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PAPER

Cognitive functioning in patients with suspected chronic toxic encephalopathy: evidence for neuropsychological disturbances after controlling for insufficient effort

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Objectives: Chronic toxic encephalopathy (CTE) caused by long term occupational exposure to organic solvents is still a controversial disorder. Neuropsychological testing is the cornerstone for diagnosing the syndrome, but can be negatively influenced by motivational problems. In this nationwide study, we investigated the neuropsychological functioning and psychological symptoms of a large group of patients with suspected CTE, and ruled out alternative explanations for their complaints, including suboptimal performance due to insufficient effort.

Methods: We studied participants with suspected CTE (n = 386) who were referred for further diagnosis to the Netherlands Centre of Occupational Diseases in the period 1998–2003 and who had completed the entire diagnostic protocol. Patients were excluded if there was the slightest suspicion that test performance had been negatively influenced by insufficient effort (n = 221), or if comprehensive assessment identified an alternative diagnosis (n = 80). Insufficient effort was defined by a combination of three indices. The neuropsychological test scores of the patient group (n = 85) were compared with those of a control group of building trade workers matched for sex, age, and educational level (n = 35).

Results: The patient group had significantly more psychological complaints and performed significantly worse than the control group on tests of speed of information processing and memory and learning. However, only a small percentage of the patients had clearly abnormal scores for cognitive speed (9%) or memory (8%). Attention, verbal abilities, and constructional functions were not disturbed. Exposure duration and cognitive complaints were significantly correlated, whereas the correlation between exposure duration and neuropsychological domain scores was not significant.

Conclusions: Insufficient effort was present in a substantial part of the patient group. After minimising the likelihood that insufficient effort negatively influenced neuropsychological scores, we still found neuropsychological deficits in speed of cognitive processing and memory; however, these scores were clearly abnormal only in a minority of patients with suspected CTE. Screening instruments should focus on these domains.

Organic solvents are widely used in industry (in paints, glues, coatings, and degreasing agents), and many of these solvents are neurotoxic. Acute exposure to organic solvents typically results in central nervous system (CNS) depression and can lead to sleepiness, dizziness, headache, and attention deficits.[1] The acute effects often resolve after exposure is stopped or decreased; however, extremely high exposure may result in irreversible neurological disorders such as ataxia, polyneuropathy, epileptic insults, and even coma and death.[2 3] Whether chronic exposure to low doses of organic solvents has lasting neurotoxic effects is still debated. Over the past decades, many epidemiological studies have investigated the neurotoxicity of solvents in occupational settings. In a comprehensive report of epidemiological studies investigating the neurobehavioural effects of long term, low dose exposure, Spurgeon *et al* concluded that 78% of their selected studies reported a (subclinical) effect of solvent exposure on at least one neuropsychological test, and 54% of these positive studies also found exposure–effect relationships.[4]

However, only a small minority of exposed workers develop a pattern of irreversible cognitive (such as attention, memory, executive function, and visuospatial skills) and neurasthenic problems (such as fatigue, instability of affect, and difficulties in impulse control) presumably caused by chronic exposure to organic solvents.[5] This syndrome is called "painters' disease", psycho-organic syndrome, solvent induced chronic encephalopathy, or chronic toxic encephalopathy (CTE). In clinical practice, it is difficult to determine whether a patient's cognitive and emotional symptoms are solvent induced. Usually, there is no significant neurological and neurophysiological impairment.[6] CTE is diagnosed by the exclusion of other causes and is based on consensus by a multidisciplinary diagnostic team.[7 8] Neuropsychological testing is the cornerstone of the diagnosis,[9] but the differential diagnosis is complicated. Many factors have to be considered when interpreting test results, such as premorbid problems in learning and attention, or the interaction between alcohol misuse and solvent exposure. Moreover, performance on neuropsychological tests can be negatively influenced by the presence of affective or somatisation disorders, pain, and motivational problems. Patients with suspected CTE are often involved in litigation or financial compensation procedures, and many such patients show insufficient effort in test situations.[10] Whatever the reason for insufficient effort, it undermines the possibility to accurately interpret the results

Abbreviations: ASTM, Amsterdam Short Term Memory Test; CNS, central nervous system; CTE, chronic toxic encephalopathy; NCTB, Neurobehavioural Core Test Battery; NES2, Neurobehavioral Evaluation System; RMT, Recognition Memory Test; TOMM, Test of Memory Malingering

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of neuropsychological tests and thus can invalidate the diagnostic process.

In previous studies concerning the effects of chronic solvent exposure, the possible influence of insufficient effort was not seriously taken into account. In this nationwide study, we investigated the neuropsychological functioning of a large group of patients with suspected CTE, carefully ruling out alternative explanations for their complaints, including insufficient effort. Patients were excluded if there was the slightest suspicion that test scores had been adversely influenced by insufficient effort, or if comprehensive assessment revealed the possibility of an alternative diagnosis. Insufficient effort was defined by a combination of three indices of insufficient effort that had showed high construct validity in an earlier study on patients with suspected CTE.[11] We compared the neuropsychological test scores of our patient group, grouped in neuropsychological domains, with those of a control group of building trade workers matched for sex, age, and educational level.

The aims of this study were to describe the neuropsychological functioning and psychological symptoms of a group of patients with possible CTE, after carefully ruling out alternative explanations for poor test performance, and to investigate possible relations between duration and severity of exposure on the one hand and psychological symptoms and neuropsychological deficits on the other.

METHODS

Participants

Patients

All subjects had been referred by general practitioners or medical officers to one of the two locations of the Netherlands Centre of Occupational Diseases in the years of 1998 to 2003, and had completed the entire diagnostic protocol. The Centre is funded by the National Health Care Insurance Board and has no connections with the referring clinics. Evaluations are not a part of an insurance process, although after diagnosis, findings can be used by the patient in any litigation procedure. Diagnosis is based upon a three stage process of assessment[12] (fig 1). Subjects passed the first stage if they met the following criteria: long and/or heavy exposure to organic solvents, relevant symptoms, a relation in time between exposure and development of symptoms and signs, and no obvious other cause for the complaints.

They passed the second stage if they had abnormal scores on two or more of six selected subtests of the computer based Neurobehavioral Evaluation System (NES2).[13] Abnormal scores were defined as below the fifth percentile (corresponding with a standard z score of –1.64) of a normal reference group, matched for age and education. The NES is a computerised testing system that incorporates cognitive tests from the Neurobehavioural Core Test Battery (NCTB), a set of tests recommended by a WHO working group for use in diagnosing neurotoxic effects of exposure.[14] The NES was adapted for Dutch subjects by Emmen *et al*.[15] The NES subtests used in the Dutch adaptation are: vocabulary, simple reaction time, colour word vigilance, symbol digit substitution, digit span forwards and backwards, hand–eye coordination, and tapping. In addition, in the Dutch diagnostic protocol, the scores on the vocabulary task and the tapping task are not included as selection criteria for enrolment in the neuropsychological assessment.

The third diagnostic stage included a clinical neurological examination, assessment of exposure, and a comprehensive psychological evaluation consisting of a standardised neuropsychological test battery[16] and an extensive interview to exclude psychiatric symptomatology, such as affective disorders and premorbid learning problems. An occupational hygienist retrospectively assessed the level of exposure, expressed in terms of duration and severity. Duration was based on number of years exposed, corrected for full time/part time differences (solvent years). Exposure severity was based on workplace concentration, symptoms of acute intoxication, and use of personal protection equipment, and was classified as low, intermediate, or high. The exposure assessment was based on patients' self report and, if available, on employment records.

Controls

The control group consisted of 43 volunteers working as carpenters, bricklayers, electricians, or cleaners, comparable in age, sex, and educational level, and not currently or previously exposed to organic solvents. They were invited to participate in this study partly via the Dutch trade union FNV, and partly via their work on a building project at Hospital Twente. The two women worked as cleaners in the same hospital. All control subjects received €25 for their participation, and travel expenses were paid. Exclusion criteria for the control group were past or current episodes of psychiatric and neurological symptoms, medication interfering with cognitive functioning, and alcohol or drug misuse.

Measures

Neuropsychological test battery

The neuropsychological tests administered were classified into five domains: (*1*) information processing speed (subdivided into (*1a*) visual motor speed and (*1b*) cognitive speed), (*2*) attention/concentration, (*3*) memory and learning, (*4*) verbal ability, and (*5*) constructional functions. A description of the neuropsychological domains and tests, and sample characteristics of the tests used in this study are shown in table 1. The psychological complaints of the patient group were recorded using the symptom checklist (SCL-90-R).[17–19]

Methods to detect insufficient effort

Three indices of insufficient effort showing high construct validity in an earlier study on patients with suspected CTE were, in combination, used to identify patients who exerted insufficient effort.[11] Two of the indices were specifically devised for the detection of insufficient effort, the Amsterdam Short Term Memory Test (ASTM)[28] and the Test of Memory Malingering (TOMM).[29] The essential feature of these tests is that they appear to be difficult memory tasks, but even people with brain damage can perform the tests well. The TOMM is a visual memory test and the ASTM a verbal memory test. Both tests have been constructed according to the symptom validity testing paradigm and have been validated in several studies.[28–32] The third indicator was Warrington's Recognition Memory Test for Faces (RMT),[33] a conventional neuropsychological test.

TOMM, ASTM, and RMT scores were dichotomised into normal or insufficient effort. The recommended cut off scores for the TOMM and the ASTM were used.[28 29] The cut off score of the RMT (25/26) was based on a study by Iverson.[34]

Subjects were defined as exerting "sufficient effort" if their scores on all three indices were normal. We used this strict criterion to ensure that the results of neuropsychological testing were not influenced by insufficient effort.

"Insufficient effort" was defined as a score below cut off on at least two of the three indices. A score below cut off on one of the three indices was defined as "dubious effort".

Statistical analyses

To reduce the large number of variables and thereby the number of statistical comparisons needed, test scores were combined into summary domain scores. Raw scores were

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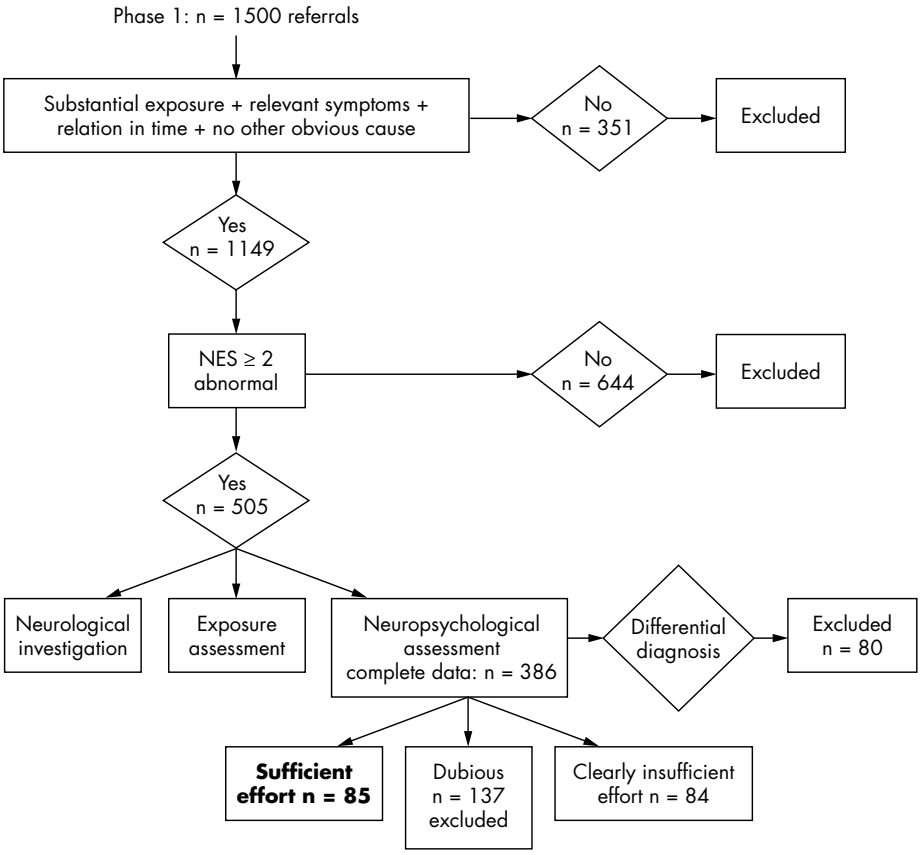

Figure 1 Flow chart of the diagnostic process.

Table 1 Neuropsychological tests and domains, and sample characteristics of the tests used in this study

Domain/Test	Author	Reference group, healthy controls	Controlled for
Information processing speed			
Visuomotor speed			
Pegboard	Heaton *et al*, 1986[20]	n = 1460	Age
Cognitive speed			
Stroop Words, Colour and Colour Words, time to completion	Schmand *et al* 2004[21]	n = 585, age 14–87 years	Age, education
Trail Making Test A and B, time to completion	Schmand *et al* 2004[21]	n = 342, age 17–87 years	Age, education
Attention			
Stroop Interference	Schmand *et al*, 2004[21]	n = 585, age 17–87 years	Age, education
Trailmaking Test B score given A	Schmand *et al*, 2004[21]	n = 342, age 17–87 years	Age, education
Memory and learning			
California Verbal Learning Test (Dutch adaptation)	Mulder, 1997[22 23]	n = 436	Education
Rivermead Behavioural Memory Test (Stories)	Schmand, 2004[21]	n = 284	Age, education
Verbal ability			
GIT, vocabulary	Luteijn & van der Ploeg, 1983[24]	n = 1570	Age, sex
GIT, fluency	Luteijn & van der Ploeg, 1983[24]	n = 1570	Age, sex
WAIS similarities	Stinissen *et al*, 1970[25]	n = 2100	Age, sex
Constructional functions			
WAIS-R block design	Wechsler, 1981[26]	n = 1800	Age, sex
Rey Complex Figure test	Visser, 1970[27]	n = 140	None
Questionnaires			
Symptom Check List (SCL-90)	Arrindell & Ettema, 2003[19]	n = 2461, normal controls	None

GIT, Groninger Intelligence Test; WAIS-R, Wechsler Adult Intelligence Scale, revised.

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converted to standard scores corrected for age, and whenever possible corrected for educational level, based on the norms given in the test manuals. All standard scores were then transformed into z scores, and mean z scores were calculated for each domain.

Mean domain scores of the patient group (sufficient effort group) and the control group were analysed by independent sample *t* tests. A multiple analysis of variance was used to analyse the overall score differences.

Next, we studied separate test scores, to analyse whether a group difference in a particular domain was demonstrable on all separate tests. Percentages of subjects with abnormal domain scores (defined as scores below the fifth percentile ($Z<-1.64$) and marginally abnormal scores (defined as scores below the tenth percentile ($Z<-1.28$) were computed for both patients and controls and analysed with χ^2 and Fisher exact tests.

Within the patient group, possible dose response relationships were studied by analysing correlations between exposure duration and exposure severity on the one hand, and neuropsychological results and psychological symptoms on the other. Multiple linear regression analysis was used to investigate whether these correlations persisted after correction for potential confounders (such as age).

RESULTS

Selection and group characteristics of patient group and control group

In the period 1998 to June 2003, 1500 people were referred to the solvent teams. A flowchart of the diagnostic process is shown in fig 1.

In total, 351 patients not meeting the inclusion criteria were excluded after the first medical intake interview (diagnostic stage 1), and 644 patients were excluded because their scores on the NES test were normal (diagnostic stage 2). Thus, 505 patients met the inclusion criteria of the solvent teams and completed the entire diagnostic procedure (diagnostic stage 3). However, neuropsychological test data were complete for only 386 patients. The incompleteness of the data was often due to scheduling problems such as subjects being late for the appointment, or to practical clinical problems in test administration, such as slowness, drop out during test administration, or adaptation of the test battery to specific individual problems. The group with complete data did not differ significantly from the group with incomplete data regarding age ($p = 0.28$), sex ($p = 0.48$), level of education ($p = 0.96$), exposure duration ($p = 0.31$), and exposure severity ($p = 0.95$); however, significantly more subjects in the incomplete data group (36%) than in the complete data group (25%) were involved in a litigation or financial compensation procedure ($p = 0.02$), and significantly more subjects performed suboptimally on the TOMM ($p<0.001$) and the ASTM ($p<0.001$), but not on the Warrington RMT ($p = 0.97$).

Most (96%; $n = 371$) of the subjects with complete data were men. The mean (SD) age of the subjects was 46 (9) years, and duration of exposure was 23 (11) years. A quarter (25%; $n = 98$) of the subjects were involved in a litigation or financial compensation procedure. Subject characteristics are presented in table 2.

There were 80 subjects excluded because the comprehensive assessment in the third stage established an alternative diagnosis such as chronic alcoholism, depression, adult attention deficit hyperactivity disorder, or a neurological disorder.

Of the remaining 306 subjects, 85 (28%) exerted sufficient effort, while 84 subjects (27%) clearly exerted insufficient effort, defined as suboptimal scores on two or more indices. The remaining 137 subjects with "dubious effort" were excluded from further analyses. The group exerting sufficient effort did not differ significantly from the group exerting insufficient effort regarding age ($p = 0.91$), sex ($p = 0.14$), level of education ($p = 0.17$), exposure duration ($p = 0.54$), or exposure severity ($p = 0.13$). Not surprisingly, significantly more subjects exerting insufficient effort (41%) were involved in a litigation or financial compensation procedure than were subjects exerting sufficient effort (17%) ($p = 0.002$).

Table 2 Demographic data for the complete data group and the case group

	Complete data, frequency (%)	Case group frequency (%)
Sex		
Male	371 (96.1)	83 (98)
Female	15 (3.9)	2 (2)
Education*		
Primary education	26 (6.7)	4 (4.7)
Lower vocational (no diploma)	90 (23.3)	16 (18.8)
Lower vocational (diploma)	195 (50.5)	48 (56.5)
Mid-level	61 (15.8)	13 (15.3)
College	14 (3.6)	4 (4.7)
Level of exposure		
Low	79 (20.5)	16 (18.8)
Intermediate	190 (49.2)	47 (55.3)
High	117 (30.3)	22 (25.9)
Exposure years		
0–5 years	13 (3.4)	2 (2.4)
5–15 years	83 (21.5)	20 (23.5)
⩾15 years	290 (75.1)	63 (74.1)
Occupation		
Painter	137 (35.5)	35 (41.2)
Spray painter	65 (16.8)	13 (15.3)
Printer	45 (11.7)	12 (14.1)
Chemical/paint industry	20 (5.2)	4 (4.7)
Upholsterer	25 (6.5)	4 (4.7)
Other	94 (24.3)	17 (20)
Work situation		
Working, exposed	107 (27.7)	35 (41.2)
Working, unexposed	42 (10.9)	9 (10.6)
Sick leave	98 (25.4)	20 (23.5)
Disability pension	123 (31.8)	15 (14.1)
Retired	5 (1.0)	–
Unemployed/welfare	12 (3.1)	2 (2.4)
Litigation		
Yes	98 (25.4)	14 (16.5)
No	288 (74.6)	71 (83.5)
Total	386 (100)	85 (100)

*The Education classification system in the Netherlands is not based on years of education, but on level of attained education.

The 85 subjects exerting sufficient effort on neuropsychological tests (referred to as the case group) were compared with a control group of 43 subjects matched for sex, age, and education. Of these 43 subjects, only 35 exerted sufficient effort according to our criteria and were included in the control group. The eight excluded subjects all failed the ASTM only. The control group did not differ from the patient group regarding age ($p = 0.87$), sex ($p = 0.35$), and education ($p = 0.17$).

Test data of case and control group (sufficient effort groups)

Mean z scores for both cases and controls for the five neuropsychological domains are given in table 3. The percentages of scores below the fifth and tenth percentiles are presented for both groups in table 4. Mean raw scores for all neuropsychological tests for both groups are presented in table 5.

As can be seen in table 3, the case group appeared to have significantly lower mean z scores than the control group on cognitive speed and memory and learning; however, only a small percentage of subjects had clearly abnormal scores

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Table 3 Domain scores for subjects exerting sufficient effortcompared with control subjects (z scores)

Domain	Cases (n = 85)	Controls (n = 35)	p*
Visuomotor speed	−0.92 (10.76)	−0.56 (10.14)	0.13
Cognitive speed	−0.70 (0.76)	−0.30 (0.62)	0.005
Attention and Concentration	−0.14 (0.67)	0.06 (0.60)	0.08
Memory and learning	−0.71 (0.65)	−0.21 (0.68)	0.0001
Verbal ability	−0.11 (0.70)	−0.05 (0.49)	0.33
Constructional functions	0.18 (0.56)	0.38 (0.64)	0.06

Values are mean (SD). *One sided p values.

(table 4). About 20% of the case group had scores below the 10% percentile on cognitive speed and memory.

A multiple analysis of variance was used for an overall analysis of score differences ($p = 0.006$; $F = 3.246$). The case group was significantly slower than the control group on all subtests reflecting cognitive speed, except for the Stroop word task. On memory and learning, the case group performed significantly worse on all test reflecting recall, except the Rivermead Stories immediate recall. On the CVLT, the recognition total score did not differ significantly between the case and the control groups. In constructional functions, patients had significantly lower scores only on WAIS-R block design. The results on the tests reflecting verbal abilities were inconsistent. Cases had significantly better scores on WAIS similarities, but did not significantly differ from controls on the vocabulary test. Cases had significantly lower scores on both fluency tests, but these are speed tests.

Mean scores on the SCL-90 scales, and percentages of abnormal scores for each scale, are given in table 6. On each scale the case group had significantly ($p<0.0001$) higher scores than the control group, indicating more complaints. On the scales reflecting cognitive complaints and somatic problems, differences between cases and controls were most pronounced. In half of the cases, the general level of physical and psychological well being (Global Severity Index) was very low, whereas none of the controls scored below the fifth percentile.

Correlation with exposure duration and exposure severity within patient group

Neither exposure duration (solvent years) nor exposure severity were significantly correlated with any of the neuropsychological domain scores. On the SCL-90, exposure duration was a significant independent predictor of reported problems in cognitive functioning (partial correlation, controlled for age 0.228, $p = 0.05$).

In the correlation of neuropsychological domain scores with psychological symptoms, psychomotor speed was a significant independent predictor of reported problems in cognitive functioning (partial correlation, controlled for age 0.29, $p = 0.02$).

Optimal versus suboptimal patient group

Differences between the subjects with suspected CTE who exerted sufficient effort and the subjects who were clearly exerting insufficient effort (on two or more indices) were also investigated. For each domain, the group with insufficient effort scored significantly below the scores of the group exerting sufficient effort. Differences varied between 0.4 SD for attention and concentration, and 1.2 SD for visuomotor and cognitive speed.

On the SCL-90, optimal performers indicated significantly less psychological and somatic complaints on each scale than the suboptimal performers. Differences varied between 0.7 SD (for interpersonal sensitivity) and 2.3 SD (for phobic anxiety).

Table 4 Abnormal domain scores ($z<-1.64$) for cases and controls

Domain	Abnormal scores		
	Cases (n = 85)	Controls (n = 35)	p*
Visuomotor speed (pegboard)	21 (28)	17 (20)	0.41 (0.24)
Cognitive speed	9 (18)	0 (3)	0.06 (0.023)
Attention and concentration (qualitative aspects)	1 (7)	0 (0)	0.71 (0.12)
Memory and learning	8 (20)	0 (6)	0.08 (0.04)
Verbal ability	0 (4)	0 (0)	– (0.35)
Constructional functions	0 (0)	0 (3)	– (0.29)

Values are % abnormal scores, with % marginal scores in parentheses. *One sided p values.

Normal versus abnormal NES group

More than 40% of the original group referred to the solvent teams was excluded according to their unimpaired performance on the NES. To study the possible influence of a selection bias, a randomly selected subgroup consisting of 27 patients with normal NES scores also completed the neuropsychological tests, of whom 14 had normal scores on the effort tests. We compared the results of this subgroup ($n = 14$) with the case group ($n = 85$) of optimal performers with abnormal NES scores. There were no significant differences between the groups on any of the neuropsychological domains. The groups did not differ significantly in age, education, exposure duration, or exposure severity.

DISCUSSION

The purpose of the present study was to compare the neuropsychological performance and psychological symptoms of patients with suspected CTE with that of a matched control group, after carefully minimising the likelihood that test results were negatively influenced by insufficient effort. Furthermore, patients with an alternative diagnosis were also excluded from the data analyses. Applying these stringent criteria resulted in the exclusion of a very large subgroup of patients with suspected CTE; 27% of the group with complete data and no alternative diagnosis clearly exerted insufficient effort, defined as suboptimal scores on two or more indices. Subjects exerting insufficient effort were significantly more likely to be involved in an ongoing litigation procedure. These results indicate that insufficient effort is a substantial problem in patients with suspected CTE, especially in those seeking compensation.

In our remaining, well defined, suspected CTE group, patients indicated significantly more psychological and somatic symptoms than controls on all scales of the SCL-90. The greatest difference between patient and controls concerned cognitive complaints (scores differed by 3.1 SD) and somatic complaints (2.4 SD). Furthermore, 50% of the patients gave evidence of a low level of general physical and psychological wellbeing compared with none of the controls. Exposure duration was a significant independent predictor of cognitive complaints.

Patients with suspected CTE differed significantly from controls in information processing speed and in memory and learning. However, cognitive speed and memory were clearly disturbed in only a small number of patients (<10%). About 20% of the patients had mild problems in cognitive speed and memory (scores below the tenth percentile). The greatest difference between patient and controls concerned memory function (mean scores differed by 0.50 SD). That our study

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Table 5 Mean raw scores for cases versus controls on separate neuropsychological tests

Tests	Cases (n = 85)	Ccontrols (n = 35)	p*
Information processing speed			
Visuomotor speed			
Pegboard dominant (s)	78 (17)	74 (10)	0.13
Pegboard Non-dominant (s)	84 (22)	82 (18)	0.33
Cognitive speed			
Stroop words (s)	54 (12)	52 (8)	0.10
Stroop colours (s)	69 (13)	64 (11)	0.04
Stroop colour word (s)	119 (30)	107 (29)	0.03
Trail Making A (s)	43 (19)	34 (9)	0.001
Trail Making B (s)	94 (35)	83 (29)	0.04
Attention and concentration (qualitative aspects)			
Stroop 3 given Stroop 2 interference score†	−0.43 (0.67)	−0.09 (0.84)	0.01
Trail Making B given Trail Making A†	0.16 (10.03)	0.15 (0.79)	0.47
Memory and learning (recall)			
CVLT total list A	44 (8)	50 (8)	0.0001
CVLT long term free recall	9 (3)	11 (2)	0.0001
Rivermead Stories immediate recall	17 (5)	19 (6)	0.09
Rivermead Stories delayed recall	13 (5)	15 (7)	0.03
Memory and learning (recognition)			
CVLT recognition total	39.4 (3)	40.3 (3)	0.11
CVLT total hits	13.6 (20.0)	14.4 (1.4)	0.01
Verbal abilities			
WAIS similarities	16 (5)	13 (4)	–
GIT vocabulary	10.6 (4.3)	11.5 (2.9)	0.13
GIT fluency - animals	19 (5)	22 (5)	0.005
GIT fluency - occupations	15 (3)	18 (4)	0.001
Constructional functions			
WAIS-R block design	29.3 (9.9)	34.7 (7.9)	0.004
Complex Figure Test copy	6.4 (4.9)	7.1 (5.9)	0.26

Values are mean (SD). s, seconds. *One sided p values; †z scores

found no relationship between subjective memory complaints and objective deficits is not surprising; many studies are in line with these findings.[35 36] In a general sense, our data are in accordance with the diagnostic criteria for CTE, which stress cognitive complaints and neuropsychological deficits. The findings corroborate previous studies documenting neurobehavioural and psychiatric symptoms in individuals exposed to solvents.[37–39] None of these studies, however, used methods to exclude insufficient effort as a confounding variable. More specifically, however, our findings are restricted to memory and speed and we did not observe specific attention problems, or problems in the domains of visual construction, verbal ability, and executive functions, although there appeared significant differences between patients and controls on single (speed) tests in these domains, such as block design and verbal fluency. This clinical picture might be related to neuropathological findings of white matter lesions associated with chronic solvent exposure.[40–42]

Exposure indices were not associated with any of the neuropsychological domain scores. On the one hand, this is a disappointing finding, but on the other hand it must be pointed out that our exposure indices are partly dependent on the patient's own recall, therefore it is often very difficult to obtain a reliable exposure history.

Some methodological issues regarding this study have to be discussed. Firstly, more than 40% of the original group referred to the solvent teams was excluded because of their unimpaired performance on the NES assessment. It is not certain whether this has biased the results. It could be argued that selecting individuals based on their poor NES scores makes it probable that they would have poor scores on the

Table 6 Mean SCL-90 z scores for the patients

	Mean (SD)		Abnormal scores, n (%)	
SCL scales* (n = 73)	Cases (n = 85)	Controls (n = 35)	Cases (<5%)	Controls (<5%)
Anxiety	1.81 (1.96)	−0.15 (0.71)	37 (44)	1 (3)
Phobic anxiety	1.71 (2.8)	0.05 (10.1)	28 (33)	1 (3)
Depression	1.69 (1.89)	−0.28 (0.58)	37 (44)	0 (0)
Somatisation/somatic symptoms	2.3 (1.90)	−0.14 (0.83)	49 (58)	1 (3)
Obsessive compulsive (cognitive problems)	3.0 (1.95)	−0.08 (0.57)	59 (69)	0 (0)
Interpersonal sensitivity/ paranoid ideation)	1.47 (1.85)	−0.24 (0.56)	34 (40)	0 (0)
Hostility	1.95 (2.04)	−0.32 (0.40)	39 (46)	0 (0)
Sleep problems	1.27 (1.55)	−0.08 (0.69)	29 (34)	1 (3)
Global Severity Index	2.01 (2.32)	−0.33 (0.77)	50 (59)	0 (0)

*The SCL-90 is a Dutch adaptation (Arrindell & Ettema, 1986, 2003) of the SCL-90-R self report inventory (Derogatis, 1977, 1994). It is designed to screen for a broad range of psychological problems and symptoms of psychopathology. The original English version contains nine scales; in the Dutch adaptation some scales (interpersonal sensitivity/paranoid ideation and psychoticism are summarised in one scale. The Dutch scale ''insufficiency in thoughts and behaviour'' reflects the scale ''obsessive compulsive behaviour''. The scale reflects problems in cognitive functioning, which is not characteristic for obsessive compulsive disorders.

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neuropsychological assessment as well. On the other hand, it could also be possible that individuals with normal NES scores who are excluded from further investigations have problems on a more comprehensive neuropsychological evaluation, and thus neuropsychological disturbances might have been underestimated. We were able to assess neuropsychologically a randomly selected subgroup of patients with normal NES scores. This subgroup did not differ significantly from the cases with abnormal NES scores on any of the neuropsychological domains. Therefore, the use of the NES as a selection criterion, albeit defendable for reasons of efficiency, did not influence our outcome measures. Our selection procedure might even have underestimated the neuropsychological problems of our patient group. Regarding clinical neuropsychological practice and further research, it seems advisable to focus on more specific tests of cognitive speed, memory, and learning in the neuropsychological battery than are advised in the Neurobehavioral Core Battery. In this sense, our data support remarks by Hawkins and Sørensen, who put forward that the Core Battery, mainly focusing on visuomotor speed, attention, and short term (working) memory, is incomplete for a population with suspected CTE.[43 44]

Secondly, we used very stringent criteria to select our subgroup of patients who exerted sufficient effort. Subjects were included as exerting sufficient effort only if they performed normally on three detection methods of effort. Even in the control group, 19% of the participants were excluded because of these criteria, owing to low scores on the ASTM, even though there was no incentive for these individuals to exhibit poor effort on the ASTM. In particular, the ASTM seems very sensitive to even slight fluctuations in effort, and thus it cannot be ruled out that the strict selection process might have resulted in an underestimation of the neuropsychological problems associated with CTE.

The fact that detection tests such as the TOMM and the ASTM really measure effort is evident from several validation studies providing data on subjects with objective brain damage, showing that most of these subjects have normal test performance. On the TOMM, even subjects with mild dementia passed the test. However, it must be mentioned that personality changes such as apathy and loss of initiative can be a consequence of the CTE syndrome. The possibility that these changes lead to insufficient effort on the neuropsychological investigation cannot be ruled out, and therefore these effort tests should be used and interpreted very carefully.

More research should be focused on the performance on detection methods such as the ASTM or the TOMM by patients with various types of psychiatric or neurological disorders. The possibility of character changes as a result of long term exposure to organic solvents and their influence on effort tests is an urgent topic for further study. Next to that, it would be interesting to study the neurophysiological background of insufficient effort.

Our data are consistent with a recent study from Loring *et al*,[45] reporting performance on the Victoria Symptom Validity Test in 120 non-litigating epilepsy surgery candidates. As in our study, Loring *et al* found that a substantial subgroup (12%) of patients had invalid scores on this test. As with our controls on the ASTM, these patients had no incentive to exhibit poor effort, therefore the possibility that test performance may be influenced by subjects not performing to the best of their ability must always be taken into account, even in healthy subjects.

Thirdly, our patients were suspected of CTE but had not yet been diagnosed with the disorder, and thus the neuropsychological problems caused by ''real'' CTE might have been underestimated. We followed this procedure to avoid circularity in our approach; limiting attention to diagnosed CTE cases would definitely result in significant differences with the control group, as the diagnosis is dependent on neuropsychological deficits. Nevertheless, not all suspected patients were clinically recognised as patients with CTE and this has possibly reduced the differences between the groups.

Fourthly, not all test scores were corrected for the relevant demographic variables because not all test manuals provide these corrections. For example, the norms we used for the grooved pegboard test were corrected for age, but not for education. This might explain why some domain scores were quite different from zero. In this test, both patients and controls performed slower than indicated by the normative data. It is possible that hard manual labour leads to coarse, rough, and ''clumsy'' hands and hence to a slower motor performance.

In conclusion, our results suggest that patients with suspected CTE differed significantly from controls in the domains of memory, learning, and speed of information processing. However, cognitive speed and memory were clearly disturbed in only a minority of patients. Furthermore, exposure duration is a significant predictor of cognitive complaints. However, we failed to find a relation between objective cognitive test performance and exposure measures.

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