Cerebral Impairment in Chronic Solvent-Induced Encephalopathy

Ieke Visser, MD, MSc,[1,2] Cristina Lavini, MPhil,[3] Jan Booij, MD, PhD,[4] Liesbeth Reneman, MD, PhD,[3] Charles Majoie, MD, PhD,[3] Angela G. E. M. de Boer, PhD,[2] Elizabeth M. Wekking, PhD,[5,6] Elisabeth A. de Joode, MSc,[2,5] Gert van der Laan, MD,[2,5] Frank J. H. van Dijk, MD, PhD,[2] Aart H. Schene, MD, PhD,[1] and Gerard J. Den Heeten, MD, PhD[3]

Objective: Worldwide, many workers experience occupational exposure to organic solvents, which may induce chronic solvent-induced encephalopathy (CSE). Disturbances within the frontostriatothalamic (FST) circuitry might explain the symptomatology of CSE. We tested the hypothesis of FST circuitry abnormalities in CSE, as well as associations with performance of psychomotor speed, attention, and solvent exposure. To detect preclinical, solvent-related effects, we also studied the FST circuitry in solvent-exposed, but asymptomatic workers.

Methods: Ten CSE patients, 10 asymptomatic but solvent-exposed house painters (EC), and 11 nonexposed asymptomatic carpenters were included. Dopamine D_2 receptor (D2R) binding, central nervous system tissue metabolites, and fractional anisotropy were measured within the FST circuitry, using single-photon emission computed tomography, magnetic resonance spectroscopy, and diffusion tensor imaging. Performance of psychomotor speed and attention, and severity of solvent exposure were assessed.

Results: Striatal D2R binding was reduced in CSE. In the solvent-exposed asymptomatic patients, striatal D2R binding and levels of *N*-acetylaspartate + *N*-acetylaspartyl-glutamate in frontal gray matter were reduced. In both exposed groups, a trend was seen for reduced choline in frontal gray matter. In CSE, the fractional anisotropy in the thalamus, caudate nucleus, and striatal D2R binding significantly predicted reduced performance of attention and psychomotor speed. In CSE, striatal D2R binding showed a negative correlation with solvent exposure.

Interpretation: This is the first study in CSE showing pronounced disturbances within the FST circuitry that are related to the clinical findings and to exposure severity to solvents. The comparable, but milder, abnormalities within the FST circuitry in the exposed asymptomatic workers may imply a presymptomatic phase of CSE.

Ann Neurol 2008;63:572–580

It is assumed that chronic exposure to organic solvents induces central nervous system (CNS) damage, usually referred to as chronic solvent-induced encephalopathy (CSE).[1] Organic solvents are incorporated in volatile liquids, such as paints, and printing or surface/dry cleaning agents, and used in many industries. The United Kingdom's Health and Safety Executive estimated that 8% of the working population regularly use organic solvents.[2] In the United States, 9 million workers are exposed to solvents, representing 3.7% of the general population.[3]

Currently, CSE is classified according to World Health Organization criteria,[4] and it is included in the ICD-10[5] and in the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition[6] as substance-induced persisting dementia. However, to date, neurobiological disturbances of CSE have not been elucidated. Consequently, CSE is still a controversial entity with a wide variation of medical and social recognition. As a result, prevention efforts remain insufficient, leaving many workers at risk to the potential neurotoxic hazards of occupational solvent exposure.

CSE is predominantly characterized by mild and sometimes severe cognitive impairment, affecting memory, attention, and psychomotor functions.[7] However, the disabilities arising from dysfunctions in memory and attention frequently persist after the exposure to solvents has ceased, compromising daily functioning, social and occupational participation, and quality of life.[8,9] The symptoms of CSE are implicitly assumed to relate to underlying disturbances in structure and function of the CNS. Associations have been reported be-

From the [1]Academic Psychiatric Center AMC; [2]Coronel Institute of Occupational Health; Departments of [3]Radiology and [4]Nuclear Medicine; [5]Netherlands Center for Occupational Diseases, Academic Medical Center, Amsterdam; and [6]Department of Psychology, Leiden University, Leiden, the Netherlands.

Received Sep 10, 2007, and in revised form Jan 14, 2008. Accepted for publication Jan 18, 2008.

Published online Apr 9, 2008, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21364

Address correspondence to Dr Visser, Academic Psychiatric Center AMC Polikliniek Psychiatrie PA1-183, Meibergdreef 15 1105 AZ. Amsterdam, the Netherlands. E-mail: i.visser@amc.uva.nl

tween the duration or severity of solvent exposure and the severity of memory and attention impairments.[10]

Various studies attempted to identify cerebral abnormalities in solvent-exposed workers by using magnetic resonance imaging (MRI) or computed tomography.[11] Solvent-exposed workers without neurological problems show no, or only mild, atrophic changes. In solvent-exposed workers with suspected neurological signs, atrophic changes have been reported in conjunction with white matter (WM) abnormalities. These changes were similar to those seen in highly exposed solvent abusers, such as loss of gray matter and WM discrimination, indicating demyelinization, and areas of abnormal intensity in the thalamus and basal ganglia. In addition, Haut and colleagues[12] found a decrease in the volume of the corpus callosum in railroad workers with chronic exposure to solvents. More recently, in solvent-exposed shoemakers, increased levels of CNS tissue metabolite choline (Cho) were reported in the thalamus, basal ganglia, and parietal WM using magnetic resonance spectroscopy.[13] In toluene abusers, the cerebellum and the centrum semiovale (CS) showed a reduction of the CNS tissue metabolite *N*-acetylaspartate (NAA)/creatine, whereas the level of myoinositol was higher.[14] Finally, animal[15] and human studies[16] have reported that exposure to organic solvents can affect the dopaminergic metabolism. However, Ridgway and colleagues[11] conclude that most of the previously mentioned studies have methodological shortcomings. Furthermore, the relation between these presumed cerebral abnormalities and clinical symptoms of CSE remains unclear.

It is well accepted that the predominating neuropsychological symptoms of CSE include psychomotor slowing and impaired attention.[1] In relating central circuits to these symptoms, an important role may be proposed for abnormalities within the frontostriatothalamic (FST) circuitry. This hypothesis is supported by the association between deterioration of this circuitry and psychomotor slowing and impairment in attention in natural aging. Particularly, reductions in striatal dopamine D_2 receptor (D2R) density, using positron emission tomography (PET), are associated with impaired attention and psychomotor speed in aging subjects.[17,18] Also, in disorders with symptoms of psychomotor slowing and impaired attention, such as Parkinson's disease[19] or bipolar disorders,[20] disturbances of the FST circuitry have been implied.

The aim of our preliminary study was threefold: (1) to evaluate possible abnormalities within the FST circuitry in patients with CSE; (2) to evaluate the association of these presumed abnormalities with performance of psychomotor speed, attention, and exposure severity; and (3) to study whether there are preclinical, solvent-related effects within FST circuitry in solvent-exposed, but asymptomatic, workers.

Subjects and Methods

Patients

Ten male CSE patients were consecutively recruited using the database of the Netherlands Center for Occupational Diseases. The diagnostic procedure of CSE includes medical and occupational history, as well as neurological and neuropsychological evaluation. All patients fulfilled the diagnostic World Health Organization criteria for CSE[4] as assessed by a standardized diagnostic protocol[21]: a verified long and/or intensive exposure to organic solvents; mild-to-severe cognitive impairment assessed by standardized neuropsychological tests; a temporal relation between exposure to solvents and the onset of symptoms and complaints; the exclusion of other plausible explanations for the symptoms and complaints, such as somatic illness, including sleep disorders or clinical signs of Parkinsonism, psychiatric disorders, including lifetime alcohol- and substance-related disorders, and a history of head trauma with loss of consciousness or hospitalization. Other exclusion criteria were suboptimal test motivation during the diagnostic neuropsychological evaluation, involvement in a litigation procedure during current study, and active solvent exposure during current study.

Twelve exposed, but asymptomatic, male control subjects (ECs) were consecutively recruited through the Dutch general trade union FNV, all working as house painters, with a verified long-term exposure to organic solvents as assessed with a retrospective exposure index. All ECs had been (at least 48 hours) free from solvent exposure before scanning.

Twelve nonexposed, asymptomatic, male control subjects (NEC) were consecutively recruited through the Dutch general trade union FNV, all working as carpenters, without any significant lifetime solvent exposure as assessed with a retrospective exposure index.

Exclusion criteria in the two control groups were somatic complaints, or complaints of memory, attention, mood and fatigue, and the presence of any somatic illness or psychiatric disorders or a history of head trauma with loss of consciousness or hospitalization.

In the EC group, two subjects were excluded from the entire study because of ischemic lesions detected on magnetic resonance images. Two NECs were excluded from the MRI analysis because of metal interference, and one NEC was excluded from the entire study because of ischemic lesions. All participants were free of alcohol use at least 12 hours before scanning.

All subjects gave written informed consent before enrollment. The study was approved by the Medical Ethical Committee of the Academic Medical Center.

Measurements

A retrospective exposure index was calculated by an occupational hygienist, consisting of the sum of four variables: duration of exposure in years, level of exposure, symptoms of acute intoxication, and the use of personal protection equipment. An exposure of 0 to 4 is classified as low, 5 and 6 as intermediate, and 7 to 9 as high exposure. Education level was assessed by a six-level scale (1 = primary school level; 6 = university level). Premorbid intelligence quotient was assessed by the Dutch Adult Reading Test.[22] Current alcohol

intake was classified as the estimated number of units per week.

In all subjects, the presence of somatic illness, sleep disorders, psychiatric disorders, including depressive symptoms, a history of head trauma, or clinical signs of Parkinsonism, was assessed by medical history, physical and neurological examination, the Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition disorders-patient version,[23] the Hamilton Rating Scale for Depression,[24] and the total score of the Unified Parkinson Disease Rating Scale.[25] Mean Hamilton Depression Rating Scale scores of the CSE group was 9.8 (standard deviation [SD], 5.4; range, 1–18). Mean total Unified Parkinson Disease Rating Scale score of the CSE group was 5.4 (SD, 3.2; range, 2–11). None of the included subjects used benzodiazepines or medication that could interfere with the dopamine metabolism or medication affecting the CNS.

MRI was performed on a 1.5-Tesla MRI scanner (Signa Horizon Echospeed, LX 9.0, General Electric Medical Systems, Milwaukee, WI). After an anatomical proton density (PD) and T2-weighted scan had been obtained, a diffusion tensor imaging scan was performed (14 axial slices; field of view = 23cm; slice thickness = 5.0mm; distance = 1.5mm; in-plane resolution = 0.89mm; b = 0 and 1,000 milliseconds; 6 noncollinear directions, 4 averages; TE = 90 milliseconds; TR = 6 seconds).[26] Fractional anisotropy (FA) maps were calculated.[27] Slices were positioned parallel to the lower edge of the corpus callosum using an accurate positioning protocol. The FA and PD images were superimposed and checked against to ensure no distortions (eg, due to eddy currents) were present in the examined regions of interest (ROIs). Average values of FA were measured in symmetric ROIs (left and right) drawn in dorsolateral prefrontal WM, thalamus, caudate nucleus (CN), and putamen (Figs, A, B). ROIs were drawn on the anatomical PD images and not on the FA maps to avoid bias.

^{1}H-magnetic resonance spectroscopy was performed in frontal gray matter (FGM) and the CS (see Figs, C, D), using a PRESS (Point Resolved Spectroscopy) sequence (voxels size, 2 × 2 × 2cm, TE/TR = 15/1,500 milliseconds). Spectra were analyzed using LC model,[28] a user-independent analysis method that provides measures of about 40 brain tissue metabolite concentrations, among which are NAA + *N*-acetylaspartyl glutamate (NAAG), Cho, myoinositol, glutamate and glutamine, and creatine. We used the absolute concentration output of LC model (Linear Combination of Model spectra) for the analysis. Concentrations are expressed in Institutional Units because they do depend on the internal reference (basis set). No T1/T2 correction was performed as we were interested only in group differences. The structural (T2-weighted) magnetic resonance images were assessed by a blinded experienced neuroradiologist for the presence of parenchymal abnormalities: 11 subjects (CSE: n = 6; EC: n = 2; NEC: n = 3) showed small parenchymal lesions, including 10 with microinfarcts (≤3mm in 5 subjects; between 3 and 10mm in the other 5 subjects) and 1 with a periventricular cyst. In one EC and in two NECs, the gray matter spectrum had insufficient quality because of insufficient magnetic field homogeneity.

Single-photon emission computed tomographic imaging was performed on a brain dedicated camera system (Neurofocus [an upgrade of the Strichman Medical Equipment 810X system]; Neurophysics Corp.). Approximately 185MBq [^{123}I]iodobenzamide ([^{123}I]IBZM) was injected intravenously, and acquisition was started 2 hours after injection. All other acquisition parameters (expect that an interslice distance of 5mm was used) and the reconstruction protocol used have been described previously.[29] All images were analyzed with a template with fixed ROIs for the whole striatum bilaterally and occipital cortex positioned manually on four consecutive slices showing most intense striatal binding. The mean striatal and occipital binding in the four slices was subsequently calculated, and the ratio of striatal-to-occipital binding was used as the outcome measure, both left and right. The observer was blinded to the clinical data.

A standardized neuropsychological test battery was administered containing validated tests that have been extensively described elsewhere. These tests were chosen because they are commonly accepted to assess performance of attention and psychomotor speed in patients suspected of CSE.[30] The Stroop Word (SW), Stroop Color (SC), and Trail Making Test Part A (TRAIL-A) tests were used for the assessment of psychomotor speed. A supplementary assessment of psychomotor speed was made using computerized (1) simple and (2) complex stimulus–response reaction time (RT) tasks (Motor Planning Task [MPT]).[31] In this RT task, the RT is split up into decision time and motor time. The decision time of a RT reflects central or cognitive processes. The motor time of an RT reflects the execution of a movement. The first subtask consists of both lifting a home button and pressing a particular target button. In the second task, the location of the target button varies but is compatible with the stimulus light. Variables were differentiated into cognitive speed (cog) and motor speed (mov) for the two subtasks, resulting in the following variables: MPT-cog 1, MPT-cog 2, MPT-mov 1, and MPT-mov 2. Finally, tests of selective attention (Stroop Color Word [SCW]) and divided attention (Trail Making Test Part B [TRAIL-B]) were administered. The time course of the study assessments was 2 weeks.

Statistical Analyses

Data were checked for normality distributions and log-transformed when appropriate (myoinositol FGM, exposure index). To assess differences in age, education premorbid intelligence quotient, current alcohol intake, exposure index and exposure duration, we used one-way analyses of variance. If significant differences appeared, these variables were included as covariate in further analysis.

Three separate multivariate analyses of covariance (MANCOVAs) were performed to analyze whether there were significant differences in (1) striatal D2R binding ratios; (2) concentrations of CNS metabolites NAA + NAAG, Cho, myoinositol, glutamine and creatine in FGM and CS; and (3) FA total (FA in DLPF WM, thalamus, CN, and putamen). To analyze whether there were significant differences in performance of attention and psychomotor speed, we performed two separate MANCOVAs, including all subtests.

If any of the MANCOVAs demonstrated a significant group effect, then we investigated group differences by

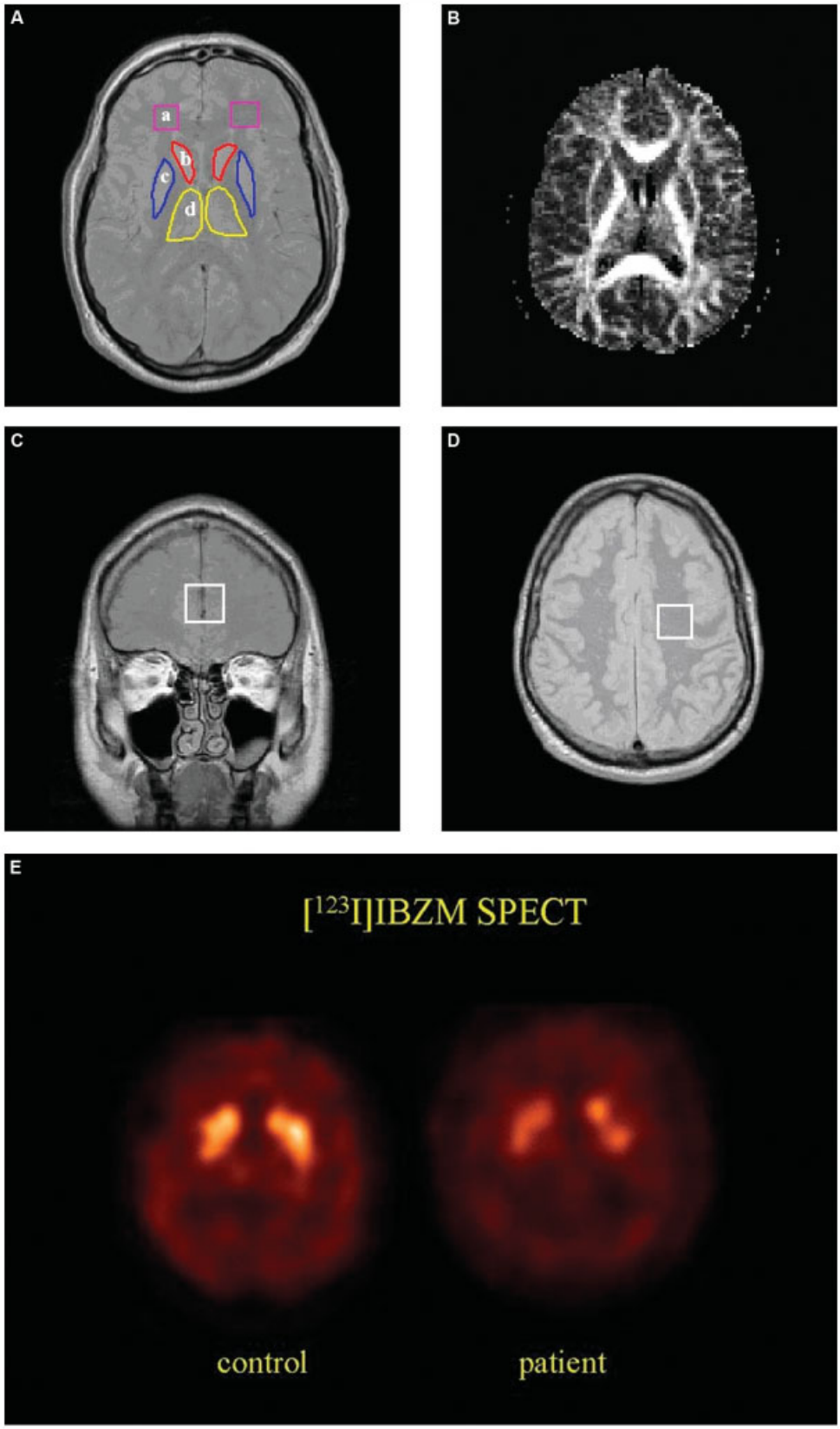

Fig. (A) Locations of the fractional anisotropy (FA) regions of interest (ROIs): (a) dorsolateral prefrontal white matter, (b) caudate nucleus, (c) putamen, and (d) thalamus. (B) Corresponding FA image. (C) Locations of the ^{1}H-magnetic resonance spectroscopy (MRS) ROIs: frontal gray matter (FGM). (D) Locations of the ^{1}H-MRS ROIs: centrum semiovale (CS). (E) [^{123}I]iodobenzamide ([^{123}I]IBZM) single-photon emission computed tomographic (SPECT) images of a nonexposed, asymptomatic (control) subject and a patient with chronic solvent-induced encephalopathy (CSE; patient). The level of [^{123}I]IBZM activity is color encoded from low (black) to high (white). Images show loss of striatal [^{123}I]IBZM binding in the striatum of a CSE patient.

means of one-way analysis of variance and performed post hoc analyses. As multiple MANCOVAs were performed, α level was set at $p = 0.01$.

To examine the relation between the exposure index and the observed cerebral abnormalities in CSE (striatal D2R binding ratios left and right), we used one-tailed Pearson Product Moment Correlations Coefficients.

To analyze whether the severity of psychomotor speed and attentional performance is predicted by the integrity of the FST circuitry in the CSE patients, we performed 12 multiple-regression analyses using forward elimination. The cognitive parameters of attention and psychomotor function (MPT-cog 1, MPT-cog 2, MPT-mov 1, MPT-mov 2, SCW, TRAIL-B) were entered separately as dependent variable. The six independent parameters were first separately tested in a univariate linear regression analysis (current alcohol intake, striatal D2R binding ratios, FA DLPF WM, FA CN, FA putamen, and FA thalamus). Only variables with $p < 0.1$ were entered simultaneously as independent variables in the final forward elimination regression analyses. The number of independent variables in each regression analysis did not exceed two. Separate analyses, both right and left, were conducted to prevent collinearity. The amount of explained variance is reported (r^2).

Results

Subject Characteristics

The patients with CSE, EC, and NEC did not differ significantly on age, sex (all men), education, and premorbid intelligence quotient. No statistically significant differences in duration and index of solvent exposure between the two exposed groups were found. Current alcohol intake was significantly lower in the CSE group compared with the two asymptomatic groups (both EC and NEC: $p < 0.001$), and was included in all further MANCOVAs and regression analyses as covariate (Table 1).

Neuroimaging Parameters

MANCOVA showed a group effect for striatal D2R binding ratios ($p < 0.001$), both for the right ($p = 0.002$) and left striatum ($p < 0.001$). The CSE patients ($p = 0.004$, striatum right; $p < 0.001$, striatum left) and the EC subjects ($p = 0.001$, striatum right; $p = 0.001$, striatum left) showed reduced D2R binding ratios, as compared with the NEC group (Table 2; see Fig, E).

Also, a significant group effect was found for FGM metabolites ($p = 0.01$), for the levels of NAA + NAAG ($p = 0.01$), and a trend for Cho levels ($p = 0.02$) (Table 3). Post hoc analyses showed that the levels of NAA + NAAG were reduced in the EC group as compared with the NEC group ($p = 0.004$). Finally, FA total did not show a significant group effect ($p = 0.08$).

Neuropsychological Performance

The MANCOVAs showed a group effect for psychomotor performance ($p = 0.004$) on the following subtests: MPT-cog 1 ($p < 0.001$), MPT-cog 2 ($p = 0.01$), and SW ($p = 0.01$). Post hoc analyses demonstrated that the CSE patients had reduced performance on MPT-cog 1 ($p < 0.001$) and on MPT-cog 2 ($p = 0.007$) as compared with the NEC, and on the SW ($p = 0.004$) as compared with the EC group. The ECs showed reduced performance on the MPT-cog 1 ($p < 0.001$) compared with the NEC group (Table 4).

Regression Analyses in Chronic Solvent-Induced Encephalopathy

LEFT. Performance of simple cognitive speed (MPT-cog 1 [$r^2 = 0.50$; $p = 0.02$]), complex cognitive speed (MPT-cog 2 [$r^2 = 0.73$; $p = 0.002$]), and divided attention (TRAIL-B [$r^2 = 0.47$; $p = 0.03$]) were predicted by FA in the left thalamus. Simple motor speed (MPT-mov 1 [$r^2 = 0.41$; $p = 0.05$]) was predicted by the left striatal D2R binding ratios. Selective attention

Table 1. **Sample and Clinical Characteristics**

Characteristics	CSE, Mean (SD)	EC, Mean (SD)	NEC, Mean (SD)	F	df	*p*
n	10	10	11			
Age (yr)	51.8 (6.3)	51.0 (4.1)	52.0 (6.4)	0.1	2	0.92
Exposure index (log)	6.1 (0.8)	5.9 (1.1)		0.2	1	0.65
Exposure duration (yr)	26.0 (9.8)	31.5 (6.4)		2.2	1	0.15
Education[c]	3.9 (0.3)	4.2 (0.4)	4.2 (0.5)	2.4	2	0.11
Premorbid IQ	91.2 (10.3)	92.8 (11.2)	91.3 (8.2)	0.8	2	0.9
Current alcohol intake (per wk)	2.1 (3.1)[a,b]	11.7 (9.1)	10.7 (5.2)	7.2	2	0.003

[a]Chronic solvent-induced encephalopathy (CSE) versus exposed asymptomatic workers (EC), $p < 0.001$.
[b]CSE versus nonexposed asymptomatic workers (NEC), $p < 0.001$.
[c]Six levels scale (1 = primary school level; 6 = university level; see Methods section).
SD = standard deviation; df = degrees of freedom; IQ = intelligence quotient.

Table 2. **Striatal Dopamine D_2 Receptor Binding Ratios in Chronic Solvent-Induced Encephalopathy Patients, Exposed Asymptomatic Workers and Nonexposed Asymptomatic Workers**

Striatal D2 Receptor Binding	CSE, Mean (SD)	EC, Mean (SD)	NEC, Mean (SD)	F	df	*p*
n	10	10	11			
D2 striatum total				6.2	4.0	<0.001
D2 striatum right	1.54 (0.08)[a]	1.59 (0.11)[b]	1.74 (0.12)	8.1	2	0.002
D2 striatum left	1.50 (0.08)[c]	1.57 (0.07)[b]	1.71 (0.09)	13.5	2	<0.001

[a]Chronic solvent-induced encephalopathy (CSE) versus NEC, $p = 0.004$.
[b]Exposed asymptomatic workers (EC) versus nonexposed asymptomatic workers (NEC), $p = 0.001$.
[c]CSE versus NEC, $p < 0.001$.
SD = standard deviation; df = degrees of freedom.

(SCW [$r^2 = 0.54$; $p = 0.016$]) was predicted by the FA in the left CN.

RIGHT. Simple cognitive speed (MPT-cog 1 [$r^2 = 0.62$; $p = 0.007$]) was predicted by striatal D2 binding ratios. Simple motor speed (MPT-mov 1 [$r^2 = 0.56$; $p = 0.01$]) was predicted by the striatal D2R binding ratios. FA in the right thalamus predicted performance on complex cognitive speed (MPT-cog 2 [$r^2 = 0.47$; $p = 0.03$]). Weekly alcohol intake together with the D2R binding ratios in the right striatum remained in the final model after forward elimination and predicted performances of divided attention (TRAIL-B [$r^2 = 0.83$; $p = 0.002$]).

Correlations Exposure Index and Striatal Dopamine D_2 Receptor Binding Ratio in Chronic Solvent-Induced Encephalopathy Patients and Exposed Asymptomatic Workers

In the CSE patients, the striatal D2R binding ratio right ($r = -0.54$; $p = 0.05$) showed a significant correlation with the exposure index, whereas the correlation of the exposure index with the striatal D2R bind-

Table 3. **Central Nervous System Metabolite Concentrations in Chronic Solvent-Induced Encephalopathy Patients, Exposed Asymptomatic Workers, and Nonexposed Asymptomatic Workers in Centrum Semiovale and in Frontal Gray Matter**

CNS Metabolites	CSE, Mean (SD)	EC, Mean (SD)	NEC, Mean (SD)	F	df	*p*
CS				0.78	10	0.64
n	10	10	9			
NAA + NAAG	21.8 (1.7)	21.2 (1.3)	21.3 (1.5)	1.06	2	0.36
Cho	3.6 (0.5)	3.9 (0.4)	3.5 (0.5)	1.03	2	0.37
mI	9.3 (1.1)	9.6 (1.5)	9.9 (1.5)	0.19	2	0.83
Glx	19.8 (3.1)	19.5 (2.0)	19.1 (2.7)	0.98	2	0.40
Cr	11.2 (1.1)	10.9 (0.8)	11.0 (0.7)	0.15	2	0.86
FGM				3.2	6	0.01
n	10	9	7			
NAA + NAAG	18.1 (1.6)	18.1 (1.6)[a]	21.0 (1.8)	5.2	2	0.01
Cho	3.7 (0.4)	3.8 (0.9)	4.1 (0.8)	4.4	2	0.02
mI (log)	2.6 (1.6)	2.4 (0.2)	2.6 (0.2)	3.0	2	0.07
Glx	28.6 (7.7)	32.3 (6.5)	31.3 (7.7)	2.3	2	0.14
Cr	13.5 (1.3)	14.2 (2.2)	15.1 (2.2)	3.1	2	0.07

[a]Exposed asymptomatic workers (EC) versus nonexposed asymptomatic workers (NEC), $p = 0.004$.
CSE = chronic solvent-induced encephalopathy; SD = standard deviation; df = degrees of freedom; CS = centrum semiovale; NAA = *N*-acetylaspartate; NAAG = *N*-acetylaspartyl glutamate; Cho = choline; mI = myoinositol; Glx = glutamine; Cr = creatine; FGM = frontal gray matter.

Table 4. **Psychomotor Performance and Attention in Chronic Solvent-Induced Encephalopathy Patients, Exposed Asymptomatic Workers, and Nonexposed Asymptomatic Workers**

Cognitive Functions	CSE, Mean (SD)	EC, Mean (SD)	NEC, Mean (SD)	F	df	*p*
Psychomotor performance				2.9	14	0.004
n	10	10	11			
MPT-cog 1 (milliseconds)	568.7 (88.9)[a]	495.7 (45.9)[b]	386.5 (49.1)	15.3	2	<0.001
MPT-cog 2 (milliseconds)	735.2 (171.9)[c]	644.8 (125.4)	511.8 (83.6)	5.2	2	0.013
MPT-mov 1 (milliseconds)	126.2 (23.7)	137.0 (22.3)	120.2 (19.5)	1.7	2	0.207
MPT-mov 2 (milliseconds)	131.9 (29.6)	135.6 (25.7)	120.9 (30.0)	0.7	2	0.489
SC (seconds)	57.7 (9.4)	50.6 (9.1)	48.2 (5.20)	1.2	2	0.314
SW (seconds)	74.6 (12.1)[d]	59.6 (7.3)	64.1 (9.1)	5.0	2	0.014
TRAIL-A (seconds)	44.9 (8.6)	33.4 (13.0)	36.4 (12.5)	3.4	2	0.046
Attention				2.4	4.0	0.06
n	10	10	11			
TRAIL-B (seconds)	123.9 (32.0)	82.8 (26.4)	90 (28.3)	5.3	2	0.012
SCW (seconds)	149.0 (33.9)	101.7 (12.2)	116.5 (43.3)	3.0	2	0.069

[a]Chronic solvent-induced encephalopathy (CSE) versus nonexposed asymptomatic workers (NEC), $p < 0.001$.
[b]Exposed asymptomatic workers (EC) versus NEC, $p < 0.001$.
[c]CSE versus NEC, $p = 0.007$.
[d]CSE versus EC, $p = 0.004$.
SD = standard deviation; df = degrees of freedom; MPT = Motor Planning Task; TRAIL = Trail Making Test; SC = Stroop Color; SW = Stroop Word; SCW = Stroop Color Word.

ing ratio left ($r = -0.38$; $p = 0.14$) was not significant.

In the EC group, no significant correlations were found between the exposure indices and the striatal D2R binding ratios.

Discussion

In patients with CSE, we found reduced striatal D2R binding ratios. Furthermore, psychomotor speed and attention were impaired, and were significantly predicted by the striatal D2R binding ratios and the FA in the thalamus and CN. In CSE patients, the exposure severity showed a negative association with the right striatal D2R binding ratios. In the exposed control subjects (EC), striatal D2R binding ratios and the levels of NAA + NAAG in FGM were reduced. In both exposed groups, a trend was seen for reduced levels of Cho in FGM. Together, these findings suggest that certain parts within the FST circuitry are compromised in CSE and, as current findings indicate, also in ECs, although to a lesser extent.

What are the clinical implications of these findings? Until now, CSE has been defined as a syndrome, but it is still a controversial entity that lacks a biological substrate. Our preliminary, but novel, findings of distinct brain abnormalities, in conjunction with their sizable associations with exposure severity and performance of attention and psychomotor speed, may improve the construct validity of CSE. A better understanding of the nature, severity, and specificity of these suspected biological markers may further validate diagnostic procedures, thus reinforcing medical and social recognition, and underlining the importance of prevention. The comparable, but less severe, abnormalities found within the FST circuitry in the ECs may imply a presymptomatic phase, which may be relevant for further studies on diagnostic screening.

How might our findings be interpreted? The loss of striatal [^{123}I]IBZM binding ratios in these CSE patients and in the exposed asymptomatic control group may be interpreted as a decreased capacity of postsynaptic D2R binding. However, IBZM also binds to D3R receptors[32] as predominantly located in the human striatum in the nucleus accumbens and the ventral putamen.[33] In our study, the striatal ROI consists mainly of the dorsal parts of the striatum. Because in this area only a minority of the D2-like receptors are D3R. Therefore, we believe that in this study striatal [^{123}I]IBZM binding predominantly represents binding to D2R.

Previous studies showed that chronic exposure to organic solvents can affect the level and turnover of catecholamines, including dopamine.[15] Animal studies showed that toluene exposure reduces D2R affinity, possibly because of a change in membrane fluidity. An increase in the rate of striatal dopamine synthesis was observed in CSE workers[16] possibly because of a solvent-induced, enhanced, catalytic activity of dopadecarboxylase in the synthesis of dopamine or as a response to the reduced D2R affinity.

Our results showing a trend for reduced Cho levels in FGM appear to be in contrast with Alkan and colleagues'[13] results; these authors report increased Cho levels, indicating demyelinization after solvent exposure. The background of our contrasting findings is yet unclear.

In CSE patients, as well as in the exposed control subjects, reductions were found in FGM metabolites NAA + NAAG. After post hoc analyses, this effect was significant in the exposed control subjects, but not in the CSE group. Both these findings may suggest abnormalities in frontal neuronal viability and axonal density.[34]

In our study, no significant differences were observed in WM integrity using a multivariate analysis including all the ROIs. This is not in line with findings in highly exposed solvent abuse cases in which demyelinization, gliosis, multifocal and diffuse WM changes, and hypointensities in the basal ganglia and thalami were reported.[11] In addition, the volume of the corpus callosum, the largest WM bundle in the brain, has shown to be affected after chronic solvent exposure.[12] It appears that current study design was slightly underpowered to detect the presumably more subtle WM abnormalities in the separate ROIs in our less intensely exposed patients and workers as compared with the highly exposed solvent abusers.

An important confounder in this type of study is the alleged presence of alcohol-related disorders in CSE, as well in the EC. Importantly, it was shown that D2R binding was also reduced in patients with a history of alcohol dependence.[35] Therefore, patients with CSE and EC with a history of lifetime alcohol- or substance-related disorders were excluded from entering our study.

The observed association between reduced striatal D2R binding and impaired simple psychomotor speed confirms the well-recognized role of dopamine receptor density in simple psychomotor speed, as was previously reported in natural aging and Parkinson's disease,[17,18] using PET. In contrast, complex psychomotor speed in our patients was adequately predicted by the integrity of both the left and right thalamus. This is in line with the observation that the thalamus is more involved in complex psychomotor behavior.[36] In our patients, the integrity of both the thalamus, the CN, and the striatum predicted the performance of attention, an association that has been reported previously in healthy adults.[17]

Interestingly, all our observations are in line with the presumed anatomic organization of the FST circuitry in functions of attention and psychomotor abilities.[37] The striatum receives topographic projections from (frontal) cortical areas and, in turn, project its own influences back on most areas of the frontal lobe via topographically organized pathways that pass through the thalamus.

Our study has some limitations such as the small number of patients. Furthermore, we cannot rule out an uncertainty factor in the validity in the diagnosis of CSE because of remaining difficulties in differential diagnostics. However, patients with major confounding disorders, such as psychiatric disorders, including alcohol- and substance-related disorders, sleep disorders, and Parkinsonian symptoms were excluded from entering the study.

The MRI study was performed on a 1.5-Tesla scanner using a diffusion tensor imaging protocol with 5mm-thick slices at 1.5mm spacing. The use of higher field scanners may permit a higher spatial resolution. Because of the limited spatial resolution of the single-photon emission computed tomography camera, we were able to assess only specific binding of [^{123}I]IBZM in the whole striatum, not in subdivisions of the striatum, or in extrastriatal brain areas. Because in this study disturbances in psychomotor speed and attention were observed in the CSE patients, it would be of interest in future research to study D2R in striatum subdivisions (CN and putamen) and extrastriatal D2R (especially in the thalamus and prefrontal cortex). Indeed, with recently developed radiotracers for PET, it is now feasible to reliably assess binding to these receptors, for example, with [^{11}C]FLB 457 PET.[38]

In conclusion, to our knowledge, this is the first study in CSE patients showing pronounced disturbances within the FST circuitry that are related to the clinical findings and to the severity of solvent exposure. The comparable, but milder, abnormalities found within the FST circuitry in the asymptomatic, but exposed, controls may imply a presymptomatic phase of CSE.

Our results can be an important incentive for further study, clarifying the nature and specificity of these disturbances, thereby improving diagnostic procedures and acknowledgment of CSE patients, as well as worldwide prevention of chronic occupational solvent exposure.

References

1. White RF, Proctor SP. Solvents and neurotoxicity. Lancet 1997;349:1239–1243.

2. HSE. Health risks management: a guide to working with solvents HSG188. Sudburry, United Kingdom: Health and Safety Executive, 1998.
3. Current Intelligence Bulletin 48. Organic solvent neurotoxicity (DHHS Publ No. 87-104). Cincinnati, OH: USDHHS/PHS/CDC/NIOSH, 1987.
4. World Health Organization. Chronic effects of organic solvents on the central nervous system and diagnostic criteria (Environmental Health 5). Copenhagen: WHO, 1985:1–39.
5. World Health Organization. The ICD 10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization, 1992.
6. American Psychiatric Association. Diagnostic and statistical manual for mental disorders, 4th ed. Washington, DC: American Psychiatric Press 1994.
7. Baker EL, White RF. Chronic effects of organic solvents on the central nervous system and diagnostic criteria. WHO (Copenhagen) and Nordic Council of Ministers (Oslo), reprinted by the US Department of Health and Human Services, Public Health Service, Washington, DC, 1985.
8. Baker EL. A review of recent research on health effects of human occupational exposure to organic solvents. J Occup Environ Med 1994;36:1079–1091.
9. Abjornsson G, Pallson B, Burgendorf U, et al. Long term follow-up of psychological distress, social functioning, and coping style in treated and untreated patients with solvent induced chronic toxic encephalopathy. J Occup Environ Med 1998;40:801–807.
10. Spurgeon A. The validity and interpretation of neurobehavioural data obtained in studies to investigate the neurotoxic effects of occupational exposure to mixtures of organic solvents. Birmingham, Health and Safety Executive Contract Research Report 355/2001. Birmingham: Health and Safety Executive, 2001.
11. Ridgway P, Nixon TE, Leach JP. Occupational exposure to organic solvents and long-term nervous system damage detectable by brain imaging, neurophysiology or histopathology. Food Chem Toxicol 2003;41:153–187.
12. Haut MW, Kuwara H, Ducatman AM, et al. Corpus callosum volume in railroad workers with chronic exposure to solvents. J Occup Environ Med 2006;48:615–624.
13. Alkan A, Kutlu R, Hallac T, et al. Occupational prolonged organic solvent exposure in shoemakers: brain MR spectroscopy findings. Magn Reson Imaging 2004;22:707–713.
14. Aydin K, Sencer S, Kultekin O, et al. Single voxel proton spectroscopy in toluene abuse. Magn Reson Imaging 2003;21:777–785.
15. Euler von G. Toluene and dopaminergic transmission. In: Isaacson RL, Jensen KF, eds. The vulnerable brain and environmental risks, vol 3. Toxins in air and water. New York: Plenum Press, 1994:301–321.
16. Edling C, Hellman B, Arvidson B, et al. Do organic solvents induce changes in the dopaminergic system? Positron emission tomography studies of occupationally exposed subjects. Int Arch Occup Environ Health 1997;70:180–186.
17. Volkow ND, Gur RC, Wang GJ, et al. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am J Psychiatry 1998;155:344–349.
18. Backman L, Ginovart N, Dixon RA, et al. Age-related cognitive deficits mediated by changes in the striatal dopamine system. Am J Psychiatry 2000;157:635–637.
19. Lewis SJ, Dove A, Robbins TW, et al. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. J Neurosci 2003;23:6351–6356.
20. Blumberg HP, Martin A, Kaufman J, et al. Frontostriatal abnormalities in adolescents with bipolar disorder: preliminary observations from functional MRI. Am J Psychiatry 2003;160:1345–1347.
21. Hoek van der JAF, Verberk MM, Laan G van der, Hageman G. A protocol for solvent induced CTE, 2 years of experience. Neurotoxicology 2000;21:887.
22. Schmand B, Bakker D, Saan R, Louman J. The Dutch Reading Test for Adults: a measure of premorbid intelligence level. Tijdschr Gerontol Geriatr 1999;22:15–19.
23. First MB, Gibbon M, Spitzer RL, Williams JBW. User guide for the Structured Clinical Interview for DSM IV axis I disorders. Washington, DC: American Psychiatric Association, 1996.
24. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296.
25. Fahn S, Elton RL, and members of the UPDRS development committee Unified Parkinsons's Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldsein M, eds. Recent development in Parkinson's Disease. New York: Macmillan Healthcare Information, 1987:153–163.
26. Le Bihan D, Mangin JF, Poupon C, et al. Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging 2001;13:534–546.
27. Hunsche S, Moseley ME, Stoeter P, Hedehus M. Diffusion-tensor MR imaging at 1.5 and 3.0 T: initial observations. Radiology 2001;221:550–556.
28. Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 1993;30:672–679.
29. Booij J, Tissingh G, Boer GJ, et al. [^{123}I]FP-CIT SPECT shows pronounced decline of striatal dopamine transporter labelling in early and advanced Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;62:133–140.
30. Wekking EM, van Hout MSE, Emmen HH. The Dutch neuropsychological test battery for diagnosing CTE, 2 years of experience. Neurotoxicology 2000;21:887–888.
31. Brand N, Wijk van der A, Hijman R. Motor planning in neurological and psychiatric patients. In: Drenth PJ, Sergeant JA, Takens RJ, eds. European perspectives in psychology. Chichester, United Kingdom: John Wiley, 2001:321–334.
32. Videbaek C, Toska K, Scheideler MA, et al. SPECT tracer [^{123}I]IBZM has similar affinity to dopamine D2 and D3 receptors. Synapse 2000;38:338–342.
33. Murray AM, Ryoo HL, Gurevich E, Joyce JN. Localization of dopamine D3 receptors to mesolimbic and D2 receptors to mesostriatal regions of human forebrain. Proc Natl Acad Sci USA 1994;91:11271–11275.
34. Jenkins BG, Kraft E. Magnetic resonance spectroscopy in toxic encephalopathy and neurodegeneration. Curr Opin Neurol 1991;12:753–760.
35. Martinez D, Gil R, Slifstein M, et al. Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. Biol Psychiatry 2005;58:779–786.
36. Newman J. Thalamic contributions to attention and consciousness. Conscious Cogn 1995;4:172–193.
37. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 1990;85:119–146.
38. Aalto S, Bruck A, Laine M, et al. Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D2 receptor ligand [^{11}C]FLB 457. J Neurosci 2005;25:2471–2477.