion: The results provide evidence that chronic H_2S exposure, at the ambient levels found in and around Rotorua, is not associated with impairment of cognitive function.

1. Introduction

Hydrogen sulfide (H_2S) is an odorous gas reported to cause eye and respiratory irritation at concentrations around 20–50 ppm and death at concentrations around 500 ppm (Guidotti, 2010). An association of H_2S concentrations in the low ppb range has been reported with eye irritation, although a role by other pollutants cannot be ruled out (Schinasi et al., 2011).

Although H_2S is naturally emitted in geothermal and volcanic areas, most human exposure is from industrial processes, such as sewage treatment plants, paper mills, oil and gas refineries, and concentrated animal farming operations. H_2S is also produced at low levels in the human body and has physiologic signaling functions (Szabo, 2007). While the geometric mean threshold for smelling the "rotten egg" odor of H_2S is reported to be 8 ppb (Amoore and Hautala, 1983), the health effects of long-term low-level (<2000 ppb) exposures to H_2S remain unknown.

Like cyanide, H_2S suppresses cellular metabolism in the brain stem. Concerns about cognitive impairment due to much lower level H_2S exposures have emerged over the last 30 years (Hua et al., 1992; Kilburn, 1993, 1997, 2003, 2012; Kilburn and Warshaw, 1995; Schneider et al., 1998; Snyder et al., 1995; Tvedt et al., 1991a, 1991b). Some case reports and case series suggest that neurological effects of acute, high H_2S exposure may not completely resolve (Schneider et al., 1998; Tvedt et al., 1991a, 1991b). Many of these cases were consequences of acute, high-level exposures in industrial accidents, with associated unconsciousness, anoxia or coma.

The literature on lower level, chronic exposures is mixed. There are reports of cognitive impairments in exposed workers who never lost consciousness and in persons living downwind from industrial H_2S

Abbreviations: BVRT, Benton Visual Retention Test; CI, confidence interval; CNS, central nervous system; GPB, grooved pegboard; H_2S, hydrogen sulfide; HVLT, Hopkins Visual Learning Test; LCD, liquid crystal display; ms, milliseconds; NART, National Adult Reading Test; NZ$, New Zealand dollar; Q, quartile; SRT, simple reaction time; TBI, traumatic brain injury; TIA, transient ischemic attack.

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sources (Haahtela et al., 1992; Kilburn, 2003, 2012; Kilburn and Warshaw, 1995). Deficits in a variety of cognitive outcomes, predominantly psychomotor speed, fine motor skills, memory, attention, and mood have been reported (Horton et al., 2009; Kilburn, 1993, 1997, 2003; Kilburn and Warshaw, 1995; Tvedt et al., 1991a, 1991b). In contrast, Inserra et al. (2004) compared neuropsychological performance in persons with long-term H_2S exposures above 130 μg/m^3 (94 ppb, 'exposed') to those with exposures below 70 μg/m^3 (51 ppb, 'unexposed'). The exposed group did the same as or better than the unexposed on 21 of 28 cognitive performance tests, but did worse on memory and grip strength. De Fruyt et al. (1998) found no evidence of effect on workers of long-term H_2S exposures of about 14 mg/m^3 (10 ppm). Complicating interpretation of most of these reports, exposures to other chemicals also occurred. Thus, the literature on cognitive effects of low-level H_2S exposure raises concerns, but is inconclusive. Most studies had small numbers of participants, often involved other exposures, or had limited H_2S exposure data. Some studies were in the context of litigation (Legator et al., 2001).

Rotorua, New Zealand (population ~60,000), sits on an active geothermal field at the southern end of Lake Rotorua, an old volcanic caldera. Vents emitting H_2S are located in and around the city. The population is probably the largest in the world with long-term exposure to levels of ambient H_2S as high as found in Rotorua. There are no known co-exposures to other potentially toxic emissions from the same sources. As part of a larger study of possible health effects of H_2S on the Rotorua population, we investigated associations between H_2S exposure and cognitive functions previously reported as negatively affected by H_2S. We hypothesized that exposure to higher ambient H_2S levels would be associated with worse performance on measures of attention, psychomotor speed, memory, fine motor skills, and mood.

2. Methods

2.1. Participants

Institutional Review Board approvals for study procedures were obtained at the University of California, Berkeley, for the University of California sites, and from the Northern Ethics Committee in New Zealand. Prior written informed consent was obtained from all participants.

We enrolled 1637 adults, aged 18–65, residing in Rotorua for at least the last 3 years. Recruitment methods have been previously described (Bates et al., 2013). In brief, we recruited participants from a comprehensive primary care medical register, using a stratification scheme designed to ensure a balanced distribution of residential H_2S exposures. We excluded persons unable to speak and write English, persons who, because of disability, were unable to visit the study clinic, blind people and pregnant women.

Participants attended the study clinic, where they were administered a questionnaire and a series of neuropsychological tests. The questionnaire sought demographics and personal data, as well as residential, school and workplace histories (including locations) going back 30 years. The neuropsychological testing was very well tolerated. Due to logistics, there was a natural break between the questionnaire and the neuropsychological tests during which participants moved about the offices. Testing was completed in 60 min or less for 90% of the participants, and additional breaks were rarely necessary. The examination site was in a low H_2S exposure area of Rotorua.

2.2. Cognitive measures

Tests assessed attention, psychomotor speed, fine motor function, memory, and mood—important cognitive functions that are sensitive to adverse effects of a wide variety of injuries and diseases (Lezak, 1995). These neurobehavioral domains have been reported as affected by H_2S or have been identified by expert panels as relevant to neurotoxic assessment (Anger et al., 1994, 2000; Kilburn, 2012; Rohlman et al., 2003; White et al., 2003). Tests (Table 1) were administered in a fixed order in a quiet, light-controlled setting. Simple reaction time, finger tapping, and Digit Span were administered as computer-driven tests using Presentation Software (http://www.neurobs.com; Neurobehavioral Systems, Inc., Albany, CA) and run on a personal computer with an LCD display and a high temporal resolution mouse (Copperhead 2000 DPI Gaming Mouse; Razer USA Ltd.).

Digit Span is a test of short-term attention and working memory (Richardson, 2007), measured using a computerized, adaptive version of the test (Woods et al., 2010). Forward and backward spans were assessed in sets of 10 trials with list lengths adjusted in response to performance. Performance was assessed using two metrics that utilized responses from all 10 trials: the maximum length, the longest list correctly reported, and mean span (MS), the list length where 50% of lists would be correctly reported, estimated using psychophysical procedures (Tillman and Olsen, 1973). Briefly, MS is calculated by using a baseline value 0.5 below the initial span length, and then adding to that the proportions of correctly recalled trials at each longer span length (Woods et al., 2010).

Simple reaction time (SRT) speed of simple motor response to a visual cue is a basic measure of psychomotor speed. Reaction time is sensitive to a wide variety of factors, including toxic exposures (Anger et al., 2000; Kilburn et al., 2010; Rohlman et al., 2003). SRT distributions were trimmed by excluding times <100 ms and >1000 ms. The primary outcome variable was mean SRT across all trials. Since SRT distributions are typically skewed, we also examined the median SRT. Another secondary measure was abnormal SRT, defined as a score >2 SD beyond the sample mean. Hit rate (number of responses within the response window—100 to 1000 ms—divided by number of targets

Table 1
Cognitive test battery and test characteristics.

Test	Abilities assessed	Administration notes
Digit span[a]	Attention, working memory	Computerized adaptive test version (Woods et al., 2011)[a]
Simple reaction time[a]	Attention, psychomotor speed	Computer driven, fixed set of 120 targets, pseudo randomly distributed to each hemi-attentional field and across 5 interstimulus intervals (600–1400 ms)
Digit symbol	Attention, psychomotor speed, visual scanning, and memory	Standard WAIS-III administration (Wechsler, 1997)
Finger tapping[a]	Fine motor speed	Computerized, index finger of each hand, 30 second interval recorded with high temporal resolution mouse (Hubel et al., 2013)
Grooved pegboard	Psychomotor speed, manual dexterity, and visual tracking	Standard (Spreen and Strauss, 1998)
Hopkins Verbal Learning Test-R	Verbal episodic memory	Form 1, standard (Brandt, 1991; Spreen and Strauss, 1998)
Benton Visual Retention Test	Visual episodic memory	Stimulus set C, 5 s exposure (Sivan, 1992)
National Adult Reading Test	Vocabulary	Standard (Crawford et al., 1990; Grober and Sliwinski, 1991)
Profile of Mood States	Mood	30 item version (Curran et al., 1995)

[a] Run on a personal computer with an LCD display.