Corpus Callosum Volume in Railroad Workers With Chronic Exposure to Solvents

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Objective: *Changes to cognition and behavior have been reported after long-term exposure to solvents. Solvents are hypothesized to affect brain white matter. To test this, we examined the volume of the corpus callosum in workers with a history of exposure to solvents.* ***Methods:*** *We manually traced (blind to group membership) the volume of the corpus callosum in 31 railroad workers and 31 matched controls.* ***Results:*** *There was a decrease in the genu of the corpus callosum in the solvent-exposed workers compared with controls. A smaller volume of the genu of the corpus callosum was associated with greater exposure and worse performance on cognitive tasks.* ***Conclusions:*** *This study supports the hypothesis that occupational exposure to solvents affects the anterior white matter of the brain and is related to extent of exposure and degree of cognitive change.* (J Occup Environ Med. *2006;48:615–624*)

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Volatile organic solvents are used in many occupational settings. Neuropsychiatric changes are well documented for persons with a history of chronic solvent exposure.[1] Commonly reported chronic symptoms include headaches, dizziness, memory loss, mental dullness, distractibility, depression, anxiety, and irritability. Symptoms often appear gradually and may initially remit when exposure ceases (eg, weekends), but with continued exposure, there is evidence that changes may be longlasting.[2,3] Significant associations with dose and cumulative time of exposure have been reported.[4] However, a concern expressed in the literature is that the behavioral testing performance used to infer damage to the central nervous system is, in part, effort-dependent.[5] Effort-independent findings are useful to address these concerns and to correlate physiological findings with behavioral data.

The etiology of the neuropsychiatric dysfunction in solvent-exposed workers has typically been attributed to either a traumatic psychologic reaction to the exposure[6] or to secondary central nervous system (CNS) damage with resultant mood disorder.[7] Neuroimaging allows for a more detailed look at CNS changes hypothesized to result from solvent exposure.

Most organic solvents are lipophilic. They can penetrate the blood–brain barrier and may disrupt membrane functions of the cell body, axon, and synapse. It has been noted that persons who chronically abuse solvents (eg, sniffers/huffers) have CNS changes on

autopsy and clinical magnetic resonance image (MRI) that are consistent with widespread loss of myelin.[8–10] Application of functional neuroimaging techniques to nonabusing populations with a history of occupational exposure to organic solvent exposure has documented changes in both cortical and subcortical areas with single photon emission computerized tomography (SPECT)[11,12] and positron emission tomography (PET).[13–15] However, functional imaging does not necessarily speak to the underlying neuropathology. Functional imaging results are amenable to a variety of explanations about altered brain function. In contrast, structural neuroimaging provides evidence in terms of what regions of the brain are affected and possibly what type of tissue is affected. A recent study by Alkan et al[16] used magnetic resonance spectroscopy to measure different levels of metabolites in the brain in a group of shoemakers with an average of 15 years of exposure to degreasers, glues, and other volatile organic compounds. Based on a difference in the ratio of choline to creatine, it was suggested there was evidence of demyelination in the workers compared with control subjects. The authors also noted a positive correlation between demyelination and years of exposure.

The lipophilic nature of solvents, the case reports of solvents affecting the brain white matter, and the recent study by Alkan et al[16] suggesting demyelination provide converging lines of evidence to examine the volume of white matter in solvent-exposed workers. The corpus callosum is the largest white matter bundle in the brain. Corpus callosum volume has been shown to be affected in other neuropsychiatric conditions, including schizophrenia and posttraumatic stress disorder.[17,18] In addition, abnormalities of the corpus callosum have been reported in alcoholism,[19] a condition of voluntary solvent exposure. Thus, the purpose of the present study was to examine the effects of occupational exposure to solvents on brain white matter by measuring the volume of the corpus callosum in railroad workers who had been chronically exposed to solvents. Our hypothesis was that exposed workers would have decreased volume of the corpus callosum compared with nonexposed controls.

Specifically, we hypothesized the anterior portion of the corpus callosum would be smaller. The genu or anterior portion of the corpus callosum sends fibers to the prefrontal cortex. Functional imaging has suggested that the prefrontal cortex may be affected by solvent exposure.[14] The genu appears to be more prone to injury.[20] In addition, we hypothesized that the anterior portion of the corpus callosum would be related to performance on behavioral measures of frontal lobe function.

Materials and Methods

Subject Selection

This article is part of a larger study that compared railroad workers with a history of solvent exposure to nonexposed controls. Outcome measures in this larger study included psychiatric status, neuropsychologic performance, functional brain imaging with PET, and structural brain imaging with MRI. The results of the neuropsychologic and PET data will be presented in future publications. This is the first study to be published from the overall dataset. Solvent exposed participants were clinic referred railroad workers with both significant exposures in their occupational environment and complaints of cognitive dysfunction (eg, memory and/or concentration problems) between 1995 and 2003. To be considered for the study, a minimum of 10 years of solvent exposure was required. Exclusion criteria included pending or ongoing litigation regarding exposure, current substance abuse or illicit drug use, history of neurologic or neurosurgical condition (eg, stroke, closed head injury, brain tumor), history of psychiatric problems before exposure, or history of other serious medical illness (eg, myocardial infarction, cardiac surgery, organ failure). Subjects with medically controlled conditions such as hypertension or noninsulin-dependent diabetes were included, although these factors were addressed in subsequent analyses. A total of 258 patient files were reviewed. Those patients that passed an initial screening based on historical information contained in the files were then contacted by telephone ($n = 113$). Of these, 37 patients agreed to participate in the study, 57 declined to participate, and the remaining 19 patients were excluded based on the previously mentioned exclusion criteria.

An equal number of control subjects were recruited from community locations and were matched to the exposed subjects in terms of age, education, similar blue-collar occupation, and socioeconomic status. The control subjects included maintenance workers at West Virginia University, trade unions in the region, and respondents to newspaper advertisements. Control subjects were not considered if they reported any solvent exposure in their occupation (eg, painters) or through other means (eg, accidental exposure). All potential control participants underwent the medical screening described previously over the telephone and were subjected to the same exclusion criteria as the solvent-exposed subjects. All participants were white males. Before participation, all subjects signed an informed consent form approved by the Institutional Review Board at West Virginia University.

Solvent Exposure Interview

The exposure environment experienced by the railroad workers in this study was briefly described in a previous publication that described a workshop on solvent exposure in railroad workers.[21] We reiterate and describe particulars of the work environment in detail subsequently. Each solvent-exposed subject underwent a structured interview to assess exposure. The exposed subjects had worked at two principal sites and described uncontrolled, long-term, intense skin contact and inhalation exposures to a variety

of cleaning solvents and solvent mixtures, including tetrachloroethylene, trichloroethylene, trichloroethane, and mineral spirits. Settings and job duties included locomotive degreasing operations that applied 55-gallon drums of solvents through a spray wand, entry into enclosed locomotive spaces still wet with evaporating solvent, part and tool cleanup operations involving inhalation and frequent skin contact, and other wheel, motor, car, and part degreasing operations. These operations required hand applications of organic solvents and solvent mixtures without personal protective equipment, frequently at rates of more than one gallon per day. Multiple job categories were involved and many employees described similar operational exposures at more than one job. For most of their work histories, workers described multiple episodes of acute neurointoxication symptoms, including headache, nausea, and a "giddy-headed" sensation, frequent permissible "fresh air" breaks to address symptoms, absence of respirator use, and intermittent or no use of protection from dermal exposure. The average number of years of exposure was 24.3 with a range of 10–35 years. The average length of time between termination of exposure and evaluation was 8.44 years (range, 1–24 years), and their most recent exposure was greater than 1 year before the study. As a means of ordering the severity of exposure, based on the exposure histories, subjects were classified on a scale of 1 to 3, with subjects in group 1 having the lowest level of exposure (ie, shortest duration of exposure and job titles and descriptions indicating less exposure) and those in group 3 having the heaviest exposures (ie, the longest duration of exposure and a history of multiple fresh air breaks). Group 2 had exposures intermediate between groups 1 and 3. The classification was based on the structured interview data and was done blind to the corpus callosum data. This classification system has been validated with other samples of solvent-exposed individuals.[22] It should be noted that all subjects provided histories of multiple episodes of intoxication over prolonged periods.

Psychiatric Interview

All subjects completed a comprehensive structured psychiatric interview, the Structured Clinical Interview for DSM-IV,[24] which was administered in person using the computer-facilitated format.[25]

Subjects

A subset of the total sample (31 of 37 solvent-exposed and 33 of 37 controls) were able to participate in MRI scans Subjects who were too large to fit in the MR scanner, had metal in their body, or experienced claustrophobia were not scanned (six subjects in the solvent-exposed group and four controls). The MRI scan of one control subject was excluded because excessive movement distorted the images and one control subject's scan was lost because technical difficulties prevented saving the data. Demographic variables for the 62 participants who were able to complete the MRI scan are listed in Table 1. There was no difference between groups for age, education, or estimated IQ using the North American Adult Reading Test.[23] There was also no difference between the groups for height and weight, which can affect brain volumes. Eleven of the 31 solvent-exposed participants included in the MRI analysis (35%) had a current psychiatric diagnosis; three had an anxiety disorder, seven had a mood disorder, and one had both a mood and an anxiety disorder. None of the exposed participants had a prior lifetime diagnosis of a psychiatric condition. Two of the controls had a current psychiatric diagnosis, one anxiety disorder, and one mood disorder, and none of the controls had a past lifetime diagnosis of any Axis I psychiatric condition (eg, mood disorder, anxiety, schizophrenia). Three of the exposed participants and four of the controls had a past diagnosis of alcohol abuse or dependence. None of the subjects had a current diagnosis of substance abuse or dependence and none had used significantly within the last year.

Magnetic Resonance Image Scanning Procedures

All imaging was acquired on a GE 1.5-T MR system. First, each participant received a three-plane localizer for slice prescription. Then, each participant received a high-resolution three-dimensional spoiled gradient recall (SPGR) image acquired in the axial plane with 1.2 mm slice thickness covering the entire brain (field of view = 22 cm, matrix 256 × 256, NEX = 0.75, TR = 30, TE = minimum full band width = 15.63).

Manual Tracing

The volume of the corpus callosum was measured using a variation of manual tracing. We used in-house software within the Matlab environment (Mathworks, Sherborn, MA). The software provides three orthogo-

TABLE 1
Demographic Variables for the Full Sample*

	Solvent (N = 31) Mean (SD)	Control (N = 31) Mean (SD)
Age	54.5 (5.3)	52.4 (5.5)
Education	12.5 (1.4)	13.1 (2.1)
NART-IQ	99.1 (9.1)	101.0 (7.6)
Height	69.7 (2.6)	70.7 (2.5)
Weight	197.0 (30.1)	193.1 (30.9)

*There were no statistically significant differences between groups. Height is in inches and weight is in pounds.

SD indicates standard deviation.

nal views to define volumes of interest (VOIs) and plots of MR intensity profiles across the three orthogonal axes at an intended point (eg, a point within the corpus callosum). Upper and lower MR intensity thresholds were defined for the corpus callosum by sliding horizontal lines on the intensity plots. Then, voxels between the thresholds were displayed in a color scale and the rest in a gray scale. Callosal voxels were registered by clicking a mouse button within the structure after manually disconnecting continuations of colored areas to structures other than the corpus callosum. The lower threshold was at roughly the middle intensity between white and gray matter intensities. The callosal VOI was defined in the sagittal plane to cover at least one half of the lateral extents of lateral ventricles as observed in the coronal plane. Because the distinction between the edges of and transition between corpus callosum and general white matter can be unclear, we used an automated procedure. First, the callosal VOI was transferred from native space to an "upright" orientation in which the midplane was in the middle of the box containing the image volume and the anterior commissure (AC)–posterior commissure (PC) plane was horizontal. Voxel values of the transferred VOI were between zero and one at the peripheries and one in the rest. The volume of the corpus callosum was obtained using the middle 10 mm of the VOI to avoid the difficulty inherent in determining the periphery of the structure. Furthermore, the corpus callosum was divided into anterior (mainly the genu), middle (the body), and posterior (mainly the splenium) by the AC and PC planes. The volume anterior to the AC was labeled anterior, the volume posterior to the PC line was labeled posterior, and the remaining volume was labeled middle. Tracings were performed blind to group membership by one of two operators (GH and MWH).

Total Intracranial Volume Measurement

To adjust for head size, we estimated total intracranial volume. Each brain was segmented into gray, white, and cerebrospinal fluid using the segmentation routine of the image processing program, Statistical Parametric Mapping 2 (http://www.fil.ion.ucl.ac.uk). A summation of the segmented images was hand-corrected for errors to exclude the sinuses, meninges, and other nonbrain parts. In addition, the cerebellum and pons were masked and excluded so that all measures were based on supratentorial volume. We calculated total intracranial volume by summing total corrected gray, white, and cerebrospinal fluid volumes. Volumes were corrected blind to group membership.

Cognitive Measures

To assess frontal lobe function, we examined a subset of the total neuropsychologic battery that was administered to each patient. These tests have been associated with frontal lobe function and include Trail Making Test part B, Stroop Color–Word Test, Letter–Number Sequencing, and Verbal Fluency.[26–29] Trail Making Test part B requires subjects to connect circles on a page alternating in order between numbers and letters (eg, 1–A–2–B). The Stroop Color–Word Test consists of three trials: 1) color name reading: subjects read the words red, green, and blue printed in black ink; 2) color naming: subjects name the color of "x"'s printed in red, green, or blue ink; and 3) interference trial: subjects must name the color of the ink that the words red, green, and blue are printed in, however, the color name does not match the ink color. For example the word red would be printed in blue ink. In this example, the subject must not read the word "red" and must instead name the ink color "blue." Letter–Number Sequencing requires subjects to listen to a string of numbers and letters (eg, 4–Z–9–B) and then repeat back the numbers in ascending order followed by the letters alphabetically (eg, 4–9–B–Z). Verbal fluency requires subjects to say as many words as they can in 60 seconds for the letters C, F, and L, respectively. We used total time to complete Trails B, the difference between Stroop Color and Stroop Color–Word performance, total raw score correct on Letter–Number Sequencing, and total number correct on Verbal Fluency as dependent measures. We included these measures to test whether changes in the anterior corpus callosum correlated with frontal lobe behavior.

Analysis

We examined the raw volume of the corpus callosum and its three segments as well as the corrected volumes adjusted for total intracranial volume: each volume divided by the total supratentorial intracranial volume. Intraclass correlations were used to examine interrater reliability for the corpus callosum volumes. We used one-way analysis of variance for each of these dependent measures to examine differences between the two groups. Spearman rank-ordered correlations were used to examine the possible dose–response relationship. Pearson product-moment correlations were used to examine the relationship between anterior corpus callosum volume and frontal lobe functioning.

Results

Using six randomly selected participants, an interclass correlation for corpus callosum volume was calculated based on the measurements of both tracers. A correlation of $r = .90$ ($P < 0.05$) was obtained. There were no differences between groups for total supratentorial intracranial volume (see Table 2); however, the standard deviation for the groups suggested greater variability in the control subjects; thus, we report raw values and values corrected for individual differences in supratentorial intracranial volume. The raw volume of the total corpus callosum was significantly lower in exposed participants (mean = 6.8) compared with

controls (mean = 7.5) (F[1,61] = 6.51, $P < 0.05$). The anterior segment of the corpus callosum was significantly different between the two groups with a smaller volume in the exposed participants (mean = 2.9) compared with the controls (mean = 3.4) (F[1,61] = 3.5, $P < 0.05$). Expressed as a percentage of total supratentorial intracranial volume, the total corpus callosum was significantly smaller in exposed participants (mean = 0.67%) compared with controls (mean = 0.74%) (F[1,61] = 6.12, $P < 0.05$). In addition, expressed as a percentage of the total supratentorial intracranial volume, the anterior segment of the corpus callosum was smaller size in subjects with exposure (mean = 0.29%) compared with the controls (mean = 0.34%) (F[1,61] = 9.49, $P < 0.05$). No other region of the corpus callosum showed a significant group effect.

We correlated exposure classification with the total volume of corpus callosum and each segment. Exposure classification was negatively related to the total volume of the corpus (r = −.41, $P < 0.05$) and to the volume of the anterior segment (r = −.39, $P < 0.05$), indicating smaller volumes were associated with greater exposures. We found no significant relationships between cognitive performance and the raw or corrected volumes of the corpus callosum segments.

Effect of Medical Variables

Hypertension and diabetes have been shown to result in whole brain atrophy, infarction of the white matter of the brain and hypertension is specifically associated with decreased volume of the prefrontal cortex and with frontal lobe cognitive deficits.[30–32] The frequency of hypertension and diabetes mellitus was greater in the solvent exposed than control subjects (12 solvent-exposed individuals and five controls with one or both conditions). To rule out the possibility that the observed differences in corpus callosum volumes could be caused by these medical conditions, we conducted an additional analysis, which excluded the subjects with hypertension and diabetes (HTN/DIAB). Of the available 26 control subjects, we selected the 19 subjects that best matched the 19 exposed subjects on age and education. When there was more than one subject who matched, random selection was used. The matching process was effective and there were no differences between groups on any of the demographic variables (see Table 3). In this sample, raw volume of the total corpus callosum was significantly lower in exposed participants (mean = 6.8) compared with controls (mean = 7.5) (F[1,36] = 4.76, $P < 0.05$). For the segments of the corpus callosum, the anterior segment exhibited significant differences between groups, with a smaller volume in the exposed participants (mean = 3.0) compared with the controls (mean = 3.4) (F[1,36] = 5.55, $P < 0.05$). The volume of the corpus callosum expressed as a percentage of the total supratentorial intracranial volume was significantly lower in exposed participants (mean = 0.67%) compared with controls (mean = 0.74%) (F[1,36] = 5.11, $P < 0.05$) (see Table 4). Expressed as a percentage of total supratentorial intracranial volume, the anterior segment was significantly lower in subjects with exposure (mean = 0.29%) compared with the controls (mean = 0.33%) (F[1,36] = 5.73, $P < 0.05$). There was a negative correlation between exposure classification and total volume of the corpus (r = −.47, $P < 0.05$) and the anterior segment (r = −.48, $P < 0.05$) in the subset of our subjects with no HTN/DIAB. Like in the whole sample, increased exposure was associated with smaller volume. We correlated cognitive performance with the raw volume of the anterior

TABLE 2
Volumetric Data for the Full Sample*

	Solvent (N = 31) Mean (SD)	Control (N = 31) Mean (SD)
TICV	1001.0 (65.0)	1003.0 (80.0)
Total CC†	6.7 (0.9)	7.4 (1.1)
Anterior CC†	2.9 (0.5)	3.4 (0.5)
Middle CC	1.5 (0.2)	1.7 (0.3)
Posterior CC	2.3 (0.4)	2.4 (0.4)
Total CC %†	0.67 (0.08)	0.74 (0.12)
Anterior CC %†	0.29 (0.05)	0.34 (0.06)
Middle CC %	0.15 (0.02)	0.17 (0.03)
Posterior CC %	0.23 (0.03)	0.24 (0.05)

*Raw volumes are expressed in milliliters.
†$P < 0.05$.
SD indicates standard deviation; TICV, total supratentorial intracranial volume; CC, corpus callosum; %, CC volume as a proportion of TICV.

TABLE 3
Demographic Variables for the Sample With No HTN/DIAB*

	Solvent (N = 19) Mean (SD)	Control (N = 19) Mean (SD)
Age	53.7 (5.7)	52.3 (5.9)
Education	12.3 (1.4)	13.1 (1.9)
NART-IQ	100.6 (7.9)	102.0 (9.3)
Height	70.0 (3.0)	70.9 (2.1)
Weight	195.5 (28.4)	196.9 (28.9)

*There were no statistically significant differences between groups. Height is in inches and weight is in pounds.
HTN/DIAB indicates hypertension and diabetes; SD, standard deviation.

segment of the corpus callosum. In the subgroup with no HTN/DIAB, Letter–Number Sequencing was significantly correlated with anterior corpus callosum volume ($r = 0.450$, $P < 0.05$) such that worse performance was associated with smaller volume. There was a significant inverse correlation between Stroop Color–Word performance and anterior corpus callosum volume ($r = -.385$, $P < 0.05$) such that smaller volume was associated with more interference (ie, worse performance). There was a trend for a relationship with Trail Making B ($r = -.254$, $P = 0.06$) such that smaller volume was associated with slower performance. There was a weak trend with verbal fluency such that smaller volume was associated with worse performance ($r = .207$, $P = 0.10$). Finally, none of the volumes of the corpus callosum correlated with age, education, estimated IQ, or history of alcohol abuse (a limited number in our sample).

To determine if medical status affected corpus callosum volume within the solvent-exposed sample, we compared the subjects with HTN/DIAB and subjects with no HTN/DIAB. There were no significant differences between the two groups for any of the demographic variables (see Table 5). There was weak a trend for higher estimated IQ in the group with HTN/DIAB ($F[1,29] = 2.12$, $P = 0.15$). There was a difference in total supratentorial intracranial volume ($F[1,29] = 4.87$, $P < 0.05$) with the group with HTN/DIAB having a smaller volume. This difference remained when covarying the height and weight of the subjects to control for differences in overall body size. When examining the corpus callosum volumes, raw and corrected, there were no differences between the two groups (all F's <1; see Table 6).

TABLE 4
Volumetric Data for the Sample With No HTN/DIAB*

	Solvent ($N = 19$) Mean (SD)	Control ($N = 19$) Mean (SD)
TICV	1020 (61)	1020 (75)
Total CC†	6.8 (0.9)	7.5 (0.9)
Anterior CC†	3.0 (0.5)	3.4 (0.5)
Middle CC	1.5 (0.2)	1.7 (0.3)
Posterior CC	2.3 (0.3)	2.4 (0.4)
Total CC %†	0.67 (0.08)	0.74 (0.09)
Anterior CC %†	0.29 (0.05)	0.33 (0.05)
Middle CC %	0.15 (0.02)	0.16 (0.03)
Posterior CC %	0.23 (0.03)	0.24 (0.03)

*Raw volumes are expressed in milliliters.
†$P < 0.05$.
HTN/DIAB indicates hypertension and diabetes; SD, standard deviation; TICV, total supratentorial intracranial volume; CC, corpus callosum; %, CC volume as a proportion of TICV.

TABLE 5
Demographic Variables for the Solvent Sample as a Function of Medical Status*

	No HTN/DIAB ($N = 19$) Mean (SD)	HTN/DIAB ($N = 12$) Mean (SD)
Age	53.7 (5.7)	55.7 (4.3)
Education	12.3 (1.4)	12.8 (1.4)
NART-IQ	100.6 (7.9)	96.1.0 (8.7)
Height	70.0 (3.0)	69.2 (2.0)
Weight	195.5 (28.4)	202.4 (32.7)

*There were no statistically significant differences between groups. Height is in inches and weight is in pounds.
HTN/DIAB indicates hypertension and diabetes; SD, standard deviation.

TABLE 6
Volumetric Data for the Solvent-Exposed Subjects as a Function of Medical Status*

	No HTN/DIAB ($N = 19$) Mean (SD)	HTN/DIAB ($N = 12$) Mean (SD)
TICV†	1020 (61)	970.7 (62)
Total CC	6.8 (0.9)	6.6 (0.9)
Anterior CC	3.0 (0.5)	2.9 (0.5)
Middle CC	1.5 (0.2)	1.5 (0.2)
Posterior CC	2.3 (0.3)	2.2 (0.5)
Total CC %	0.67 (0.08)	0.68 (0.08)
Anterior CC %	0.29 (0.05)	0.29 (0.05)
Middle CC %	0.15 (0.02)	0.15 (0.03)
Posterior CC %	0.23 (0.03)	0.23 (0.03)

*Raw volumes are expressed in milliliters.
†$P < .05$.
HTN/DIAB indicates hypertension and diabetes; SD, standard deviation; TICV, total supratentorial intracranial volume; CC, corpus callosum; %, CC volume as a proportion of TICV.

Effect of Psychiatric Diagnosis

Of the 31 solvent-exposed subjects, 11 met criteria for current or past psychiatric diagnosis. Because the size of the corpus callosum has been related to psychiatric status,[17,18] we undertook an additional analysis to control for the effect of psychiatric diagnosis on corpus callosum volume. The solvent-exposed group was divided between those subjects that did ($n = 11$) and did not ($n = 20$) have a current or past psychiatric diagnosis. The groups were not significantly different for age, education, and estimated IQ (see

TABLE 7
Demographic Variables for the Solvent-Exposed Subjects, Divided Between Those With a Psychiatric Diagnosis ($N = 12$) and Those Without a Psychiatric Diagnosis ($N = 19$)*

	Psychiatric Diagnosis ($N = 12$) Mean (SD)	No Psychiatric Diagnosis ($N = 19$) Mean (SD)
Age	52.5 (5.1)	55.5 (5.5)
Education	12.7 (1.3)	12.5 (1.5)
NART-IQ	100.3 (7.1)	98.4 (10.1)
Height	69.8 (2.7)	69.7 (2.7)
Weight	189.8 (25.9)	201.0 (32.2)

*There were no statistically significant differences between groups. Height is in inches and weight is in pounds.
SD indicates standard deviation.

TABLE 8
Volumetric Data for the Solvent-Exposed Subjects, Divided Between Those With a Psychiatric Diagnosis ($N = 12$) and Those Without a Psychiatric Diagnosis ($N = 19$)*

	Psychiatric Diagnosis ($N = 12$) Mean (SD)	No Psychiatric Diagnosis ($N = 19$) Mean (SD)
TICV	1001 (69)	1001 (64)
Total CC	6.9 (0.8)	6.7 (0.9)
Anterior CC	3.1 (0.4)	2.9 (0.6)
Middle CC	1.6 (0.2)	1.7 (0.2)
Posterior CC	2.3 (0.4)	2.3 (0.4)
Total CC %	0.69 (0.08)	0.67 (0.08)
Anterior CC %	0.30 (0.04)	0.29 (0.05)
Middle CC %	0.16 (0.02)	0.15 (0.02)
Posterior CC %	0.23 (0.04)	0.23 (0.04)

*Raw volumes are expressed in milliliters.
SD indicates standard deviation; TICV, total supratentorial intracranial volume; CC, corpus callosum; %, CC volume as a proportion of TICV, there were no statistically significant differences between groups with all F's <1.

TABLE 9
Demographic Variables for the 'Medically Clean' Solvent-Exposed Subjects ($N = 19$), Divided Between Those With a Psychiatric Diagnosis ($N = 9$) and Those Without a Psychiatric Diagnosis ($N = 10$)*

	Psychiatric Diagnosis ($N = 9$) Mean (SD)	No Psychiatric Diagnosis ($N = 10$) Mean (SD)
Age	52.2 (5.4)	55.0 (5.9)
Education	12.4 (1.3)	12.3 (1.5)
NART-IQ	103.4 (7.9)	98.2 (7.5)
Height	70.0 (3.1)	70.1 (2.9)
Weight	186.4 (27.5)	200.1 (30.1)

*There were no statistically significant differences between groups. Height is in inches and weight is in pounds.
SD indicates standard deviation.

Table 7). There were no significant differences between those exposed subjects with and without a psychiatric diagnosis on any of the measures of the corpus callosum (see Table 8). The same analysis was undertaken within the subgroup of solvent-exposed subjects who did not have any medical problems. Of those 19 subjects, nine carried a current or past diagnosis and 10 did not. Again, no differences in any demographic variables or corpus callosum volumes were observed (see Tables 9 and 10).

Discussion

This study revealed a decrease in the volume of the corpus callosum in railroad workers with a history of chronic exposure to solvents. The corpus callosum volume difference was largely accounted for by the significant difference in the anterior portion of the corpus callosum. The volume of the corpus callosum in workers with solvent exposure was dose-dependent, with smaller volume associated with higher levels of exposure. This structural difference in the volume of the corpus callosum is consistent with the hypothesis that chronic exposure to solvents affects the white matter of the brain. The difference in brain volume was not the result of other medical conditions that can affect the white matter (hypertension, diabetes). When this potential confounding factor was removed from the analysis, the relative reduction in corpus callosum volume in solvent-exposed subjects was maintained. In addition, controlled hypertension and diabetes did not affect the volume of the corpus callosum within the solvent-exposed group. Although the group with hypertension and diabetes had a smaller total supratentorial intracranial volume, the volumes of the corpus callosum did not differ between the solvent-exposed subjects with and without HTN/DIAB.

The difference in corpus callosum volume was not related to the presence or absence of a current mood or anxiety disorder. When we compared solvent-exposed subjects with and without psychiatric diagnoses, no differences in corpus callosum volumes were observed between subgroups. This similarity between groups remained when the solvent-exposed subjects with no HTN/DIAB with and without psychiatric diagnoses were compared. This implies that the changes in the volume of the corpus callosum were not the result of the

TABLE 10
Volumetric Data for the 'Medically Clean' Solvent-Exposed Subjects ($N = 19$), Divided Between Those With a Psychiatric Diagnosis ($N = 9$) and Those Without a Psychiatric Diagnosis ($N = 10$)*

	Psychiatric Diagnosis ($N = 9$) Mean (SD)	No Psychiatric Diagnosis ($N = 10$) Mean (SD)
TICV	1021 (56)	1019 (68)
Total CC	7.1 (0.8)	6.7 (0.9)
Anterior CC	3.2 (0.4)	2.9 (0.6)
Middle CC	1.5 (0.2)	1.5 (0.2)
Posterior CC	2.4 (0.3)	2.2 (0.3)
Total CC %	0.65 (0.08)	0.69 (0.09)
Anterior CC %	0.28 (0.05)	0.31 (0.04)
Middle CC %	0.15 (0.02)	0.15 (0.02)
Posterior CC %	0.22 (0.03)	0.23 (0.03)

*Raw volumes are expressed in milliliters.

SD indicates standard deviation; TICV, total supratentorial intracranial volume; CC, corpus callosum; %, CC volume as a proportion of TICV, there were no statistically significant differences between groups with all F's <1.2.

effects of psychiatric symptoms on the brain, but rather the effect of solvents themselves on brain structure. Exposure to solvents commonly results in psychiatric symptoms.[22] None of our sample had a history of psychiatric symptoms before exposure, and thus we hypothesize that these psychiatric symptoms are a product of solvent exposure. Indeed, the rate of current anxiety and mood disorders obtained in this study was comparable to previous reports of psychiatric symptoms as a result of solvent exposure.[22]

There are two plausible explanations for the absence of an effect of psychiatric diagnosis on the corpus callosum volume in the solvent-exposed subjects. One possibility is that the lack of an effect of psychiatric diagnosis on corpus callosum volume was a function of the specific diagnosis, which pertains to most of our solvent-exposed sample, (ie, a mood disorder). Differences in the volume of the corpus callosum in mood disorders is not commonly reported,[33,34] and when differences are present, it occurs in bipolar depression[35] and not the unipolar depression our subjects experienced. Thus, the severity or type of the psychiatric symptoms in our sample may not have been enough to impact the volume of the corpus callosum. Another possibility is that solvents affect the volume of the corpus callosum to the same degree regardless of whether or not there are psychiatric symptoms present. Thus, patients with solvent exposure who have cognitive changes alone versus cognitive and emotional changes together appear to have the same degree of change to the volume of the corpus callosum. This implies that the changes to the volume of the corpus callosum were not secondary to the effects of psychiatric symptoms alone on the brain, but rather the effect of solvents themselves on brain structure.

This is the first study we are aware of to document changes in the volume of white matter of the brain in workers involuntarily exposed to solvents. There have been previous reports of solvent abuse leading to white matter changes in individual cases and groups.[8,36,37] In addition, a recent report of decreased metabolites, found by means of magnetic resonance spectroscopy, suggests demyelination is associated with solvent exposure.[16] Previous reports have documented that dependence on alcohol (a solvent) leads to impairment of the white matter of the brain. This has been documented by manual tracing of the volume of the corpus callosum and automated measurement.[18] In addition, the relatively new technique of diffusion tensor imaging has shown impairment of the corpus callosum in alcoholism.[38] Diffusion tensor imaging allows for measurement of the microstructure of the white matter of the brain and appears more sensitive to diseases that affect white matter than standard clinical imaging or volumetric studies. For example, normal-appearing white matter, based on standard clinical imaging, has been shown to be impaired with diffusion tensor imaging in patients with multiple sclerosis and small-vessel ischemic disease.[39,40] Replication of the results of the present study with diffusion tensor imaging appears warranted.

The difference in the corpus callosum volume between the groups was greatest in the anterior segment, which consists primarily of the genu. The genu completes development later than the splenium. This is thought to make it more vulnerable to injury,[19] and it is found to be injured in other populations.[36] Studies of the morphology and projections of the corpus callosum suggest that the anterior part or the genu projects to prefrontal cortex.[41–43] Consistent with this, we observed a relationship between the volume of the anterior segment and cognitive measures of frontal lobe function with smaller volume being associated with poorer performance. We only observed this relationship in the subgroup with no HTN/DIAB, which suggests that hypertension and diabetes introduced uncontrolled variance into the behavioral performance of the sample. One might also predict that the volume of the prefrontal cortex might also be affected in individuals with exposure to solvents as the fibers from the genu project to the prefrontal cortex. Whether the better hypothesis is that impairment exists in the genu and affects the prefrontal cortex or that the impairment is in the prefrontal cortex and affects the white matter is not clear. Further study is needed to examine the volume of the prefrontal white

matter and gray matter in samples of solvent-exposed workers.

We observed a dose–response relationship between corpus callosum volume and exposure similar to what was reported in the MRS study of Alkan et al.[16] The subjects enrolled in this study reported repeated episodes of high-dose exposure, including intoxication symptoms, and accepted permissible fresh air breaks as a safety response to symptoms during workplace operations. Our method of classifying exposure to include duration and severity was sensitive to group levels changes on MRI. However, there are limitations to this type of retrospective assessment from occupational history data, and conclusions in this area should be made cautiously and the findings replicated.

There are other limitations to this study. Although the manual tracing technique is expensive and time-consuming, it should be replicated in other exposed populations. Nevertheless, the data are robust within this study. Second, the results may not apply to all individuals with a history of solvent exposure because exposure will vary depending on the workplace, ventilation, and use of protective equipment. Our population reported frequent episodes of intoxication associated with high-volume, unprotected use. In addition, our population was not randomly selected. Therefore, it is not clear how well these findings will generalize to less-exposed populations. In addition, it is not clear that these findings can be applied to individual patients, because the differences we observed were found in group data. The topic of low-level nonintoxicating exposures also holds substantial research importance. It is unclear whether these results can be generalized to lower-exposure populations commonly reported in the literature. Finally, our population was a clinical population and as such may not be representative of solvent-exposed workers as a whole. Replication of our finding with a nonclinical population would add strength to the hypothesis that solvents affect the white matter of the brain. An epidemiologic study would be required to determine the extent to which solvent exposure results in changes to the corpus callosum in the population of workers at large.

In summary, we have documented changes in the volume of the white matter, specifically, the anterior corpus callosum, in workers who have been exposed to solvents. A dose–response effect was present. The results are consistent with hypothesized mechanisms of damage to the CNS white matter after solvent exposure.

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