2014

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Neurotoxicology and Teratology 42 (2014) 68–76

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Chronic ambient hydrogen sulfide exposure and cognitive function

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ARTICLE INFO

Article history:
Received 10 October 2013
Received in revised form 8 February 2014
Accepted 9 February 2014
Available online 16 February 2014

Keywords:
Cognitive function
Cross-sectional study
Geothermal
Hydrogen sulfide
Neuropsychological tests
New Zealand

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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http://dx.doi.org/10.1016/j.ntt.2014.02.002
0892-0362/

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.

presented) was examined. Finally, increased response variability can indicate attention problems, so we examined the SD of the mean.

Digit symbol requires multiple cognitive processes and cortical systems, including the key functions of psychomotor speed, attention and memory. It is thus a sensitive measure to a wide variety of cerebral insults, including toxic exposures (Anger et al., 2000) (Joy et al., 2003, 2004). The test was administered using standard materials and methods (Wechsler, 1997). The primary outcome measure was the number of correct responses in 90 s.

Finger tapping (Cousins et al., 1998; Jobbagy et al., 2005) speed for the index fingers was measured over 30 second intervals using Presentation software, as described in Hubel et al. (2013). The timing of each press and release was recorded using the Windows programmable clock, which has a temporal resolution of 0.1 ms, to provide a temporal uncertainty measure for each response. Post-processing was identified where the participant failed to close or release the mouse button ("tap failures") (Hubel et al., 2013). Outcome variables were taps per 30 s (separately for left and right hands) and the number of tap failures.

Grooved pegboard (GPB) was administered using standard materials and methods (Spreen and Strauss, 1998). The primary outcome variable was the total time to insert pegs in 5 rows using the dominant and then the non-dominant hand. Secondary measures were total number of dropped pegs and the standard deviation of times of row completion across the 10 rows (5 rows × 2 hands).

Memory was assessed with the Hopkins Verbal Learning Test-Revised (HVLT) (Brandt, 1991) and the Benton Visual Retention Test (BVRT) (Sivan, 1992), using standard procedures. HVLT performance was summarized with 4 outcome variables: HVLT-learning is the total correct responses across the 3 learning trials (maximum = 36). HVLT-recall is the number of correct responses on the delayed free recall trial (maximum = 12). HVLT recognition is the sum of correctly identified targets and foils. "HVLT Errors" is the sum of intrusions made on all learning and recall trials plus false positive errors on recognition. The BVRT was administered using stimulus set C and a 5-second exposure duration. Two measures quantified BVRT performance: "BVRT Correct" (number of items correct; 0–10) and "BVRT Errors" (sum of item error scores; 0–40).

Baseline verbal abilities were estimated using the National Adult Reading Test (NART) (Crawford et al., 1990; Grober and Sliwinski, 1991). The NART requires pronunciation of 50 irregularly spelled English words. Correct pronunciation indicates knowledge of the word. Vocabulary tests correlate strongly with education and moderately with verbal IQ, and are relatively insensitive to brain injury. Developed in England, the test performs similarly in New Zealand (Freeman et al., 2001).

Mood was assessed using the Profile of Mood States (POMS)—part of the battery recommended by the WHO-NCTB (Anger et al., 2000) for neurotoxicity assessment. The 30-item version was used (Curran et al., 1995).

2.3. Exposure estimation

As described elsewhere (Bates et al., 2013), we estimated H_2S concentrations at each participant's residential, workplace and school locations across Rotorua using data from H_2S monitoring networks deployed across the city. Data from three monitoring networks—summer and winter, 2010, and winter, 2011, were used to calculate weighted average H_2S concentrations at each location. For calculation of mean concentrations, each of the two winter concentrations received 25% weight and the summer concentration 50% weight, to avoid overweighting the winter results. Two types of H_2S exposure metric were used: 1) the mean time-weighted average exposure, based on hours at work or school, and assuming the remainder was spent at home; and 2) the maximum average exposure, derived by selecting the higher of the average home, work or school exposure. Exposure metrics were created for both time of participation ('current') and for the last 30 years ('long-term'). We chose 30 years because pre-testing of the questionnaire showed it to be a practical length of time to inquire about. The 'current' exposure metrics have previously been used to examine associations with self-reported asthma and asthma symptoms (Bates et al., 2013).

The long-term exposure metrics were based on data for residential, workplace and school locations over the 30 years prior to participation, including dates of beginning and ending residence, employment and school attendance, collected by questionnaire. Since actual H_2S exposure measurements were made only at the time of the study, the long-term metrics necessarily incorporate the assumption that the distribution of sources and their emissions remained approximately constant over the previous 3 decades. The two long-term exposure metrics were average yearly H_2S exposure over the last 30 years and average annual peak (school, workplace or home) exposure across those years. All locations outside Rotorua were assigned an H_2S concentration of zero.

To create the long-term metrics, year-by-year H_2S exposure estimates were first created for each of the last 30 years or for a shorter period for participants younger than age 30. Using geocoded H_2S concentrations, plus reported daily hours at work and hours at school, an average H_2S exposure concentration was estimated for each year. Sites (home, work or school) associated with the maximum H_2S exposure concentration in each year were also identified. To compute the long-term exposure metrics we took the averages of the 30 year concentration averages or peaks, including zeroes for non-residence in Rotorua.

2.4. Statistical analysis

Age and NART were used as continuous variables. Ethnicity was a categorical variable, European, Maori, or "Other", based on self-reported first choice of ethnic identity. Education was a categorical variable with 5 levels: no secondary school qualification, secondary school qualification, trade certificate, bachelor's degree, and post-graduate degree. Income was an ordinal variable with 8 levels.

Three potentially co-morbid conditions, current alcohol consumption, history of traumatic brain injury (TBI), and a history of stroke or transient ischemic attack (TIA), were examined as potential confounders. Neither TIA nor TBI was associated with any of the H_2S metrics. Therefore, they were not likely to act as confounders and were not included in exposure models. The distribution of weekly alcohol consumption showed three distinct groups, non-drinkers, persons with greater than zero but less than 13 drinks per week, and those consuming 13 or more drinks. These categories of alcohol consumption were statistically associated with H_2S exposure such that the persons in the middle category had higher H_2S exposures (p values 0.07 and 0.02 for current exposure metrics). Alcohol consumption was also associated with some of the neuropsychological outcomes. Consequently, alcohol consumption was included in all exposure models. We found some associations of other socio-demographic covariates commonly associated with differences in neuropsychological test performance, namely gender, age, ethnic group, income and educational level, with both exposures and outcomes, and included them in the models. Although not all covariates were associated with all of the outcomes or all of the exposure metrics, for simplicity and comprehensibility, we have chosen to use a common set of covariates that are associated with most outcomes and exposures.

Each neuropsychological test was evaluated separately following a common analytic approach. First, the participants whose test scores may have been invalidated were excluded. Invalidating factors included equipment failure, disruption during testing (e.g., cell phone ringing), and sensory or motor problems that compromised the test (e.g., a finger splint would invalidate finger tapping). Also excluded were 67 participants for whom the electronic questionnaire software did

not capture answers to questions about alcohol. This only affected the initial participants, as the problem was identified and corrected early in the study.

The primary analyses were carried out with multiple linear regression, using quartiles of H_2S exposure, according to each of the four exposure metrics. A parallel set of analyses was run using the four exposure metrics as continuous variables, with the same covariate set. Where relevant, secondary analyses examined error scores, variability in responding, and frequency of highly deviant scores on each test, as more subtle measures of potential pathology. We also carried out an investigation of possible effect modification of H_2S exposure, particularly by age, sex, and education, covariates which might most plausibly interact with H_2S exposure, using models with (demographic × exposure) interaction terms.

3. Results

Attempts were made to contact 6573 people using the last recorded telephone number in their medical records. Contact was made with 4498 people, of whom 976 were ineligible. Of the remainder, 1927 (54.7%) agreed to participate, but because of timeframe constraints, only 1639 people actually participated, during 2008–10.

Study participants had lived in Rotorua for between 3 and 64 years (median 18 years). The median H_2S concentration for current residences was 20.3 ppb, with mean 20.8 ppb (standard deviation (SD), 15.5 ppb). For current workplaces, the median and mean (SD) were 26.4 and 27.0 (17.7) ppb, respectively. The range for both residences and workplaces was 0–64 ppb. Table 2 presents covariate data for the study participants, by quartile of the current time-weighted exposure metric. Some small differences are evident, but there are no major differences between quartiles. Similar patterns—no major differences between quartiles—are evident for the other exposure metrics.

Table 3 shows results for the current exposure metrics and Table 4 shows results for the long-term exposure metrics. They present differences between the mean cognitive function scores for the higher exposure quartiles (2 to 4) relative to the mean for the lowest exposure quartile (1). All difference values are fully adjusted for covariates.

Generally, results for analyzing H_2S metrics as continuous variables and secondary analysis results are not presented, unless they indicate any variation from what was observed with the categorical variables.

3.1. Attention

The primary scores for Digit Span were forward mean span (FMS) and backward mean span (BMS). Neither the H_2S exposure quartile nor continuous models, for either current or long-term exposure, produced evidence of association between H_2S and FMS or BMS.

A backward span abnormally low relative to the forward span can be indicative of impaired working memory. Therefore, we additionally tested two measures of this discrepancy: a difference score calculated as FMS–BMS, and the residual score of the regression of BMS on FMS. No H_2S association was evident, regardless of how H_2S was modeled and there was no evidence of effect modification (results not shown).

3.2. Psychomotor SPEED

3.2.1. Simple reaction time

With quartiles of maximum current H_2S as the exposure, estimated differences between quartile 1 and quartiles 2–4 all excluded the null value, although there was not a trend (Table 3). Generally, for all exposure metrics, higher H_2S exposure quartiles had slightly shorter

Table 2
Covariates, by quartiles (Q1 to Q4) of Estimated Time-weighted Average H_2S Exposure Concentration for Current Home and Workplace of Participants, Rotorua, New Zealand, 2008–2010.

	N	Q1 (0–10 ppb)	Q2 (11–20 ppb)	Q3 (21–30 ppb)	Q4 (31–64 ppb)	P value[a]
N	1637	410	409	410	408	
Sex						
Female	981 (60%)	62.2%	56.0%	59.7%	61.9%	
Male	656 (40%)	37.8%	44.0%	40.3%	38.1%	0.24
Age group (years)						
18–29	168 (10.3%)	13.2%	9.8%	9.3%	8.8%	
30–39	305 (18.6%)	19.5%	20.8%	17.1%	17.1%	
40–49	454 (27.7%)	29.3%	26.2%	32.3%	23.2%	
50–59	471 (28.8%)	24.4%	31.3%	29.6%	29.8%	
60+	239 (14.6%)	13.7%	12.0%	11.7%	21.0%	<0.001
Ethnic group						
European	1146 (70.0%)	67.3%	71.6%	72.1%	68.9%	
Maori	397 (24.3%)	27.3%	22.0%	23.0%	24.7%	
Other	94 (5.7%)	5.4%	6.4%	4.9%	6.4%	0.48
Education						
No qualification earned	215 (13.1%)	17.8%	13.0%	7.8%	13.9%	
Secondary qualification	374 (22.8%)	20.2%	23.0%	23.5%	24.7%	
Tertiary non-degree	744 (45.4%)	47.3%	45.5%	48.4%	40.6%	
University degree	304 (18.6%)	14.6%	18.6%	20.3%	20.8%	0.002
Income (NZ$)						
$0–$20 K	357 (21.8%)	30.7%	13.2%	21.0%	22.2%	
>$20 K–$40 K	473 (28.9%)	25.6%	31.3%	27.4%	31.3%	
>$40 K–$60 K	339 (20.7%)	21.2%	24.7%	18.1%	18.8%	
>$60 K–$80 K	227 (13.9%)	10.7%	15.4%	17.4%	12.0%	
>$80 K	192 (11.7%)	8.3%	13.2%	13.7%	11.7%	
Don't Know/Refuse	49 (3.0%)	3.4%	2.2%	2.4%	3.9%	<0.001
Usual weekly alcohol drinks:						
None	422 (25.8%)	32.2%	25.2%	24.6%	21.1%	
> 0 to < 13	920 (56.2%)	50.7%	56.2%	58.8%	59.1%	
≥ 13	228 (13.9%)	12.4%	13.9%	12.4%	16.9%	
Missing	67 (4.1%)	4.6%	4.7%	4.2%	2.9%	0.02
NART score (mean and SD)		39.1 (13.8)	40.4 (12.9)	41.3 (12.4)	41.7 (11.5)	0.02
Total	1637 (100%)	100%	100%	100%	100%	

Abbreviations: N, number of participants; NART, National Adult Reading Test; NZ$, New Zealand dollars; ppb, parts per billion; Q, quartile; SD, standard deviation.
[a] Calculated using Chi-square tests (categorical variables) and analysis of variance (NART).

Table 3
Cognitive function and mood—test score differences from the first quartile (Q) of current H_2S exposure concentration in ppb, after controlling for covariates.

Test	N[a]	D[b]	Time-weighted mean exposure				Maximum exposure at work or home			
			Q1 (0–10 ppb)	Q2 (11–20 ppb)	Q3 (21–30 ppb)	Q4 (31–64 ppb)	Q1 (0–17 ppb)	Q2 (18–29 ppb)	Q3 (30–44 ppb)	Q4 (45–64 ppb)
			Mean (SE)[c]	Difference (95% confidence interval) from Q1[d]			Mean (SE)[c]	Difference (95% confidence interval) from Q1[d]		
Attention										
Digit span—mean span forward	1439	>0	6.4 (0.1)	0 (−0.2,0.1)	0 (−0.1,0.2)	−0.1 (−0.2,0.1)	6.4 (0.1)	0 (−0.2,0.1)	0 (−0.1,0.2)	0 (−0.2,0.1)
Digit span—mean span reverse	1435	>0	4.8 (0.1)	0 (−0.1,0.2)	0.1 (0,0.2)	−0.1 (−0.2,0)	4.7 (0.0)	0.1 (−0.1,0.2)	0 (−0.1,0.2)	0 (−0.1,0.1)
Psychomotor speed										
Simple reaction time (ms)	1408	<0	234 (1.4)	0.3 (−3.8,4.0)	−5.8 (−9.7,−1.8)	−2.3 (−6.3,1.6)	236 (1.5)	−7.0 (−10.9,−3.1)	−4.7 (−8.7,−0.7)	−4.1 (−8.0,−0.1)
Digit symbol # correct	1440	>0	52 (0.6)	0.6 (−0.9,2.0)	1.4 (−0.4,2.8)	1.1 (−0.4,2.5)	52 (0.6)	1.4 (−0.1,2.8)	0.6 (−0.9,2.0)	1.2 (−0.2,2.7)
Memory										
HVLT[e] learning # correct	1459	>0	25.3 (0.3)	0.5 (−0.2,1.1)	0.6 (0,1.2)	0.3 (−0.3,0.9)	25 (0.2)	0.8 (0.2,1.4)	0.6 (0,1.2)	0.3 (−0.3,1.0)
HVLT[e] recall # correct	1459	>0	9.1 (0.1)	0.1 (−0.2,0.4)	0 (−0.3,0.3)	−0.1 (−0.4,0.2)	9.0 (0.1)	0.2 (−0.1,0.5)	0 (−0.3,0.3)	−0.1 (−0.5,0.2)
HVLT[e, f] errors combined count	1459	<0	1.8 (0.1)	−0.1 (−0.4,0.2)	−0.1 (−0.3,0.2)	−0.1 (−0.4,0.2)	1.8 (0.1)	0 (−0.3,0.3)	0.2 (−0.1,0.5)	0 (−0.3,0.3)
BVRT[g] correct	1465	>0	5.9 (0.1)	0 (−0.3,0.3)	−0.1 (−0.3,0.2)	−0.1 (−0.4,0.2)	5.8 (0.1)	0.1 (−0.2,0.3)	0.1 (−0.2,0.4)	0.1 (−0.2,0.3)
BVRT[e] errors	1465	<0	5.7 (0.2)	−0.1 (−0.6,0.3)	0.1 (−0.4,0.5)	0.1 (−0.3,0.6)	5.8 (0.2)	−0.2 (−0.6,0.3)	−0.2 (−0.7,0.2)	−0.1 (−0.5,0.4)
Fine motor function										
Grooved pegboard right + left, s	1323	< 0	73 (0.9)	−0.8 (−2.7,1.2)	−0.1 (−2.0,1.9)	−0.3 (−2.2,1.8)	74 (0.8)	−1.2 (−3.1,0.8)	0.3 (−1.6,2.4)	0.2 (−1.8,2.2)
Tapping, dominant hand, # taps	1408	>0	151 (1.3)	2.1 (−1.3,5.5)	2.2 (−1.2,5.6)	0.1 (−3.4,3.5)	152 (1.3)	1.9 (−1.5,5.4)	1.0 (−2.5,4.4)	−2.1 (−5.6,1.3)
Tapping, non-dominant, # taps	1408	>0	132 (1.1)	1.0 (−2.1,4.2)	1.3 (−1.9,4.4)	−0.1 (−3.3,3.1)	134 (1.1)	1.4 (−1.7,4.6)	0.7 (−2.5,3.9)	−1.3 (−4.5,1.9)
Mood										
POMS[h]-Tension	1484	<0	8.4 (0.2)	−0.2 (−0.7,0.3)	0 (−0.4,0.5)	0.1 (−0.4,0.6)	8.4 (0.2)	0 (−0.5,0.4)	0 (−0.5, 0.4)	0.3 (−0.2,0.8)
POMS[h]–depression	1484	<0	7.3 (0.2)	−0.1 (−0.5,0.4)	0 (−0.5,0.4)	0.2 (−0.3,0.6)	7.4 (0.2)	−0.2 (−0.7,0.2)	−0.3 (−0.1,0.7)	0.3 (−0.1,0.7)
POMS[h]–anger	1484	<0	8.6 (0.2)	−0.3 (−0.8,0.2)	−0.2 (−0.7,0.3)	−0.2 (−0.8,0.3)	8.6 (0.2)	−0.4 (−0.9,0.1)	−0.3 (−0.8,0.2)	0 (−0.6,0.5)
POMS[h]–fatigue	1484	<0	11 (0.2)	0.1 (−0.6,0.8)	0 (−0.6,0.7)	0.1 (−0.5,0.8)	11 (0.2)	−0.1 (−0.8,0.5)	0.1 (−0.6,0.8)	0.4 (−0.3,1.1)
POMS[h]–confusion	1484	<0	9.3 (0.2)	−0.4 (−0.8,−0.1)	−0.4 (−0.8,0)	−0.1 (−0.4,0.3)	9.2 (0.2)	−0.3 (−0.6,0.1)	−0.3 (−0.7,0.1)	−0.1 (−0.5,0.3)
POMS[h]–vigor	1484	>0	13 (0.2)	0.2 (−0.4,0.8)	−0.1 (−0.7,0.5)	0.3 (−0.3,0.9)	14 (0.2)	−0.3 (−0.8,0.3)	−0.2 (−0.8,0.4)	0 (−0.6,0.6)

[a] N, number of participants in the model.
[b] D, direction of better performance.
[c] Unadjusted values.
[d] Tabled values are the mean (95% CI) of the difference between the estimated outcome mean for exposure quartile 1 and quartiles 2–4 in models adjusted for age, sex, ethnicity, education, income, alcohol consumption, NART, examiner.
[e] HVLT, Hopkins Verbal Learning Test.
[f] Combined total of intrusion errors on learning and recall trials plus false positive errors on recognition.
[g] BVRT, Benton Visual Retention Test.
[h] POMS, Profile of Mood States.

Table 4
Cognitive function and mood—test score differences from the first quartile (Q) of long-term (up to 30 years) estimated H_2S exposure concentration in ppb, after controlling for covariates.

Test	N[a]	D[b]	Time-weighted mean exposure				Maximum exposure at home, work or school			
			Q1 (0–6 ppb)	Q2 (7–11 ppb)	Q3 (12–18 ppb)	Q4 (19–58 ppb)	Q1 (0–10 ppb)	Q2 (11–20 ppb)	Q3 (21–31 ppb)	Q4 (32–60 ppb)
			Mean (SE)[c]	Difference (95% confidence interval) from Q1[d]			Mean (SE)[c]	Difference (95% confidence interval) from Q1[d]		
Attention										
Digit span—mean span forward	1439	>0	6.5 (0.1)	0.1 (−0.1,0.2)	0 (−0.1,0.2)	0.1 (−0.1,0.2)	6.4 (0.1)	0 (−0.2,0.1)	0 (−0.1,0.1)	0.1 (0,0.3)
Digit span—mean span reverse	1435	>0	4.9 (0.1)	0.1 (0,0.2)	0 (−0.1,0.1)	0 (−0.1,0.2)	4.8 (0.0)	−0.1 (−0.2,0.1)	−0.1 (−0.2,0)	0.1 (−0.1,0.2)
Psychomotor speed										
Simple reaction time (ms)	1408	<0	233 (1.4)	0.7 (−3.2,4.6)	−1.9 (−5.9,2.1)	−1.8 (−5.9,2.2)	231 (1.3)	−2.1 (−6.0,1.8)	−2.7 (−6.7,1.3)	−3.0 (−7.1,1.1)
Digit symbol (# correct)	1440	>0	54 (0.6)	0.6 (−0.9,2.0)	0.5 (−1.0,1.9)	0.7 (−0.8,2.2)	54 (0.6)	−0.5 (−1.9,1.0)	−1.4 (−2.8,0.1)	0.6 (−0.9,2.1)
Memory										
HVLT[e] learning (# correct)	1459	>0	26 (0.2)	0 (−0.7,0.6)	0 (−0.7,0.6)	0.3 (−0.4,0.9)	26 (0.2)	0.2 (−0.4,0.9)	0.2 (−0.4,0.8)	0.6 (−0.1,1.2)
HVLT[e] recall (# correct)	1459	>0	9.3 (0.1)	0 (−0.3,0.3)	−0.1 (−0.4,0.2)	0 (−0.3,0.3)	9.4 (0.1)	0.3 (0,0.6)	0.2 (−0.1,0.5)	0.3 (0,0.6)
HVLT[e, f] errors (combined total)	1459	<0	1.7 (0.1)	0 (−0.3,0.3)	0 (−0.3,0.3)	0 (−0.3,0.3)	1.8 (0.1)	0.1 (−0.1,0.4)	0.1 (−0.2,0.4)	0 (−0.3,0.3)
BVRT[g] correct	1465	>0	6.2 (0.1)	0.2 (0,0.5)	0 (−0.2,0.3)	−0.1 (−0.3,0.2)	6.2 (0.1)	0 (−0.3,0.3)	−0.1 (−0.4,0.1)	0 (−0.3,0.2)
BVRT[g] errors	1465	<0	5.0 (0.2)	−0.4 (−0.8,0.1)	0 (−0.4,0.4)	0.2 (−0.3,0.6)	5.1 (0.2)	0 (−0.4,0.5)	0.3 (−0.1,0.8)	0.2 (−0.3,0.6)
Fine motor function										
Grooved pegboard right + left, s	1323	<0	72 (0.8)	−1.1 (−3.0,0.9)	−0.8 (−2.8,1.2)	0 (−2.0,2.0)	73 (0.9)	0.6 (−1.4,2.5)	−0.4 (−2.4,1.6)	0.6 (−1.5,2.6)
Tapping, dominant hand, # taps	1408	>0	152 (1.3)	0.3 (−3.0,3.7)	1.9 (−1.5,5.3)	−0.5 (−4.0,2.9)	153 (1.3)	−1.5 (−4.9,1.9)	0.3 (−3.2,3.7)	0.5 (−3.0,4.1)
Tapping, non-dominant hand, # taps	1408	>0	134 (1.2)	1.5 (−1.6,4.6)	2.0 (−1.2,5.1)	1.2 (−2.0,4.4)	135 (1.1)	0.2 (−2.9,3.3)	1.0 (−2.2,4.2)	3.1 (−0.1,6.4)
Mood										
POMS[h]-Tension	1484	<0	8.1 (0.2)	−0.1 (−0.6,0.4)	0.1 (−0.3,0.6)	−0.2 (−0.6,0.3)	8.0 (0.2)	−0.1 (−0.6,0.4)	0.2 (−0.3,0.7)	−0.1 (−0.6,0.4)
POMS[h]—depression	1484	<0	7.4 (0.2)	0.3 (−0.1,0.7)	0.2 (−0.2,0.7)	0.1 (−0.3,0.5)	7.3 (0.2)	0.3 (−0.1,0.7)	0.2 (−0.2,0.7)	−0.1 (−0.5,0.4)
POMS[h]—anger	1484	<0	8.3 (0.2)	0 (−0.5,0.5)	0.2 (−0.4,0.7)	−0.3 (−0.8,0.2)	8.2 (0.2)	−0.1 (−0.6,0.4)	0.4 (−0.1,0.9)	−0.3 (−0.8,0.2)
POMS[h]—fatigue	1484	<0	11 (0.3)	0.4 (−0.2,1.1)	0.2 (−0.5,0.8)	−0.2 (−0.9,0.5)	11 (0.2)	0 (−0.7,0.7)	0 (−0.7,0.7)	−0.1 (−0.8,0.6)
POMS[h]—confusion	1484	<0	9.0 (0.2)	0.3 (−0.1,0.7)	0.1 (−0.3,0.4)	0.1 ((−0.3,0.5)	9.0 (0.1)	0.2 (−0.1,0.6)	0.1 (−0.3,0.4)	−0.1 (−0.5,0.3)
POMS[h]—vigor	1484	>0	14 (0.2)	−0.5 (−1.0,0.1)	−0.2 (−0.8,0.4)	−0.4 (−1.0,0.2)	14 (0.2)	−0.3 (−0.9,0.3)	0 (−0.6,0.6)	−0.5 (−1.1,0.1)

[a] N, number of participants in the model.
[b] D, direction of better performance.
[c] Unadjusted values.
[d] Tabled values are the mean (95% CI) of the difference between the estimated outcome mean for exposure quartile 1 and quartiles 2–4 in models adjusted for age, sex, ethnicity, education, income, alcohol consumption, NART, examiner.
[e] HVLT, Hopkins Verbal Learning Test.
[f] Combined total of intrusion errors on learning and recall trials plus false positive errors on recognition.
[g] BVRT, Benton Visual Retention Test.
[h] POMS, Profile of Mood States.

(better) mean adjusted reaction times than those in the lowest quartile. Continuous exposure models supported the results of the categorical exposure analysis—all regression coefficients were negative, and coefficients for both current and long-term exposure metrics based on weighted average H_2S exposures had p values of 0.08.

Secondary analyses examined the possibilities that higher H_2S exposure might be related to abnormal reaction times or increased variability of responding (results not shown). Abnormal scores were most common in the lowest quartile of maximum H_2S exposure (6.2%, 1.9%, 4.2%, 2.9%, for quartiles 1–4, respectively; $p = 0.03$). Testing for increased variability, we analyzed the coefficient of variation of SRT scores but found no evidence of an association with H_2S exposure, either using a simple correlation or in the fully adjusted models. There was no association of H_2S with hit rate in any of the models and no evidence of effect modification.

3.2.2. Digit symbol

In the categorical exposure models, there was no evidence that performance was associated with H_2S exposure (Tables 3 and 4). However, for most models, higher H_2S exposure quartiles were associated with slightly better performance than in the lowest quartile. Modeling H_2S exposure continuously, the current mean weighted H_2S concentration metric showed slight evidence of a trend ($p = 0.09$), such that higher levels of H_2S were associated with better test performance, but there was no evidence from the other continuous exposure metrics. Errors were not available, as there are no commonly used error scores for digit symbol. There was no evidence of effect modification for any of the exposure variables.

3.3. Episodic memory

3.3.1. HVLT

Judging from the categorical analysis results, both for current and long-term H_2S exposure, there was little evidence of any association with HVLT-learning. If anything, higher H_2S exposures were associated with marginally better scores than found for the lowest exposure quartile. For HVLT-recall there was no evidence of an association with any of the categorical metrics—current or long-term. None of the continuous measures of H_2S exposure showed any indication of an association with HVLT-learning or HVLT-recall.

3.3.2. BVRT

None of the exposure metrics, categorical or continuous, showed even slight evidence of an association with either BVRT correct or BVRT errors.

Neither HVLT nor BVRT showed evidence of effect modification of the exposure variables.

3.4. Fine motor function

3.4.1. Grooved pegboard

None of the current or long-term H_2S exposure metrics, as quartiles or continuous variables, were associated with GPB performance. Secondary analyses investigated whether H_2S exposure was associated with error rates—number of dropped pegs. A number of metrics for GPS errors were used, including dominant hand drops, non-dominant hand drops, total drops, and dichotomous versions of these measures. No association was found with any of the exposure metrics. Additionally, we investigated the standard deviation of the times for completing individual rows, as a measure of variability and/or fatigue, but found no significant association with H_2S, regardless of whether exposure was modeled categorically or continuously. There was no evidence of effect modification of the exposure variables.

3.4.2. Finger tapping

No clear evidence of associations between H_2S and tapping rate for either the dominant or non-dominant hands was observed when exposure was modeled in quartiles of either current or long-term exposure metrics (Tables 3 and 4). However, a trend in the direction of better performance associated with higher H_2S exposure was apparent for the long-term exposure metric based on maximum exposures at home or work. The analysis using this metric as a continuous variable produced a corresponding slope ($p = 0.03$). Otherwise, none of the continuously modeled H_2S exposure metrics showed any evidence of an association with tapping by the dominant and non-dominant hands. For tapping with the non-dominant hand there was some evidence of an interaction between age and the H_2S exposure metric for current maximum exposure at work or home. This was in the direction of improved performance by older people associated with higher H_2S exposures. However, since a corresponding effect was not observed with the dominant hand or with the other exposure metrics, we think it most likely that this observation was a chance consequence of carrying out many statistical tests of association. Tap failures, which may indicate subtle motor regulation problems, had no association with any of the H_2S exposure metrics, considered categorically or continuously (results not shown).

3.5. Mood

There are 6 subscales on the POMS. Five represent negative mood states (anger, tension, fatigue, confusion, depression) and one a positive state (vigor). We evaluated each scale separately, and also combined the 5 negative states into a single factor. Using either current or long-term H_2S exposure metrics, in quartiles or continuously, produced no evidence of associations between H_2S exposure and mood. There was no evidence of effect modification of the exposure variables.

4. Discussion

In this study, we used naturally occurring variations in H_2S concentrations to create estimates of exposures for the time of participation and over the past 30 years for over 1400 participants. This is considerably more extensive than for any previous study of elevated ambient H_2S exposures. We evaluated a range of cognitive functions: attention, memory, psychomotor speed, fine motor function, and mood. The predominant finding was that H_2S exposure was not associated with cognitive function. Further, higher levels of H_2S were sometimes associated with slightly better performance. This was most evident with tests of psychomotor speed where, for both current and long-term exposures, persons in the higher exposure quartiles had faster average reaction times compared to the lowest exposure group. In the absence of confirmatory data from other settings, these results most likely represent random variation, although other explanations are possible (see below).

Most importantly, we found no evidence of harmful effects in any cognitive function, regardless of how exposure was quantified and modeled. These results provide reassurance about the cognitive effects of chronic exposure to H_2S, at least up to the levels found in Rotorua, which are comparable with or higher than other reported ambient H_2S concentrations in Iceland, Finland, and the United States (Carlsen et al., 2012; Jaakkola et al., 1999; Legator et al., 2001; Wing et al., 2008).

In evaluating the results, certain tests stand out as particularly important. Digit symbol requires sustained attention, visual search and tracking, rapid copying of small designs, working memory, learning, and a degree of executive cognitive control (Lezak, 1995; Shuttleworth-Edwards, 2002). As a speed test invoking multiple cognitive systems, it is broadly sensitive to factors affecting cognition (Lezak, 1995; Shuttleworth-Edwards, 2002). This makes digit symbol one of the most favored screening tests for cognitive deterioration. Similarly, SRT is sensitive to a wide variety of brain disorders

and stressors. It is thus reassuring that for both tests almost all exposure quartile contrasts revealed differences in mean scores that were in the direction of better performance, although slight, in the higher exposure groups.

These results may be a consequence of the well-known "multiple comparisons" problem, or a consequence of residual confounding. However, an emerging literature provides some plausibility to the idea that low-level H_2S might have beneficial effects on CNS function. About 10 years ago it was recognized that H_2S is endogenously produced by mammals, becoming the third known gaseous signaling molecule ('gasotransmitter') in humans (Szabo, 2007). Since then, it has been found that H_2S regulates blood pressure and inflammation, and plays a role in metabolic disease (Whiteman et al., 2011). A protective role for H_2S in neurodegenerative and cerebral ischemic disease has been proposed (Gong et al., 2011). So far, almost all research has been carried out with animals (Whiteman et al., 2011). Our results suggest further epidemiologic investigation of the relationship between low-level H_2S exposure and processing speed may be worthwhile.

It is important to place these results in the context of findings from comparable studies. There are few, if any, that report measured exposures comparable to this study. The most highly exposed of our participants had two-week average H_2S exposures up to 64 ppb, although we can be confident that for shorter periods their exposures would have been appreciably higher than that. Spot measurements we have taken show that H_2S concentrations greater than 1000 ppb sometimes occur in some areas. Possibly the most comparable other study is by Inserra et al. (2004), who administered a neuropsychological test battery to residents of two Nebraska cities with H_2S exposures, occasionally in excess of 1000 ppb. The study area was divided into an "exposed" area, which sometimes experienced H_2S concentrations $\geq$90 ppb (171 participants), and a comparison area with <50 ppb exposures (164 participants). Of the 9 cognitive tests, 7 showed equal or better performance in the exposed group. No outcome was significantly worse in the exposed group. Fiedler et al. (2008) carried out a controlled chamber study with 74 healthy non-smokers, exposed to H_2S concentrations up to 5000 ppb for 2 h. No association with H_2S was found for any of the 5 cognitive function tests, including SRT, symbol-digit, tapping, and a memory test. Our results are broadly consistent with these two studies.

Most other H_2S studies with cognitive function tests have involved occupationally or industrially exposed populations (De Fruyt et al., 1998; Farahat and Kishk, 2010; Kilburn, 1997) where H_2S exposure can be difficult to quantify. Some used duration of H_2S exposure, rather than H_2S measurements (Kilburn, 1997, 2003), while others reported few measurements (Kilburn et al., 2010). Some studies used self-selected participants (Kilburn, 1997, 2003, 2012; Kilburn et al., 2010), raising the possibility of selection bias.

Potential impacts of selection bias, information bias and confounding on our study results should be considered. Selection bias could be problematic if participants had a different exposure pattern than non-participants. We were able to examine this to some degree, as we also had data on age, sex, ethnic group and exposure area of the non-participants (Bates et al., 2013). Women and older people were most willing to participate, although this is consistent with what epidemiologic studies have frequently found (Galea and Tracy, 2007). We also found Maori and Pacific Island people to be less likely to participate than people of self-reported European ethnicity. This is consistent with what other studies in New Zealand have found (Fink et al., 2011; Mannetje et al., 2011) and we see no reason to believe it has any particular implications for our study. Of most importance, there was no suggestion that participation was in any way differential according to the H_2S exposure status of the current residence.

Information bias is possible if there were misclassification of either outcomes or exposures. We measured outcomes using standard and well-validated methods and test administrators were thoroughly trained, with extensive investigator oversight throughout the data collection phase. Therefore, we consider that misclassification of outcomes should not be a major concern.

Of more concern is the possibility of exposure misclassification. Test administrators were blind to participant exposure status and exposures were estimated using much more comprehensive methods than in any previous study of ambient H_2S exposures (Bates et al., 2013). However, a key assumption for the long-term exposure estimates is that there was little change in H_2S sources over the last 30 years. We consider this a not unreasonable assumption, since the distribution of geothermal features generating H_2S has changed only slowly in Rotorua. Nevertheless, there was certainly exposure misclassification because we computed our estimates solely on the basis of when and where participants lived, worked, and went to school. Since exposure misclassification is unlikely to be related to outcome status, it would probably have attenuated any actual exposure–response relationships—in either direction.

Uncontrolled confounding can never be ruled out. However, when we compared unadjusted measures of association with H_2S with the corresponding measures adjusted for a range of socio-demographic variables, we found little change. We know of no factors not taken into account in the data analysis that are likely to be associated with both H_2S exposure and cognitive outcomes.

5. Conclusion

This was the largest epidemiologic study that has investigated cognitive effects of ambient H_2S concentrations. It had a population-based participant selection process, objective tests of relevant cognitive functions, absence of potentially confounding co-pollutants, and a comprehensive modeling of H_2S exposures, including estimates of both current and long-term exposure, although these exposures were estimated from H_2S measurements in 2010/11. The results provide no evidence that chronic H_2S exposure, at the ambient levels found in and around Rotorua, is associated with impairment of cognitive function or mood.

Conflict of interest statement

The authors declare they have no actual or potential competing financial interests.

Transparency document

Transparency document associated with this article can be found, in the online version.

Acknowledgments

This work was supported by the National Institute of Environmental Health Sciences of the National Institutes of Health (grant number R01ES014038). Support for the study was also provided by the Regional Councils Environment Bay of Plenty and Environment Waikato. The authors thank Shane Iremonger (Environment Bay of Plenty) and Nick Kim (Environment Waikato) for assistance.

Thanks to Melinda Sando, Dr Sandra Linenberger, Fiona Paignton, Kataraina George, Nerene Lynskey and John McKeogh for data collection and management.

Assistance with participant recruitment and data management was provided by the Rotorua Area Primary Health Service (RAPHS). Thanks to Kirsten Stone, David Bradford, Chris Walmsley, Jennifer Anastasi and Miranda Whitwell.

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