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"Chronic painter's syndrome". A reanalysis of psychological test data in a group of diagnosed cases, based on comparisons with matched controls

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ABSTRACT - Twenty solvent-exposed workers, most of them painters, had been diagnosed as cases of toxic encephalopathy in 1978/79. Two years later they were re-examined with an extensive battery of neuropsychological tests. Their performance was unchanged on retesting. We have now compared their test results with those of non-exposed control subjects. Previous impressions of significant intellectual impairment in the solvent-exposed patients could not be confirmed when the influence of age, education, and intelligence was taken into consideration. The present group with presumed toxic encephalopathy is assumed to be representative of other patients who were similarly diagnosed in our department. The presently reanalyzed cases had been diagnosed as brain damaged and reported as such in the literature. Thus, they may have contributed to the formation of the concept of the "chronic painters' syndrome" with dementia.

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International concern has been raised over the possibility that sustained low-grade exposure to organic solvents may cause permanent brain damage with intellectual impairment (1, 2). A recent review identified clinical studies from our department (3, 4) as "the most disturbing reports" suggestive of such effects (5, p. 58). These studies were based on non-standardized tests, yet contained no control groups. They were presented in conjunction with related work (6–9) to the WHO Working Group on Chronic Effects of Organic Solvents on the Central Nervous System and Diagnostic Criteria (1) in June 1985.

Following recent standardization of our neuropsychological tests, we have now reanalyzed the evidence of intellectual impairment in groups of solvent-exposed workers who were previously diagnosed as cases of chronic toxic encephalopathy with intellectual impairment. Here we report the results of a reanalysis of the test data of 20 patients. These patients were diagnosed at our department in 1978/79 and re-examined 2 years later; the results were reported by Browne (10) and Arlien-Søborg et al (9). This group of solvent-exposed patients was chosen for reanalysis

Results of this reanalysis were presented briefly at the Second International Symposium on Neurobehavioral Methods in Occupational and Environmental Health, Copenhagen, August 6–9, 1985, and more fully before the Danish Neurological Society on January 27, 1986, and at the Third Nordic Meeting in Neuropsychology, Bergen, August 12–15, 1986.

because it was the only one from our department assessed with all the tests used in the standardization project.

Material and methods

Solvent-exposed patients

Twenty workers, most of them painters, who had been exposed to mixtures of organic solvents for an average of 24 years were neuropsychologically re-examined in connection with a study of cerebral blood flow (9). For reasons related to the study of blood flow, patients both with (Group T2; N: 10; mean age 53.6 years) and without (Group T1; N: 10; mean age 42.5 years) a clinical diagnosis of cerebral atrophy on computed tomography (CT), were selected. (This diagnosis had been based on clinical impression rather than on measurements or comparisons with control CTs, and the validity of the diagnosis has not been examined). All were cases who had previously received a diagnosis of solvent-induced toxic encephalopathy in our department. Cases with "significant" alternative etiologic factors in their medical history were not included, although the criteria tended to be less strict than those

Table 1
Vital data of solvent-exposed patients

No.[a]	Age	Educ. score[b]	Vocational training/ exposure	Exposure duration	Occupation at retest	Compensation[c]
1	37	5	House painting	20 y	House painter	yes
2	41	5	Photography/ spray painting	18 y	Photographer	yes
3	39	7	House painting	20 y	Vocational teacher	yes
4	53	5	House painting	34 y	Disability pension	yes
5	62	5	House painting	42 y	Disability pension	yes
6[d]	25	9	Laboratory technician/ mixed solvent exp.	2 y	University student	no
7	28	5	House painting	9 y	Museum functionary	yes
8	46	3	None/mixed exp. in factory	16 y	Theatre worker	pending
9	42	7	House painting	24 y	Sick leave	NE
10	52	5	Bookbinding-restoration/ benzene, ethanol	12 y	Disability pension	NE
11	60	5	House painting	44 y	Sign painter	no
12	60	5	House painting	44 y	Sick leave	NE
13	49	5	Laboratory technician/ CS_2 accident[e]	20 min	Unemployed	yes
14	60	5	House painting	44 y	Diability pension	yes
15	55	5	House painting	30 y	Sick leave	NE
16	45	5	Cabinet making/ lacquering	11 y	Sick leave	NE
17	45	5	House painting	22 y	Storeman	yes
18	60	5	House painting	42 y	Disability pension	yes
19	48	5	Photo-engraving/ toluene, white spirit	18 y	Printer	yes
20	54	3	None/spray painting	15 y	Disability pension	yes

Abbreviations: NE: Not eligible (as self-employed). CS_2: Carbon disulphide. [a] Nos. 1-10: Group T1; nos. 11-20: Group T2. [b] The education score was based on both school level completed and the level of vocational training. A higher score indicates a longer education. [c] Financial compensation received from the State Industrial Injuries Security Office. [d] Female. [e] Details published in J Soc Occup Med 1982, *32*, 44-45.

described below for control subjects, particularly with respect to alcohol consumption. At the initial neuropsychological assessment 16 of the patients had been rated as "mildly" or "moderately" intellectually impaired, 3 as "possibly impaired", and one as unimpaired. During a brief hospitalization retesting was carried out by a psychology student under the supervision of the first author. The results of the neuropsychological re-examination were compared with the data from then available 62 controls and reported in a thesis (10). At that time, no attempt was made to control for the influence of background variables. Individual background data of the 20 exposed patients are listed in Table 1.

Controls

During 1980–83, 120 non-exposed control subjects were tested in our department. These subjects were recruited from the Department of Orthopedic Surgery (mainly with lower limb fractures) and from the Neurosurgical Department (with peripheral nerve lesions, mainly due to lumbar disc herniation). The sampling was stratified with a measure of education held constant over age groups. All patients with symptoms or signs of cerebral disease as well as patients with somatic disease possibly associated with impaired test performance were excluded. In the actual selection the ward charts and staff were first consulted, and the candidates eligible on this basis were then interviewed regarding the exclusion criteria listed in Table 2. This led to the exclusion of 70 interviewed subjects; 29 subjects declined to participate in the study.

Table 2
Exclusion criteria employed in the selection of normal controls

1. All CNS diseases, inc. epilepsy and migraine.
2. Previous head traumas with affection of consciousness > 1 h.
3. All metabolic diseases.
4. Diabetes.
5. Diseases of heart and circulation, inc. hypertension.
6. Diseases of liver and kidneys (exc. kidney stones).
7. Daily alcohol consumption exceeding four beers or equivalent, either presently or previously during at least 2 years.
8. Occupational exposure of organic solvents.
9. Psychiatric diagnoses, or a history of psychiatric treatment.
10. Regular consumption of psychotropic drugs or analgesics.
11. Impaired sight or hearing.
12. Discontinuation of occupation (exc. age pensioning in 6 cases above 60 years of age).
13. Uncertain diagnosis.

Of the 120 subjects tested 82 were examined before surgery, and 38 were examined a mean of 7.5 days after surgery with general anesthesia. In this latter group subsequent analyses have disclosed no relationship between performance and the length of the postoperative period before examination.

Our normal sample covers the ages from 20 to 73 years, a very broad educational spectrum, and its composition, in terms of social group classification, is nearly identical to that of the Danish population. The subjects were examined during at least two sessions.

From the pool of 120 subjects a subsample of 20 were individually matched to each of the 20 solvent-exposed patients on sex, age and education. Subjects matched to Groups T1 and T2 patients constituted Groups C1 and C2, respectively. The vital data of these 20 control subjects are listed in Table 3. The mean difference in age between paired subjects was 2.8 years; 18 pairs had identical education scores. (We subsequently attempted matching 4 criteria: sex, age, education and vocabulary score in this sequence, but this resulted in group differences in vocabulary. To correct for this presumed difference between groups in premorbid intelligence, we used data from all 120 control subjects as described below in the section on methods of analysis.)

Tests and test measures

The tests used are listed in Table 4. In order to reduce the number of scores and to increase reliability (11), scores from highly correlated tests presumably measuring similar abilities were averaged in factor scores, listed in the first column. (The combination of the test scores to factor scores was based on the correlations observed in the 120 normal subjects.) Raw scores were converted to standard scores (T-scores with a mean of 50 and a standard deviation of 10 in the normal controls (14)). Factor scores represent the mean of their component test scores. The mean of the 13 test measures included in our standard basic battery is named the mean BB

T-score (BB). Mean Total T-score (TOT) is the mean of all test scores excluding the 4 Verbal Intelligence measures and the 3 Memory Span measures. Verbal Intelligence (VI) tests were included in the battery as indicators of premorbid intelligence.

Methods of analysis

Test scores from the second neuropsychological assessment were used in comparisons with controls, since data from the examination at the time of the diagnosis were fewer and often incomplete. To evaluate the possible retest effect, all available raw test scores from patients tested twice were compared in paired t-tests.

In order to determine the sensitivity of the tests, we had previously computed F-values in within-pairs analysis of variance between a mixed group of 95 neurological patients with a clinical diagnosis of cerebral atrophy and 95 normal controls matched on age and education. These F-values may be seen in the third column of Table 4. Note that the Verbal Intelligence factor comprises 4 tests with weak sensitivity to cerebral atrophy in this sample; thus, this factor may be used as an indication of premorbid

Table 3
Vital data of matched controls. Each control was individually matched to the exposed patient with the equivalent number in Table 1

No.	Age	Educ. score	Vocational training/ present occupation	Medical diagnosis	Days[d] postop.
1	37	5	Bricklayer	Lumbar disc hermiation (LDH)	–[a]
2	41	5	Commerce[b]	LDH	–
3	38	8	Accountant	Femoral lipoma	6
4	51	5	Smith	LDH	–
5	57	5	Plumber	LDH	–
6[c]	33	8	Nurse	Cervical disc herniation	4
7	28	5	Mechanic/ salvage man	LDH	–
8	42	3	None/ refuse collector	LDH	–
9	33	7	Plumber[b]	LDH	–
10	49	5	Commerce/ janitor	Hip luxation	18
11	62	5	Commerce/ retired driver	Knee arthrosis	5
12	58	5	Commerce[b]	Ulnar nerve entrapment	–
13	49	5	Smith/ bricklayer's assistant	LDH	6
14	63	5	Hairdressing/ hospital orderly	Knee fracture	4
15	56	5	Radio mechanic/ insurance agent	Lumbar recess stenosis	–
16	47	5	Plumber	LDH	–
17	48	5	Industrial drawing/ alcohol consultant	LDH	–
18	57	5	None/ bricklayer's assistant	LDH	–
19	42	5	Mechanic/ vocational teacher[b]	LDH	–
20	52	3	None/driver	LDH	–

[a] – indicates examination preoperatively; [b] self-employed, employer or manager; [c] female; [d] Surgery was performed under epidural analgesia (Case 11) or general anesthesia with halothane (Cases 3, 10 and 14) or mebumal and pethidine (Cases 6 and 13).

Table 4
Test battery and raw test scores in the exposed patient Groups T1 (mean age 42.5 years) and T2 (mean age 53.6 years)

Factor	Test/Reference	F	T1		T2	
			x̄	SD	x̄	SD
VI	DART (12)	7.6	18.8	8.6	21.5	6.8
	Information (13)	10.9	17.4	4.7	17.8	3.3
	Similarities (13)	9.2	16.5	3.7	17.6	2.7
	Vocabulary (13)	6.0	49.6	12.9	58.4	7.4
A	Proverb interpretation	30.7	6.6	3.3	6.7	3.1
	Classification Test (Sorting) (14)M	7.9	8.3	1.9	8.9	1.5
MS	Digits forward (15)	9.6	9.3	1.0	10.0	1.6
	Digits backward (15)	25.8	7.5	1.2	7.4	1.8
	Sentence repetition (15)	18.2	16.0	1.7	15.4	2.3
VL	Paired associates; learning* (16)	31.5	31.0	15.7	34.8	16.0
	Paired Associates; retention* (16)	11.1	7.2	2.1	7.6	1.9
	Serial learning* (17)	39.6	15.9	5.5	18.7	8.9
RM	Word recognition (18, 19)	25.8	42.1	3.3	42.9	5.9
	Face recognition (18, 19)	21.0	46.9	2.2	43.5	5.7
	Fragmented words* (20)	11.4	2.5	3.0	2.3	1.8
	Cued recall (21)	5.7	10.5	4.4	11.4	4.4
	Yes/no recognition (21)	9.7	15.2	3.8	16.1	4.0
V-MS	SDMT	91.0	34.4	9.6	31.4	6.2
	Trail making A* (22)	22.5	49.2	14.8	42.3	10.0
	Trail making B* (23, 24)	46.8	126.1	50.5	114.1	39.4
V-S(M)	Visual Gestalts; learning* (16)	25.0	7.2	6.6	4.3	3.8
	Visual Gestalts; retention* (16)	10.3	6.0	4.5	4.0	2.3
	Block design; sec.* (13)M	20.4	24.4	9.9	29.6	11.0
	Fragmented picts.* (20)	15.8	3.4	2.5	3.8	5.2
WP	Picture completion (13)	20.8	13.3	1.4	13.6	1.8
	Picture arrangement (13)	29.4	21.4	3.5	20.8	5.4
PA	PASAT 1; errors* (25)M	8.2	5.3	4.7	3.3	2.1
	PASAT 1; sec.* (25)M	28.0	70.9	41.2	58.2	17.0
	PASAT 2; errors* (25)M	5.7	8.6	4.4	7.5	4.7
	PASAT 2; sec* (25)M	10.4	108.5	42.4	104.7	34.2

* Score expressed in errors or completion time. Scores in WAIS subtests are raw scores. M indicates a modification of the published version. F-values are included as a measure of test sensitivity. Their origin is explained in the text.

intelligence, as we have done previously for other patients (26, see also references 1, 12).

The scores of solvent-exposed patients and normal controls were compared in several ways. Background variables and uncorrected factor T-scores in the 2 subgroups of exposed patients and their respective controls were first examined in paired t-tests. In further analyses, the scores were first corrected for the effect of age and education, and then also for Verbal Intelligence. The correction was based on regression analyses of the test data from the 120 normal subjects as previously described (26). The expected individual T-scores were computed by the application of the resulting regression equations, and differences (residuals) between the expected and the observed scores were calculated. For each Difference Score in individual subjects, the deviation from zero was tested by a t-test. Also mean values in Difference Scores in the group of 20 exposed patients were tested for deviation from zero by t-tests. Thus, the statistics in the final analyses were based on comparison of the 20 exposed patients to all 120 control subjects. Since it is debatable whether the solvent-exposed patient groups should be combined or not in the final analyses, we calculated mean values and tested their deviation from zero in the subgroups both separately and combined.

Results

Retest effect

In 18 of the 20 patients with diagnosed toxic encephalopathy, data from the first examination were available for comparison with the data used in reanalysis (Table 5). None of the differences reached the 0.05 level of significance in paired t-tests. Although in 7 of the 11 test measures a better mean score was seen at retest, a weighted mean change of 2.9% of the standard deviation was in the direction of poorer performance at retest.

Background variables and Verbal Intelligence

The mean age and education in the subgroups of solvent-exposed patients and their matched controls are listed in Table 6. The educational score used in matching was based on level of school and of occupational training. The non-atrophic patients (T1) are younger and have received more schooling. The table also lists the Verbal Intelligence scores obtained in the 4 groups. Whereas the solvent-exposed patients with cerebral atrophy and their controls have nearly identical scores, the non-atrophic patients score significantly ($P < 0.01$) below their controls in Verbal Intelligence.

Raw test scores and factor scores

All raw scores in subgroups T1 and T2 are listed

Table 5
Raw change scores (1st exam. - 2nd exam.) in 18 patients with test scores available from both examinations[a)]

Test measure	N	1st exam. - 2nd exam.	*P*	Amount[b)] and directions[c)] of change
Paired associates; learning	17	0.8	0.70	+5.0
- - ; retention	17	-1.2	0.07	-60.0
Visual gestalts; learning	18	-1.3	0.33	-25.0
- - ; retention	16	0.3	0.67	+8.8
Digits forward	17	0.2	0.69	-15.4
Digits backward	17	-0.5	0.19	+33.3
Sentence repetition	15	-0.2	0.60	+10.0
Block design; sec.	15	2.7	0.20	+25.8
Trail Making A	7	1.3	0.83	+10.5
- - B	7	-10.4	0.53	-23.1
SDMT	11	-0.2	0.93	+2.5

[a)] Tests with N < 7 have been omitted. [b)] In percentage of the standard deviation. [c)] + indicates better performance at retest; - indicates poorer performance at retest.

in Table 4 which also specifies the test composition of factors used in further analyses.

T-scores in factors and summary measures for the exposed subgroups and their controls are presented in Table 7. Higher values indicate better performance. There are no systematic or significant differences between patients with a clinical diagnosis of atrophy (T2) and their controls (C2). The non-atrophic patients (T1) had a poorer performance than their controls in all test factors, including the measure of premorbid intelligence (VI).

Corrected factor and summary scores

In Tables 8 and 9 corrected scores are listed as Difference Scores, where positive values indicate

Table 6
Mean background variables and Verbal Intelligence (T-score) in 2 groups of solvent-exposed patients (T1 and T2) and their respective control groups (C1 and C2). Standard deviations in brackets

	T1	C1	T2	C2
Age	42.5	40.9	53.6	53.4
	(10.7)	(8.6)	(6.1)	(6.5)
Education score	5.6	5.6	4.8	4.8
	(1.6)	(1.5)	(0.6)	(0.6)
School level	1.5	1.3	1.0	1.1
	(0.8)	(0.5)	(0.0)	(0.3)
Occupational level	2.6	3.0	2.8	2.6
	(0.8)	(0.8)	(0.6)	(0.8)
School years	8.2	8.2	7.3	7.4
	(1.5)	(1.2)	(0.5)	(0.7)
Verbal Intelligence	40.5**	51.4	44.8	44.0
	(9.8)	(3.3)	(6.6)	(5.4)

** Significantly (paired t-test: $P < 0.01$) below controls.

Table 7
Mean T-scores in 2 groups of solvent-exposed patients (T1 and T2) and their respective control groups (C1 and C2)

Factor		T1	C1	P[a)]	T2	C2	P[a)]
Verbal intelligence	x̄	40.5	51.4	0.003	44.8	44.0	
V1	SD	9.8	3.3		6.6	5.4	
Abstraction	x̄	46.6	52.0	-	48.4	41.0	
A	SD	11.2	7.9		7.1	11.6	
Memory span	x̄	43.5	50.1	0.031	44.0	44.6	
MS	SD	4.8	8.0		8.9	9.3	
Verbal learning	x̄	45.5	47.3		42.9	44.8	
VL	SD	6.4	10.9		6.0	9.1	
Recognition memory	x̄	41.6	48.4		41.8	40.5	
RM	SD	13.9	9.3		14.8	10.3	
Visuo-motor speed	x̄	38.5	46.8	0.039	40.6	43.5	
V-MS	SD	11.6	8.9		6.8	6.8	
Visuo-spatial (memory)	x̄	49.3	50.2		49.4	48.5	
V-S (M)	SD	5.5	5.4		6.5	7.7	
WAIS performance	x̄	43.8	51.3	0.013	43.9	46.9	
WP	SD	4.8	5.3		6.2	11.7	
PASAT	x̄	38.9	52.6		45.1	44.0	
PA	SD	17.0	7.5		11.5	15.9	
Mean total	x̄	40.4	51.9	0.023	44.5	42.9	
x̄ TOT	SD	12.9	4.8		7.7	8.5	
Mean basic battery	x̄	42.0	49.2	0.001	43.0	42.9	
x̄ BB	SD	7.9	4.7		3.8	8.5	

[a)] P-values in paired t-tests in subgroups. Unlisted P-values > 0.05.

Table 8
Mean Difference Scores (with corrections for age and education) in 2 groups of solvent-exposed patients (T1 and T2) separately and combined, and in their controls (C1 + C2)

Factor		T1	Pa	T2	Pa	T1 + T2	Pa	C1 + C2	Pa
VI	$\bar{x}$	-8.1	0.004	-3.5		-5.8	0.004	-0.8	
	SD	8.7		7.1		8.1		6.3	
A	$\bar{x}$	-3.2		+2.2		-0.5		-1.8	
	SD	11.8		8.7		10.4		10.1	
MS	$\bar{x}$	-6.3	0.016	-3.8		-5.0	0.008	-1.7	
	SD	5.2		9.2		7.4		8.1	
VL	$\bar{x}$	-4.3	0.036	-2.8		-3.6	0.016	-2.3	
	SD	6.1		5.9		5.9		9.5	
RM	$\bar{x}$	-7.4		-3.1		-5.3		-2.9	
	SD	12.0		15.8		13.8		8.0	
V-MS	$\bar{x}$	-11.6	0.001	-4.0		-7.8	0.002	-2.8	
	SD	11.9		6.0		10.0		6.7	
V-S(M)	$\bar{x}$	-0.9		+5.1	0.020	+2.1		+1.4	
	SD	7.1		5.5		6.9		6.0	
WP	$\bar{x}$	-6.0	0.013	-1.1		-3.5	0.035	+1.1	
	SD	7.4		6.4		7.2		7.6	
PA	$\bar{x}$	-10.9	0.032	-1.4		-6.2		-0.2	
	SD	17.8		11.4		15.3		11.4	
$\bar{x}$ TOT	$\bar{x}$	-9.7	0.016	-0.2		-5.0		-0.5	
	SD	14.4		7.8		12.3		6.8	
$\bar{x}$ BB	$\bar{x}$	-7.8	0.002	-1.4		-4.6	0.009	-1.7	
	SD	8.9		4.2		7.6		5.4	

a) *P*-values in t-tests of deviation of mean value from zero. Unlisted *P*-values > 0.05.

Table 9
Mean Difference Scores (with corrections for age, education and Verbal Intelligence) in 2 groups of solvent-exposed patients (T1 and T2) separately and combined, and in their controls (C1 + C2)

Factor		T1	*P*a	T2	*P*a	T1 + T2	*P*a	C1 + C2	*P*a
A	$\bar{x}$	+1.9		+4.5		+3.2		-1.3	
	SD	9.0		6.7		7.8		8.0	
MS	$\bar{x}$	-1.2		-1.6		-1.4		-1.3	
	SD	5.4		8.8		7.1		7.6	
VL	$\bar{x}$	-0.7		-1.3		-1.0		-1.9	
	SD	4.3		5.9		5.0		9.6	
RM	$\bar{x}$	-2.7		-0.6		-1.7		-2.4	
	SD	11.2		14.0		12.4		8.2	
V-MS	$\bar{x}$	-7.2	0.032	-2.1		-4.7	0.047	-2.4	
	SD	11.3		7.9		9.9		7.6	
V-S(M)	$\bar{x}$	+2.5		+6.6	0.008	+4.5	0.010	+1.7	
	SD	6.6		7.4		7.2		6.0	
WP	$\bar{x}$	-2.3		+0.5		-0.9		+1.5	
	SD	6.5		4.8		5.7		6.8	
PA	$\bar{x}$	-7.9		+0.3		-3.8		+0.4	
	SD	17.7		12.6		15.6		11.1	
$\bar{x}$ TOT	$\bar{x}$	-5.2		+1.7		-1.8		-1.0	
	SD	13.7		9.3		12.0		6.6	
$\bar{x}$ BB	$\bar{x}$	-2.1		+1.1		-0.5		-1.2	
	SD	7.3		5.7		6.6		4.6	

a) *P*-values in t-tests of deviation of mean value from zero. Unlisted *P*-values > 0.05.

better performance, and negative values indicate poorer performance than expected on the basis of regression equations. Table 8 gives scores obtained after correction for the effect of age and education alone, whereas Table 9 also presents the results of correction for Verbal Intelligence. Difference scores in Group T2 and controls are close to zero after correction for age and education. In Group T1 this is also the case after correction for Verbal Intelligence, and in the final summary measures (mean TOT and mean BB; Table 9) the 2 groups separately and combined do not differ from controls. (The combination of Groups T1 and T2 may be considered justified by the absence of significant differences between them in all summary measures and factor scores except in factor V-S(M), where $P = 0.047$ in t-test.) Individual T-scores in matched pairs are listed in Table 10. Fig. 1 illustrates the distribution of individual Difference Scores in mean BB in the 20 solvent-exposed patients and their controls.

Discussion

The most important outcome of the present reanalysis is disappearance of apparent and previously reported evidence of impairment in psychometric test scores in our group of solvent-exposed patients after appropriate correction for the effects of age, education, and intelligence. Similar results have already been reported in studies which compared groups matched on premorbid levels of intelligence (27, 28), and in a Swedish follow-up study of diagnosed cases group differences were also attenuated following statistical corrections for differences in intelligence (29). Our negative results are also consistent with results from cross-sectional psychometric studies of solvent-exposed workers and controls, where significant group differences have generally been small, acute effects have not been ruled out, and exposure-effect relations have been conspicuously absent (30).

Table 10
Verbal Intelligence score (VI) and mean observed (obs), expected (exp) and Difference Score (Diff) in basic battery tests ($\bar{x}$ BB) in matched pairs of exposed patients (T) and controls (C)

Pair no.[a]	VI		$\bar{x}$ BB obs.		$\bar{x}$ BB exp.		$\bar{x}$ BB Diff.	
	T	C	T	C	T	C	T	C
1	28	47	30	42	38	52	-8	-8
2	29	48	46	53	38	51	8	2
3	51	53	44	49	55	57	-11	-6
4	38	53	35	40	38	50	-2	-8
5	49	53	44	49	40	46	4	3
6	53	54	58	54	58	58	0	-3
7	36	50	42	49	47	57	-3	-7
8	35	57	48	55	38	56	9	-1
9	35	48	38	51	42	54	-3	-2
10	51	50	37	48	48	49	-10	0
11	53	38	48	30	44	32	3	-1
12	43	46	37	44	37	40	0	4
13	40	51	42	51	42	49	0	2
14	34	35	45	30	31	30	14	1
15	40	51	45	44	39	46	7	-1
16	41	42	43	47	45	44	0	3
17	41	41	45	49	45	43	0	6
18	51	43	42	39	43	39	0	0
19	55	49	47	56	53	52	-5	5
20	46	45	37	39	41	42	-4	-2

Decimals omitted in the table have been retained in calculations of Difference Scores and mean values. Regression equations for expected scores include age, education score, and VI. All scores are T-scores. [a] Nos. 1-10: groups T1 and C1; Nos. 11-20: groups T2 and C2.

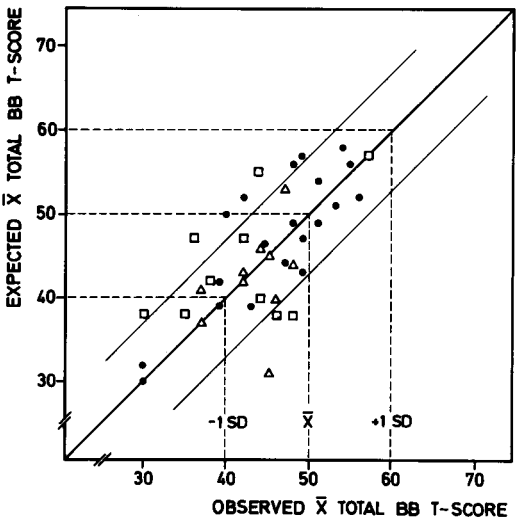

Fig. 1. Distribution of individual subjects as a function of the observed mean BB scores and the expected mean BB scores. The expected mean scores were computed with a regression equation including age, education score and Verbal Intelligence. Control subjects are indicated by solid circles. Solvent-exposed patients with and without a clinical neuroradiological diagnosis of cerebral atrophy are indicated by open triangles and squaes, respectively. The solid diagonal line indicates zero Difference Score, and the thin diagonal lines indicate 90% confidence limits. A position to the upper left of the normal distribution indicates a high probability of intellectual impairment.

Validity of uncontrolled studies

The main significance of our results lies in their implications for uncontrolled clinical studies and the validity of diagnostic procedures used in the clinic. At the time of the initial diagnosis 16 of the 20 presently reported, solvent-exposed patients had been rated by neuropsychologists as mildly to moderately demented, and 3 more had been rated as possibly demented. Only one had been found unimpaired. This rating represents a synthesis of complaints, test results and clinical impression, and, thus, cannot be considered synonymous with intellectual impairment, which was the only parameter considered in the reanalysis. However, by any current definition (31–33), intellectual impairment is the essential symptom of the dementia syndrome. The present results suggest that our group of solvent-exposed patients were not intellectually impaired and, thus, not demented, but had been so diagnosed erroneously.

Different possible reasons for the discrepancies between the original diagnoses of dementia and the lack of objective evidence of intellectual deterioration can be considered. It should be recalled that the previous results had been obtained without adequate control. Empirically based normative neuropsychological test data have not before been available in Denmark (with 2 exceptions (16)), and published criteria for the distinction between normal and impaired performance in some tests (34) rested on untested assumptions (35). The relationships between background variables and test scores were until recently unknown in this country, and serious mistakes were probably in part a consequence of uncontrolled estimations of these relations.

Control subjects

Previous practice, as described, places in perspective legitimate questions concerning our standardization sample of 120 subjects, from which the present controls were drawn. Questions may be raised concerning its size and representativeness, and about tester-influence and the effect of hospitalization and surgery. The importance of these factors have all been considered (see below). No set of reference data is ever ideal and perfect for every purpose, and continued data collection is obviously mandatory. We do believe, however, that we have secured a satisfactory sample of subjects without central nervous system damage. On a number of tests we have been able to compare our normal data to similar material of other authors (including material recruited from the community and trade unions), and have generally found good comparability without systematic differences (36).

Six of the 20 matched controls were examined 4 to 18 (median 5.5) days after surgery. The results of these 6 subjects did not differ from those of subjects examined preoperatively (Tables 3, 10). In the total control group of 120 subjects regression analyses have disclosed a significantly ($P < 0.05$) poorer performance of subjects studied postoperatively in 2 tests only.

Performance was unrelated to the time interval between anesthesia and examination, and the difference is practically negligible. (Treating "examination postoperatively" as a confounder can be estimated to affect the mean BB Difference Score with less than 1/2 T-score unit.) The inclusion in the control group of subjects studied after surgery is thus of no consequence for the results of the present study.

Twenty matched controls might be considered to be too few. By computing Difference Scores we also, in essence, carried out a comparison with all 120 normal controls, with the same negative results.

The 20 solvent-exposed patients and the controls were examined by different psychologists. This may have influenced the results, but hardly to any great extent. The instructions and scoring criteria were identical, and all testing took place in the same department. If expectation bias was operative, its effect would presumably have tended to create rather than erase differences between the groups (10).

Our comparisons involved multiple tests of significance, and this could have been a matter of concern if our results had been positive and not negative, as was the case.

On the other hand the small samples might be considered to involve risks of Type 2 errors. This would only have been a problem, however, if the purpose of our research had been to evaulate whether organic solvents, at least in some circumstances, may cause intellectual deficits. Obviously our study was not planned to test this kind of hypothesis.

Correction for premorbid intelligence

In our reanalysis we corrected for Verbal Intelligence, defined as the mean score on 3 verbal WAIS subtests and a reading test reflecting vocabulary. This correction procedure is based on the assumption that the Verbal Intelligence score is minimally affected by the condition under study. This assumption cannot be expected to be met in all brain diseases, nor in all individuals with a given disease. Correction for Verbal Intelligence did not diminish the mean Difference Score in a group of 60 non-exposed neurological patients compared to Difference Scores based on age and education alone (unpublished observations), however, and the tests included in the Verbal Intelligence factor did in fact discriminate minimally between the normal controls and atrophic patients (Table 4). An assumption that such commonly accepted dementia-resistant measures of intelligence as tests of general knowledge and vocabulary, might be selectively affected by solvents would be novel and does not seem plausible (1).

Other tests in our battery are highly sensitive to the effects of diffuse brain damage and discriminate well between groups of patients with and without brain disease (see F-values in Table 4).

Generalization

Can our negative results be generalized to other neuropsychologically uncontrolled studies used in the clinical delineation of the "chronic painter's syndrome" in our department (3, 4, 6–9), and to other solvent-exposed groups of presumably brain damaged workers, on which the clinical practice in Denmark with several hundred diagnosed cases each year (37) is based? The only published test scores from a comparable group examined with the same test battery are the median values obtained at 2 examinations with an interval of 2 years in 26 house painters with a diagnosis of toxic encephalopathy (4, 7). These values may be compared with median values in the present group of 20 solvent-exposed patients (Groups T1 and T2), and median values in 27 skilled male workers from our normal standardization sample, presented as T-scores in Table 11. The lack of systematic differences between the median values in the 3 groups does indicate that our negative results can be generalized, at least to other exposed patients diagnosed in our own department.

We do not know to what extent we can generalize from the present findings of normal performance to still other series of cases with diagnosed toxic encephalopathy. In the presently described series, patients presenting evidence of significant alternative etiologic factors had been excluded, which has generally not been the case in later series and official statistics in Denmark. The possibility of overdiagnosis of intellectual im-

Table 11
Mean age and median T-scores[a] in 2 groups of solvent-exposed patients with a dianosis of toxic encephalopathy and a group of non-exposed control subjects (all male skilled workers in the standardization population)

	27 controls	26 painters (ref. 4, 7)		20 exposed (present study)	
		I	II	I	II
Age	42	42	44	46	48
Associate learning	49	49	50	45	45
Associate retention	47	53	47	47	47
Visual gestalts learning	52	51	48	51	51
Visual gestalts retention	53	51	44	53	51
Sentence repetition	49	49	45	45	43
Block design	53	51	54	50	51
Mean of medians	50.5	50.7	48.0	48.5	48.0

[a] The table includes the results of all neuropsychological tests administered to all subjects in the patient groups at both examination I and II.

pairment in other neurological patient groups has not yet been systematically explored. We find no *a priori* reason to suspect that the problem of faulty criteria affected only the assessment of solvent-exposed patients.

Complaints and social consequences

The present reanalysis has concerned neuropsychological test scores, whereas subjective complaints have not been considered. A variety of subjective symptoms were common in the 20 solvent-exposed patients (10), as described earlier for similar series of painters in our department (3, 4, 6, 7). Their mean score on the Örebro screening questionnaire with 16 items (38) was 10.6. (Further investigations have been recommended in patients with scores exceeding 6.) The complaints are non-specific (1, 32), however, and are therefore of little value in differential diagnosis.

At the time of re-examination, 8 of the patients were employed (5 in new trades, without exposure, found on their own initiative). One was a student, one was unemployed, 4 were on sick leave, and 6 had received disability pension (Table 1). Of 15 patients eligible for financial compensation (5 self-employed patients being non-eligible, according to Danish regulations), 12 had received compensation from the State Industrial Injuries Security Office (Sikringsstyrelsen). Fifteen of the 20 patients had experienced significant decrease of income connected with the recommended changes in work consequent upon the diagnosis (10). Disappointment, bitterness and dysphoria were commonly expressed. The workers' psychological predicament serves as a reminder that an erroneous diagnosis of dementia may reinforce feelings of inadequacy and disability.

Solvent exposure as a cause of chronic brain damage is currently a matter of scientific investigation and, in some countries, a matter of considerable clinical and public concern. In Denmark, the "painter's syndrome" continues to attract the attention of the public media. The present results remind of the dangers and pitfalls inherent in uncontrolled or poorly controlled studies. We suggest that future publication of studies based on neuropsychological test data in this and related areas be limited to reports in which the questions of control are adequately dealt with.

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