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Validity of a Computer-Assisted Neurobehavioral Test Battery in Toxicant Encephalopathy

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Abstract: *The computer-assisted Neurobehavioral Evaluation System 2 (NES2) test battery provides an efficient method of measuring neurobehavioral effects in epidemiological studies, and a newer computer-assisted battery, NES3, has been developed to assist in neuropsychological assessment. This study assesses the validity of some NES2 and NES3 tests in patients diagnosed with toxicant encephalopathy (TE) following exposure to lead or to mixed solvents. This information can be used to improve the interpretation of NES test results in research studies and clinical evaluations examining central nervous system function. Performance on a battery of computer-assisted tests, consisting of several NES2 and NES3 tasks, by persons diagnosed with TE was compared to that of control subjects to determine if performance differences reflected a priori hypothesized brain-behavior relationships. Performance on the NES2 and NES3 tests was also correlated with performance on analogous standard neuropsychological tests. Significant performance differences between the patient cases and controls were observed in most of the predicted domains on the NES tests. Overall, moderate correlations were obtained between standard neuropsychological tests and NES2 and NES3 tests from the same functional domains. The results suggest that a test battery composed of NES2 and NES3 tests can identify clinically significant performance deficits in solvent-exposed patients who have been diagnosed with TE using traditional clinical neuropsychological test methods. The results with lead-exposed TE patients are less robust. Possible explanations for these differences are discussed.* © *2000 Intox Press, Inc.*

Key Words: Toxicant Encephalopathy, Validation, Computer Assessment

INTRODUCTION

The Neurobehavioral Evaluation System (NES) was a battery of computer-assisted tests designed for use in epidemiological investigations of the neurobehavioral effects of chronic environmental and/or occupational toxicant exposures (Baker *et al.*, 1985a; Letz and Baker, 1986). The NES and its successor, NES2, were based on standard neuropsychological tests that have been well characterized in terms of the brain-behavior relationships revealed by test performance. To date, performance on specific NES and NES2 tests has been shown to be sensitive to experimental exposure to solvents and nitrous oxide (Greenberg *et al.*, 1985; Mahoney *et al.*, 1988; Hooisma *et al.*, 1988; Echeverria *et al.*, 1989) and to exposure to solvents, pesticides, and mercury in field studies (Baker *et al.*, 1988; Fidler *et al.*, 1987a; Albers *et al.*, 1987; Hrychorczuk *et al.*, 1987; Letz *et al.*, 1990; Spurgeon *et al.*, 1992; Steenland *et al.*, 1994). The NES battery was initially designed to detect group effects rather than identify clinical cases and has not been studied in persons with a clinical diagnosis of toxicant encephalopathy (TE).

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However, the latter exercise is necessary to determine if the tests adequately measure performance deficits in the functional domains found to be impaired in these diagnosed patients via traditional clinical neuropsychological tests (the gold standard).

Various measures of reliability and validity of some of the NES and NES2 tests have been evaluated in prior studies. Test-retest reliabilities (test-retest correlations) of NES and NES2 tests have ranged from 0.51 to 0.92 in several experimental studies where the test-retest interval ranged from AM-PM on the same day to 14 days (Baker *et al.*, 1985b; Mahoney *et al.*, 1988; Echeverria *et al.*, 1989; Echeverria *et al.*, 1991; Emmen *et al.*, 1987; Arcia and Otto, 1992). Tests of response speed and attention had the highest reliability estimates; two tests of intermediate memory had moderate estimates (0.61-0.80); and three tests involving learning/memory (e.g., Associate Learning) had reliabilities that were generally low to moderate (0.27-0.67). In field study investigations, the NES and NES2 tests were considered to be adequately reliable for repeat testing situations, with reliabilities ranging from 0.61 to 0.87 (Letz 1990; Maizlish *et al.*, 1987; Baker *et al.*, 1988; Letz *et al.*, 1990). Correlations between performance on three NES tests (Digit Span, Hand-Eye Coordination, Symbol-Digit) and performance on standard neuropsychological tests were moderate for the first two tests and highest for the latter at 0.76 (Baker *et al*, 1985b). Moreover, variables such as age, gender and education level have been demonstrated to be important covariates in the performance on NES2 tests just as they are on standard neuropsychological tests (Letz, 1993).

The ability of the NES2 test battery to detect predicted performance impairments in neurological patients with specific diseases (e.g. Parkinson's disease (PD), multiple sclerosis (MS)) was examined in a recent study by White *et al.* (1996). These two patient groups were selected because they exhibit well-defined contrasting neuropathology and these sites of CNS damage (basal ganglia and white matter, respectively) have been implicated in neuropathology secondary to exposure to particular neurotoxicants. Performance on NES2 tests was affected in expected ways in both MS and PD patients, but was more impaired in MS than PD patients relative to controls. Moreover, the NES2 battery was found to be relatively insensitive to deficits in some predicted cognitive domains (executive function, visuospatial ability, memory). Correlations between NES2 and analogous standard neuropsychological tests were low to moderate (lower when modality of presentation and/or responses were different) (Krengel *et al.*, 1996).

The impetus to develop the NES3 test battery was the result of several factors: improvement in computer technology, the findings from earlier validation studies indicating more appropriate test modalities were needed to detect CNS dysfunction in specific brain sites, and the desire to be able to identify individuals having subtle as well as clear-cut CNS impairment. NES and NES2 tests were given on a portable, suitcase-type Compaq computer with software running under a DOS operating system. With more advanced computer technology (such as the advent of pen-based laptops, touch screens, and Windows-type operating systems), it was possible to update the presentation and administration of neurobehavioral tests to more appropriate modalities thus allowing the inclusion of tests closer in design and administration to the standard neuropsychological tests. The first phase of NES3 development was to implement a small set of neuropsychological tests in the new hardware/software environment for use as a screening tool to identify individuals having CNS impairment (Letz *et al.*, 1996).

The present study investigates the validity of several NES2 and NES3 tests in patients diagnosed with TE based on World Health Organization criteria (Johnson, 1987; Baker, *et al.* 1985c). Patients with solvent encephalopathy have been found to show deficits primarily in the domains of executive function (cognitive tracking and flexibility), attention, visuospatial abilities, short-term memory, and mood (cf. White *et al.*, 1992). In epidemiologic studies of solvent-exposed workers employing standard neuropsychological tests, impaired performances have been observed in Trail-Making Test, Wisconsin Card Sorting Test, Wechsler Adult Intelligence Scales-Revised (WAIS-R) Digit-Symbol Substitution Test, Moss Delayed Recognition Span Test, Wechsler Memory Scale (WMS) Visual Reproductions, and Profile of Mood States (POMS) (Echeverria *et al.*, 1995; White *et al.*, 1992; Anger, 1990) compared with non- (or less-) exposed workers. Adult patients diagnosed with lead encephalopathy have been reported to shown deficits primarily in the domains of motor skills, attention, learning and short-term memory, visuospatial abilities, and mood (cf. White *et al.*, 1992). In epidemiologic studies of lead-exposed workers employing standard neuropsychological tests, impaired performances have been observed in Santa Ana Formboard Test; WAIS-R subtests including Digit Span, Digit-Symbol Substitution, Vocabulary, Similarities; WMS Visual Reproductions and Verbal Paired Associate Learning; Embedded Figures, and POMS (Baker *et al.*, 1984; Yokoyama *et al.*, 1988; Hanninen, 1988; Anger, 1990) compared to non-(or less) exposed workers. Although there is considerable overlap in the functional domains affected in solvent and lead TE, the cerebral loci of these chemical exposures are somewhat different. Patients with significant organic solvent exposures have demonstrated changes in white matter and subcortical areas in multifocal patterns (White *et al.*, 1993). Evidence from animal histopathological studies suggests more localized effects of lead in the hippocampus and limbic system (Walsh *et al.*, 1986). Exposure to lead in adult humans is thought be associated with hippocampal

damage (Feldman, 1999) and thus present with more focal domain difficulties.

There were two primary aims of this study. The first objective was to determine if hypotheses regarding expected patterns of performance in solvent and lead TE patients would be observed on NES2 and NES3 tests designed to measure the same functional domain as the traditional neuropsychological tests. It was predicted that patients diagnosed with solvent encephalopathy would perform more poorly than controls on Sequences A&B (NES3), Continuous Performance Test (NES2-Letters; NES3-Animals), Pattern Memory (NES2), Visual Spans (NES3), Digit-Symbol Test (NES3), List Learning and delayed recognition (NES3), and Mood scales (NES2) (representing the domains of executive function, attention, visuospatial abilities, short-term memory, and mood). In patients diagnosed with lead encephalopathy as adults, poorer performances relative to controls on Finger Tapping (NES2), Continuous Performance Test (NES3-Animals), Digit-Symbol Test (NES3), List Learning and delayed recognition (NES3), Pattern Memory (NES2), and Mood scales (NES2) (representing the domains of motor skills, attention, short-term memory, visuospatial abilities, and mood) were predicted. The second objective was to examine the correlation between scores on NES2 and NES3 tests and on analogous standard neuropsychological tests.

METHODS

In this study design, patients diagnosed with TE were compared to control subjects on their performances on neurobehavioral and neuropsychological test outcomes. The Institutional Review Board Committees of the Boston VA Medical Center and the Boston University Medical Center approved all procedures. As part of their participation in this study, subjects were asked to complete a questionnaire that included questions about demographic characteristics and medical and occupational histories. A set of NES2 and NES3 tests and a battery of traditional neuropsychological tests were administered to each subject individually by a qualified examiner trained appropriately in all test administration procedures.

Subjects

All subjects included in this study had at least 8 years of education and were at least 18 years old.

Toxicant Encephalopathy (TE) Cases. Potential cases were patients identified as diagnosed with solvent and lead encephalopathy that were being followed at a university occupational neurology clinic or Boston-area occupational medicine clinics. Cases selected for recruitment into this study were those clinically diagnosed according to the following criteria (Johnson, 1987):

Evidence of Toxicant Txposure(s) in the Appropriate Temporal Pattern. Information from a work history, subjective symptom checklist, and family and personal medical history supporting the occurrence of exposure to neurotoxicant exposure (solvents or lead) in the appropriate temporal sequence, i.e. signs and symptoms of exposure developed after exposure, was present. A documented history of exposure to either mixed solvents or lead in the medical records (obtained and confirmed by the referring occupational health physicians) was a requirement for all cases. For the purpose of this study, cases were not considered if they had a history of both mixed solvent and heavy metal exposure.

Confirmed Signs of Central Nervous System (CNS) Deficits on Clinical Examination, Including Neuropsychological Tests. Cases chosen for recruitment into this study demonstrated evidence of organic damage in a clinical neuropsychological evaluation that had been carried out prior to this study. Performance deficits on an appropriately designed clinical neuropsychological test battery (White and Proctor, 1992), in a pattern meeting the definition of mild to severe chronic toxicant encephalopathy (Baker *et al.*, 1985c; White *et al.*, 1992; White and Proctor, 1997), were evaluated to identify cases. None of the cases recruited in this study had severe chronic TE.

Differential Diagnosis. As part of making the diagnosis of TE, evaluation of other factors such as past medical, school and family history as well as drug and alcohol history were considered. Alcohol abuse, long-term use of prescription medications such as anti-hypertensive medication, and psychotropic drugs may produce similar CNS effects or could modify the effects of exposure to industrial chemicals (Sato *et al.*, 1980; Katz, 1985). Also, premorbid cognitive deficits (such as occur in persons with residual developmental learning disabilities), psychiatric disorders (such as personality disorders and affective/anxiety disorders), and primary neurological diseases (White *et al.*, 1992) were considered as possible alternative diagnoses to TE.

One of the co-authors (RFW) was responsible for confirming the diagnoses of the potential TE cases, given the above criteria, having either supervised the initial diagnostic evaluation of the recruited cases directly or confirmed a diagnosis made by other neuropsychologists in referred patients. A total of 9 solvent TE and 11 lead TE cases met the above criteria and consented to participate in the study. All cases had chronic exposure to these neurotoxicants. Some of the solvent TE cases were exposed via hobbies or non-work

TABLE 1. Test Battery

Domain	NES Test Name	Standard Neuropsychological Tests
Motor	Finger Tapping: preferred and nonpreferred hand (NES2)	Finger Tapping Test (Halstead, 1947)
Attention	CPT (Letter S)*: latency; # false positives & non-responses (NES2)	WAIS-R Digit-Symbol Substitution (Wechsler, 1981)
	CPT (Animals): latency; # false positives & # non-responses (NES3)	WAIS-R Digit Spans (Wechsler, 1981)
	Digit Symbol: latency (NES3)	
Executive Function	Sequences A & B: latency, # errors (NES3)	Trail-Making Test (Halstead, 1947; Reitan, 1958) Wisconsin Card Sorting Test (Grant and Berg, 1948)
Visuospatial/ Memory	Visual Spans: forward, backward (NES3) Pattern Memory: latency (NES2)	WAIS-R Picture Completion (Wechsler, 1981) WMS-R Visual Spans (Wechsler, 1987) WMS or WMS-R Visual Reproductions (Wechsler, 1945; 1987)
Verbal/ Memory	List Learning: learning trials, delayed recognition (NES3)	WMS Verbal Paired Assoc. Learning (Wechsler, 1945) California Verbal Learning Test (Delis *et al.*, 1987)
Mood	Mood scales: tension, depression, anger, fatigue, confusion (NES2)	Profile of Mood States (McNair *et al*, 1971)
Motivation		Test of Memory Malingering (Tombaugh, 1996)
Academic/ Verbal Knowledge	Vocabulary (NES2) *	WAIS-R Information (Wechsler, 1981)

* performed by solvent TE cases and controls only

experiences (i.e., studio painting); all of the lead TE cases were occupationally exposed.

Controls. Potential control subjects were recruited through other outpatient medical services and among family or friends of cases and were screened initially via a structured telephone interview to exclude persons reporting a history of CNS or psychiatric disorders that affect cognitive function or ability to work (e.g., closed head injury, epilepsy, stroke, bipolar disorder). Potential controls also were screened regarding past environmental and occupational exposures and excluded if they had significant toxicant exposures. For this study, significant exposure was defined as having worked greater than one year in an occupation (or hobby) with potential regular exposure to neurotoxicants without the use of protective gear (such as mask or gloves).

Previous studies have described the utility of questionnaire data in making a determination of long-term exposure history (Fidler *et al.*, 1987b; Nelson *et al.*, 1993) and have concluded that information so collected can provide useful relative information about exposure when absolute estimates of exposure are usually not possible. Mikkelson *et al.* (1988) estimated that the no-effect level for the induction of neuropsychological dysfunction occurs at less than 15 years of 1 liter/day solvent exposure, or less than 6 years working with solvents less than 100 ppm, the TLV. Questions similar to those used in prior research were asked in this study in order to assess past exposure histories.

A total of 50 control subjects completed the study. One subject was excluded from the analyses due to a significant psychiatric history that was identified after review and follow-up of his medical history information.

In order to have adequate power of at least 80% to detect clinical meaningful differences of 15-25% in test performance between the control and TE groups, it was necessary to include a control group of approximately 50 subjects.

Measures

The study protocol included a questionnaire (medical and occupational history), a test battery consisting of several NES2 tests and five newer NES3 tests (referred to collectively in this study as NES2/3 tests), and a traditional neuropsychological test battery. A list of the NES2/3 tests and the standard neuropsychological tests administered is presented in Table 1. The NES2/3 tests were presented on a pen-based, IBM laptop computer with an external keyboard and took about one hour to complete; the traditional neuropsychological test battery took subjects 75-90 minutes to complete.

NES2/3 Tests. *List Learning (NES3).* A list of 12 nouns is presented orally and then 12 pairs of pictures appear on the screen. The subject is instructed to use the pen to touch the one of the pair that represents a word on the list. Three acquisition trials are given with the same list of 12 words

(trials #1-3). Then a single interference trial is given with a new orally presented 12-item list (trial #4). The sum of the number of items correctly answered for trials #1-3 and the number correctly answered in trial #4 were analyzed. Approximately 15 minutes after this task is completed, the List Learning Delayed Recognition task is begun. For this latter task, the subject is instructed to touch the picture representing the nouns heard on the first list of words. Twelve pairs of items, consisting of correct pictures from the first list paired with either incorrect foils from the first list or correct pictures from the second list, are presented. The number of items correctly answered was analyzed.

Sequences A & B (NES3). This test is a computerized version of the Trail-Making Test in which a subject alternates between number and letter sequences. After a practice trial, in which the subject is asked to touch circles numbered 1 through 6 in order, the subject is asked to do the same for circles numbered 1 through 16 (Sequences A). Then a practice trial for Sequences B is presented in which the subject is instructed to touch the screen alternating between digits and letter circles (i.e., to touch '1', then 'A'; '2' then 'B'; '3' then 'C'). Sequences B consists of circles labeled 1 through 8 and letters A through H. Throughout the test, when a circle is touched out of order, an error sound is heard and the last correct answer remains highlighted. The latencies (in sec) to complete Sequences A and B and the number of errors counted in each of these two tasks are recorded and were analyzed.

Visual Span (NES3). In this test, sequences of blocks on the screen are highlighted in a temporal-spatial pattern and the subject is asked to reproduce the sequence by pointing to the blocks in the same order. Practice trials are given for both forward and backward tasks. For the test, successively longer sequences are presented until the subject cannot reproduce the sequence correctly. Separate maximum spans are recorded for forward and backward production. The primary summary measures are maximum span reproduced correctly forward and maximum spans reproduced correctly backward. Valid scores range from 3-9 for forward spans and between 2-8 for backward spans.

Digit-Symbol (NES3). This is a visual scanning and psychomotor coding task in which the subject must find a target digit in a paired digit-symbol array and point, using the pen to the screen, to the paired symbol located in a second array with a different sequence of the symbol. A row of 9 symbols paired with 9 digits is presented across the top of the computer screen. A target stimulus is presented in the middle of the screen and the nine symbols are presented in scrambled order across the bottom of the screen. The summary measure is the latency (in sec) to complete responses to 27 target digits. Incorrect responses result in an error sound and the target stimulus remains; the subject must make the correct response before a new target digit is presented.

Continuous Performance Test; CPT (Animals, NES3). This is a sustained attention task using animal silhouettes and was designed for use in subjects who may not be able to recognize letters, such as young children. After a practice block of trials, a pseudorandom sequence of shadow drawings of common animals is presented on the screen. The subject is asked to respond by pressing a large key on an external keyboard when he/she sees the target animal flash on the screen but not other animals. A response within 1500 msec of the critical stimulus is considered a correct response and the response latency is recorded. The mean reaction time for responding to the target stimuli is recorded across all non-practice trials, along with the number of total number of false positive and non-responses.

Finger Tapping (NES2). This is a test of manual motor speed requiring key tapping with the index finger of the preferred and nonpreferred hands. A large key on the external keyboard was used for tapping. The recorded measure is the number of taps in 30 sec in each condition.

Pattern Memory (NES2). A matrix of 10 X 10 blocks, where the blocks are either dark or light, is presented alone on the screen. After an unfilled interval, a matching pattern and two other patterns (each of which differs from the target in four blocks) are presented. The subject is asked to choose the matching pattern; measures are the number correct and mean latency on correct trials.

Mood Scales (NES2). An inventory assessing self-report of degree of tension, depression, anger, fatigue, and confusion for the preceding week is administered. Subjects are asked to indicate degree of endorsement (extremely, quite a bit, moderately, a little, not at all) of five descriptors for each scale presented in a semirandom sequence. Each scale is scored for number of items endorsed, weighted for severity.

The following two tests were performed by the solvent TE cases and the controls only:

Vocabulary (NES2). This test involves a multiple-choice recognition of word meanings to estimate native intellectual ability. There is a maximum of 25 trials with items increasing in difficulty over trials. The test ends when four of five successive items have been answered incorrectly. The measure analyzed is the estimated number correct out of a possible 25.

CPT (Letters; NES2). A task measuring reaction time, omissions (non-responses), and false-positive responses

TABLE 2. Group Characteristics

	Solvent cases (n=9)	Lead cases (n=11)	Controls (n=49)
Age (years)	55.3 (11.0) *	43.5 (9.0)	43.7 (14.0)
Education level (years)	13.6 (3.4)	12.5 (1.1) **	14.8 (3.0)
WAIS-R Information	11.0 (3.1)	7.6 (1.1) **	11.9 (2.3)
WAIS-R Picture Completion	11.3 (2.3)	8.0 (2.2) *	10.6 (2.5)
Mean TOMM score +	45.0 (8.8)	44.0 (7.5)	48.3 (2.3)
% Female	22.2%	36.4%	42.9%
% Current smoker	22.2%	45.5%	18.4%
% Prior alcohol problem	0%	9.1%	10.2%
% Currently working	22.2%	75.0%*	36.7%

+ Test of Motivation and Malingering
Differences compared to control subjects: * $p \leq 0.05$ ** $p \leq 0.001$

to a large target letter semirandomly embedded in a series of five other single letters is given. If more than five omissions or false positives occur in one trial, then the subject is reinstructed and the trial begins again. Measures are mean latency, omissions, and number of false positives over the series of four 1-minute blocks of trials (an initial 1-minute trial block is given for practice and is not scored).

Neuropsychological Test Battery. The following tests were included in the neuropsychological test battery: WAIS-R Information, Picture Completion, Digit Symbol, and Digit Spans tests (Wechsler, 1981); Finger Tapping (Halstead, 1947); Wisconsin Card Sort Test (Grant and Berg, 1948); Trail-Making Test (Halstead, 1947; Reitan, 1958), WMS-R Visual Span (Wechsler, 1987); WMS Paired Associate Learning and Visual Reproductions (Wechsler and Stone 1945; Osborne and Davis, 1978); California Verbal Learning Test (CVLT; Delis *et al.* 1987); and POMS (McNair *et al.*, 1971).

In addition, all subjects (except 3 solvent TE patients) completed the Test of Memory Malingering (TOMM; Tombaugh, 1996). This is a simple 50-item visual memory test assessing the inclination to conserve effort. It has been well validated in neurologic patient groups as well as in normal control populations who were asked to feign poor performance.

Data Analyses

Crude comparisons of demographic variables were made across the patient and control groups. The Student's t-test statistic was used to compare continuous variables, and the chi-square statistic was used to evaluate the difference between categorical variables. Because there were important differences between the subject groups on several demographic variables, analyses run to test the hypotheses concerning NES test performances were performed adjusting for various covariates.

Analyses of covariance (ANCOVA), adjusting for age, gender, and education level were performed in SPSS (version 9.0, 1999) using general linear models with simple contrasts in order to compare the adjusted means between the two patient groups to the control group for the different test outcome measures. Analyses of the error rates (for Sequences A and B and the number of false positives and non-responses on the CPT) were performed on the natural log-transformed values; the scores were converted back by taking the anti-log and presented as geometric means with standard error (SE).

Pearson product moment correlations between pairs of traditional neuropsychological and computer-assisted test scores considered to measure cognitive function in the same behavioral domain were calculated.

RESULTS

Demographic Data and Standard Neuropsychological Test Performances

Table 2 gives demographic characteristics for each of the two patient groups and the control group, along with their scores on the several traditional neuropsychological tests (WAIS-R Information and Picture Completion) and the TOMM. Solvent TE patients were significantly older than the lead TE patients and the control group. The lead TE group had significantly lower education levels compared to the solvent TE group and the control group. Performance on both the WAIS-R Information and Picture Completion tests were significantly lower in the lead TE group, presumably reflecting lower education levels. However, after adjustment for age, education, and gender differences between the

TABLE 3. Mean (S.E.) Performance of the 3 groups on the computer-assisted tests

	Solvent cases (n=9)	Lead cases (n=11)	Controls (n=49)
MOTOR			
Finger Tapping: (NES2)			
Preferred Hand	111.4 (8.4) **	152.5 (7.5)	158.9 (3.5)
Non-Preferred Hand	104.8 (6.7) **	143.4 (6.0)	147.8 (2.8)
ATTENTION			
CPT (Letters): (NES2)			
Mean latency	510.2 (25.7) *	- -	434.1 (8.6)
# of false positives †	0.84 (0.31)	- -	0.65 (0.09)
# of non-responses †	1.1 (0.3) +	- -	0.24 (0.09)
CPT (Animals): (NES3)			
Mean latency	578.0 (19.1)	572.5 (17.0)	553.3 (7.9)
# of false positives †	0.81 (0.22)	1.2 (0.20) +	0.56 (0.09)
# of non-responses †	1.3 (0.2) **	0.72 (0.19) *	0.08 (0.09)
Digit Symbol latency (NES3)	73.1 (3.3) **	65.6 (2.9) *	59.2 (1.4)
ATTENTION/EXECUTIVE FUNCTION			
Sequences: (NES3)			
Sequence A latency	38.5 (2.3)**	23.5 (2.1)	20.5 (0.96)
Sequence A, errors †	0.08 (0.04)	0.0 (0)	0.02 (0.02)
Sequence B latency	60.3 (5.7)**	44.0 (5.3)	36.8 (2.3)
Sequence B, errors †	0.36 (0.18)	0.84 (.17) +	0.30 (0.07)
VISUOSPATIAL FUNCTION/MEMORY			
Pattern Memory: (NES2)			
# correct	18.6 (1.1) *	20.8 (1.0)	21.3 (0.5)
latency, for correct trials	7.2 (0.4) **	5.3 (0.4)	5.1 (0.2)
Visual Spans: (NES3)			
Forward	4.5 (0.4)	4.6 (0.4)	5.2 (0.2)
Backward	4.0 (0.4) *	4.4 (0.4)	5.0 (0.2)
VERBAL MEMORY			
List Learning: (NES3)			
trials 1-3: sum of # correct	30.3 (2.0)**	34.3 (1.0)	35.0 (0.5)
trial 4: # correct	8.5 (0.6)**	9.6 (0.5)*	11.0 (0.2)
delayed recall: # correct	9.9 (0.4)**	10.7 (0.4) +	11.6 (0.2)
MOOD (NES2)			
Tension	3.1 (0.3) *	3.0 (0.3) *	2.5 (0.1)
Depression	2.2 (0.2) +	2.3 (0.2) *	1.8 (0.1)
Anger	2.1 (0.2)	1.9 (0.2)	1.8 (0.1)
Fatigue	3.7 (0.3) *	3.3 (0.3)	2.9 (0.1)
Confusion	2.9 (0.2) *	2.8 (0.2) *	2.2 (0.1)

** $p \leq 0.001$, * $p \leq 0.05$, + $p \leq 0.10$ compared to control group mean after adjustment for age, gender, education
† raw data were ln-transformed; geometric means are presented.

groups, the mean scores for these WAIS-R tests remained significantly lower for the lead TE cases.

On the standard neuropsychological tests (after adjustment for age, education, and gender differences), significant performance differences in the domains of executive function, attention, visuospatial abilities, short-term memory, and mood, as represented by the Trail-Making Test, Visual Reproductions, Verbal Paired Associate Learning (delayed recall), CVLT (delayed recall), and POMS were observed between solvent TE cases and controls. Additionally, the solvent TE subjects had significant deficits on the Finger Tapping test. Similarly, after controlling for age, education and gender, significant performance differences were observed between lead TE cases and controls on the Trail-Making Test, Wisconsin Card Sorting Test, CVLT

TABLE 4. Correlations between selected NES and traditional Neuropsychological tests

Function	Tests Compared	Correlation
Motor	Finger Tapping Preferred hand: NES2 vs. Traditional	0.59
	Finger Tapping Nonpreferred hand: NES2 vs. Traditional	0.53
Motor/Attention	CPT latency: NES3 (Animals) vs. NES2 (Letters)	0.65
	Digit Symbol Substitution: NES3 vs. WAIS-R	0.70
Attention/	NES3 Sequences A vs. Trail-Making Test A latency	0.44
Executive Function	NES3 Sequences B vs. Trail-Making Test B latency	0.60
Visual functioning /	NES3 Visual Span F vs. WAIS-R Vis. Rep. immed. recall	0.20
Memory	NES3 Visual Span B vs. WAIS-R Vis. Rep. immed. recall	0.35
	NES3 Visual Spans F vs. WAIS-R Vis. Rep. delayed recall	0.35
	NES3 Visual Spans; B vs. WAIS-R Vis. Rep. delayed recall	0.56
	NES2 Pattern Memory vs. WAIS-R Vis. Rep. immed. recall	0.14
	NES2 Pattern Memory vs. WAIS-R Vis. Rep. delayed recall	0.25
Verbal ability /	NES3 List Learning (sum 3 trials) vs. CVLT (sum trials 1-5)	0.40
Memory	NES3 List Learning delay vs. CVLT, short delay	0.38
	NES3 List Learning delay vs. CVLT, long delay	0.43
	NES3 List Learning delay vs. Verbal PAL diff. items immed. recall	0.44
	NES3 List Learning delay vs. Verbal PAL: diff. items delayed recall	0.51
Mood	NES2 Mood (range over subsets) vs. POMS (range over subscales)	0.76-0.81
Academic/ Verbal Knowledge	NES2 Vocabulary vs. WAIS-R Information	0.45

For correlations where $r \geq 0.25$, $p \leq 0.05$; where $r \geq 0.35$, $p \leq 0.001$.

(on learning trials and delayed recall), Verbal Paired Associate Learning (delayed recall), WAIS-R Digit Span, Digit- Symbol Substitution Test, Visual Reproductions, and POMS (tests of attention, learning and short-term memory, visuospatial abilities, and mood). Specifically on the POMS subscales, significant adverse mood effects were observed for tension, depression, anger, fatigue, and confusion for the solvent TE cases compared to controls and for all but depression for the lead TE cases.

Performance on the NES2/3 Tests

Results for the NES2/3 tests are reported in Table 3 grouped by functional domain. For most all test comparisons, as expected, the control group performed better than both patient groups after controlling for age, education and gender differences. Also, age effects on these tests were observed as expected, especially on tests involving latency outcomes.

Significant motor deficits were noted on fingertapping in solvent TE cases, but not lead TE cases. This result coincides with the results from the administration of the traditional Finger Tapping test in which the solvent but not the lead TE cases showed significant impairments. Expected attentional impairments associated with TE were observed on the CPT tests in latency (solvent TE) and number of non-response errors (both solvent and lead TE). For the Digit Symbol test, expected impairments for both solvent and lead TE were observed. On Sequences A&B, attentional and executive function impairments expected in association with solvent TE were revealed. Increased errors (of borderline significance) were observed with lead TE for the more complex Sequences B as was expected, but not for the simpler Sequences A test.

Pattern Memory and Visual Spans (backward) detected expected deficits in the solvent TE group, but not in the lead TE group. Performance on a verbal learning and memory task (List Learning) was impaired in the solvent TE group. The performances were impaired in the lead TE group for the trial after the interference list and delayed recognition task, but these were lesser performance impairments than expected given the extent of the deficits detected for this group on the CVLT test, the analogous traditional test.

The NES2 Vocabulary was significantly lower for the solvent cases (mean=16.9; SE=1.4) compared to that of controls (mean=20.2; SE=0.6) after adjustment for age, education, and gender differences.

Significant mood effects, as are frequently seen in both solvent and lead TE, were detected on the NES Mood scales, although the results were not as definitive as was detected with the POMS.

Correlations Between NES2/3 Tests and Standard Neuropsychological Tests

Moderate (0.40 to 0.59) to relatively high (above 0.60) correlations between the NES and standard neuropsychological test scores (Table 4) were found for the simple motor task of fingertapping and latency measures for several tests of involving attention (Digit Symbol, Sequences A & B). Comparisons of delayed recognition of verbal information between the NES List Learning test and two traditional tests (CVLT and Verbal Paired Associate Learning) were also moderately correlated (0.38-0.51). Five pairs of measures involving visual processing were poorly correlated (0.14-0.35). However, there was a moderate correlation between the NES backward Visual Span test and Delayed Recall on the Visual Reproductions test (0.56). The correlations between the NES Mood scales and POMS subscales were quite high, with the correlation between the fatigue scales being the highest at 0.81. The correlation between NES Vocabulary and WAIS-R Information was moderate within the solvent TE cases and controls.

DISCUSSION

Significant performance differences between TE cases and controls were noted on standard neuropsychological tests for all predicted domains, as expected; the one major exception was the domain involving motor skills. Contrary to the *a priori* hypotheses, solvent but not lead TE cases demonstrated significant motor difficulties on the neuropsychological Finger Tapping task.

Significant performance differences between the solvent TE cases and controls were observed in the predicted domains on the NES2/3 tests, with predicted deficits observed in tasks involving the domains of executive function, attention, visuospatial abilities, and memory, as well as mood. The NES2 and 3 tests were less sensitive to impairments in the lead TE cases. These results suggest that these NES 2 and 3 tests are able to detect effects observed with solvent TE, but are not quite as robust in detecting impaired functioning in lead TE. There may be several explanations for the relative insensitivity of the NES2/3 tests to detect predicted impairments in the lead TE group. First, although there were no differences in the severity of TE between the solvent and lead TE cases, a significant percentage of the lead TE cases were currently working and working in largely manual labor jobs. Therefore, it seems plausible to assume that their level of motor skills have been maintained through regular use and may explain the fingertapping results. Second, it is also possible that the neuropathological consequences present in solvent TE (white matter changes) affect performance on these NES 2/3 tests more profoundly than the neuropathological consequences of lead TE. A similar observation was made in the validation study of the NES2 on patients with MS and PD (White *et al.*, 1996) in which the NES2 tests were more sensitive to the cognitive and affective impairments associated with MS (white matter lesions), in contrast with the impairments associated with PD.

Overall, the correlations between traditional neuropsychological and NES 2/3 tests from the same functional domains were moderate. The computer and standard neuropsychological tests of motor skills were the most highly and consistently correlated tests (aside from mood), a finding similar to that seen in the earlier NES2 validation study with PD patients (Krengel *et al.*, 1996). In some instances, the newer response methods (using a pen indicator) appear to have enhanced the correlation, as the correlation between the NES3 Digit Symbol test and the analogous WAIS-R subtest was 0.70 in this study but was 0.45 with NES2 version. The magnitude of this correlation is probably limited by differences in the response in the NES3 (a simple pointing maneuver) and WAIS-R (a complex graphomotor component) variants of the test. Additionally, the latencies measured in the new NES3 Sequences test, compared to the Trail-Making Test from which it was based (a test involving simple and complex attention skills), were generally moderately correlated. The NES3 Sequences differs in two significant ways from the Trail-Making Test: in the way that errors are handled and in the absence of drawn lines that limit the number of circles to be scanned as the task progresses. These differences may represent improvements of the NES3 test over its traditional counterpart.

The less well-correlated pairs of computer-assisted and traditional neuropsychological tests included complex tracking of visually presented information (forward spans on the NES3 Visual Span test, NES2 Pattern Memory). There may be several explanations for these discrepancies. As described by Krengel *et al.* (1996), the different response requirements of the NES2 Pattern Memory task (multiple choice) and WMS Visual Reproductions (drawing from memory) may account for the low correlation between these test performances. In some instances, different levels of test difficulty are being compared: the NES3 List Learning task involves simpler processing skills (recognition of pictures of 12 verbally presented nouns) compared to the learning trials of the CVLT (verbal recall of 16 words). In addition, some low correlations may be due to imprecision in some of the NES3 measures. For example, in this implementation the NES3 Sequence A task included a verbal prompt to respond quickly after a relatively short non-response time by the subject, which may have distracted some subjects and reduced the Sequence A vs. Trails A correlation. Also, the NES3 Visual Span Forward did not include sufficient practice in this implementation, and some subjects with initial slight confusion obtained a minimum score.

Interestingly, lower NES2 vocabulary scores were observed in the solvent TE cases compared to controls, although there were no significant differences in education level and WAIS-R Information. This raises the issue of whether the NES Vocabulary test is useful as a measure of native academic abilities ('hold' test) in studies of neurotoxicant effects. Several studies report that the results of vocabulary tests (NES2 version and WAIS-R Vocabulary) are related to or influenced by exposure to solvents (Bolle *et al.*, 1996; Michelsen and Lundberg, 1996; Viaene *et al.* 1998) and lead (Baker *et al.*, 1984; Stewart *et al.*, 1999), or other factors (such as increased overtime work; Proctor *et al.*, 1996). In the latter study, it was hypothesized that the test's administration modality (i.e., computer presentation of a series of multiple choice questions) may affect its ability to exclusively assess native academic abilities and instead represents a test additionally involving attention. Indeed, the correlation between NES Vocabulary and WAIS-R Information was only moderate (r=0.45) within the solvent TE cases and controls.

It is recognized that one limitation of this study is the relatively small sample of TE cases. Every effort was made to recruit eligible cases. However, fewer individuals who meet these stringent diagnostic criteria are being referred currently to Boston area clinics. By including a larger sample of control subjects, we were able to maintain adequate power to detect clinically significant differences (greater than 15-20%) in test performances between groups. In this study we were able to assess the impact of malingering on test performance (via controlling for TOMM scores) and found that it did not significantly impact test performances. However, several other factors that might explain group differences (i.e., socioeconomic status, familiarity with computers) were not examined because complete information was not available.

In conclusion, the NES3 tests created to better reflect the modalities of standard neuropsychological tests represent a step forward in detecting differences in predicted functional domains in diagnosed TE cases compared to controls. This battery of selected NES2 and NES3 tests adequately measures domain-specific performance deficits and provides supportive evidence that these new tests may be useful as part of a screening battery to potentially identify individuals with significant CNS impairments due to solvent exposure, and to a lesser extent due to lead exposure. As computer usage and visual presentation of information become more a part of our individual lives, further study of the impact that familiarity with computers has on NES3 test performances in relationship with levels of pre-morbid intellectual abilities as assessed by WAIS-R subtests or the NES Vocabulary test is warranted. Continued study to address potentially better test assessment methods for native academic ability in toxicant-exposed groups and follow-up in other groups of lead-exposed persons is planned.

This experience with these NES2/3 tests has already led to improvements in the NES3 testing system. The NES2 Finger Tapping and Pattern Memory tests have been implemented in the NES3 hardware/software environment. Changes to the initial instructions of Sequence A and Visual Span Forward have been implemented. Computer-assisted versions of several tests with interviewer entry of responses to more closely mimic traditional neuropsychological tests such as list learning tasks have also been implemented. Development and study of additional administration and response modalities improvements to the additional NES3 tests is ongoing (White *et al.*, 1999) and NES3 test validation studies are continuing on well-defined patient groups (with specific neurologic and/or psychiatric disorders).

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