Final Performance Report: Validity of Computerized Testing in Toxic Encephalopathy

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- White RF, Letz R, James K, Marans K, Vasterling J, DeLaney R, Krengel M, Rose F, **Proctor SP**. NES3: A computer-based system for clinical neuropsychological assessment.

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II. **Proctor SP**, Letz R, White RF. Validity of a computer-assisted neurobehavioral test battery in toxicant encephalopathy. Manuscript submitted to NeuroToxicology.

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List of Abbreviations (listed alphabetically):

ANCOVA	Analysis of Covariance
CNS	Central nervous system
CPT	Continuous Performance Test
CVLT	California Verbal Learning Test
FL	focal cortical lesions
MS	Multiple Sclerosis
NES	Neurobehavioral Evaluation System
PD	Parkinson's Disease
POMS	Profile of Mood States
SE	standard error
TE	toxicant encephalopathy
TOMM	Test of Memory Malingering
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WMS or WMS-R	Wechsler Memory Scale (-Revised)

Abstract

The computer-assisted Neurobehavioral Evaluation System (NES) test battery was developed for the purpose of detecting brain dysfunction resulting from exposure to neurotoxicants. The NES tests are derived from standard neuropsychological tests that have been well characterized in terms of brain-behavior relationships. However, as the NES tests are designed for administration via a computer, they differ in the administration and response modalities from the traditional tests. Previous studies have shown that NES tests provide an efficient method of measuring neurobehavioral effects in epidemiological studies and that a number of the tests are sensitive to exposure to neurotoxicants. A recent study by White et al. (1996) has examined the validity of NES2 tests in patients with known brain damage (i.e., patients with multiple sclerosis (MS), Parkinson's Disease (PD), and focal cortical lesions (FL)) and found that the test battery was good at identifying behavioral impairment in subjects with neuropathology involving the white matter of the brain (subjects with MS), but not the basal ganglia (subjects with PD). The researchers suggested that the NES2 test battery lacked in tasks that were sensitive to deficits in complex attention, visuospatial function, verbal encoding known to be associated with PD and they concluded that an expansion of the NES battery be initiated to improve its effectiveness in detecting brain damage in patients with clinical disease. For this reason, additional computer-based tasks that more closely approximate the stimulus and response characteristics of traditional neuropsychological tests with known sensitivity to basal ganglia and other types of cerebral dysfunction have been developed. These newer NES3 tests included List Learning, Visual Spans, Sequences, Digit Symbol, and List Learning Delayed Recognition. These new tasks were designed for administration via a pen-based laptop computer and available for test administration in the fall of 1996.

The purpose of this study was to assess the validity of the updated NES test battery in patients diagnosed with toxicant encephalopathy (TE) either due to exposure to lead or to mixed solvents to improve the interpretation of NES test performance in research studies and clinical evaluations examining central nervous system (CNS) function and neurotoxicant exposure. Performance on a hybrid NES2/3 test battery, consisting of several NES2 and the above listed five NES3 tests, by persons diagnosed with toxicant encephalopathy (TE) was compared to that of controls to determine if performance differences reflect a priori hypothesized brain-behavior relationships. Performance on the NES tests also was correlated with performance on the analogous traditional tests.

Significant performance differences between the TE case groups and controls were observed in the predicted domains on the NES test battery, thus confirming the sensitivity of the NES2/3 test battery to CNS dysfunction. The results indicating differences between TE cases and controls were observed to be more robust for solvent TE cases with predicted deficits observed in tasks involving motor, attention and tracking, visuospatial, and memory abilities, as well as mood. Overall, moderate correlations between standard and NES tests from the same functional domains were observed.

In conclusion, these results suggest that the updated NES2/3 test battery does identify clinically significant performance deficits in the functional domains found to be impaired in diagnosed TE patients via traditional clinical neuropsychological tests. Expansion of the NES battery has continued; currently a complete NES3 battery (made up of 17 tests) is available by

contacting neurobehav@mediaone.net. [1] Further research is either planned or is ongoing to validate the complete NES3 battery in a clinical neurological population and to examine is effectiveness as a screening battery for the assessment of toxicant-induced cognitive impairments.

Significant Findings

The primary findings of this study are that expected patterns of performance impairments in solvent and lead encephalopathy patients are observed on specific subtests of the updated NES2/3 test battery compared to controls (*Specific Aims #1 and #2*). The data collected indicate that the control subjects perform better overall than the two TE groups, confirming that the hybrid NES2/3 battery (consisting of several NES2 and the above listed five NES3 tests) is sensitive to CNS pathology in these patients groups. However, the results suggest that the sensitivity of the battery differed for the two patient groups with more robust results observed for the solvent TE cases compared to controls. For the solvent TE patients, significant performance deficits were observed in tests measuring motor abilities, attention and executive function, visuospatial skills, verbal and visual memory, and affect. However, fewer NES tests revealed significant impairments in the lead TE group compared to controls, even though significant differences were noted when comparing performances on standard tests between lead TE cases and controls. For example, both the solvent and lead TE cases performed significantly worse on a number of the subtests of the California Verbal Learning Test (CVLT), but few significant performance differences were noted for the lead TE cases on the NES3 test measuring similar functional skills, i.e., List Learning.

Most performances on the computer-assisted NES2/3 test battery were moderately correlated with performance on the associated standard neuropsychological tests (*Specific Aim #3*) with correlation coefficients ranging overall between from 0.25 to 0.81. The computer and standard tests of motor skills and affect/mood were the most highly and consistently correlated tests, 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 Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit-Symbol Substitution Test was 0.70 in this study but was 0.45 with NES2 version. 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 less well-correlated pairs of tests included complex tracking of visually presented information (forward spans on the NES3 Visual Span test, NES2 Pattern Memory) and the learning trials of the NES3 List Learning test. There may be several explanations for these discrepancies. Similar to that described by Krengel et al. (1996), the different response requirements of the NES2 Pattern Memory task (multiple choice) and Wechsler Memory Scale (WMS) Visual Reproductions (drawing from memory) may account for the low correlation between these test performances. Additionally, different levels of test difficulty are being compared as the NES3 Sequences A and the List Learning tasks involve

[1] The website address for Neurobehavioral Systems, Inc. is http://people.atl.mediaone.net/neurobehav.

simpler processing skills compared to Trails A and the 16-word learning trials of the CVLT, respectively.

Usefulness of Findings

The findings indicate the updated NES2/3 test battery examined in this study is sensitive to CNS dysfunction seen in solvent and lead encephalopathy patients, with more robust results observed in persons with solvent TE. Thus, these findings provide additional supportive evidence that the NES test battery is useful in studies examining the CNS effects of neurotoxicant exposures. Further expansion of the NES battery to include a wider variety of tests with increased sensitivity will continue to extend the battery's usefulness particularly to detect subtle brain dysfunction secondary to neurotoxicant exposure. Indeed, a complete NES3 test battery has been finalized (since the onset of this study) and is now available for ongoing studies examining the validity and clinical utility. It is anticipated that this new computer-assisted NES3 battery represents the needed improvement to the breadth and sensitivity of the NES2/3 battery, although studies of its validity in clinical populations and a determination of its use as a screening instrument are currently ongoing.

Study Report and Conclusions

A. Background and Significance

Neurotoxic disorders rank among the ten leading work-related diseases and injuries in the United States (CDC, 1986) and almost one third of the standards for workplace chemicals recommended by the American Conference of Governmental Industrial Hygienists are based on neurotoxic effects (Anger, 1984). Thus, nervous system dysfunction secondary to chemical exposure is of considerable public health significance. In recent years, the inclusion of more sophisticated measures of neurobehavioral outcomes from the field of neuropsychology (Lezak, 1995; Grant and Adams, 1986) and exposure assessment techniques in occupational and environmental epidemiologic studies has lead to increased recognition of central nervous system (CNS) outcomes of toxic exposures (White et al., 1992).

It was the epidemiologic study of workers exposed chronically to carbon disulfide (CS_2), by Hanninen et al. (1971) that first characterized chronic toxic encephalopathy and first revealed that the measurement of neuropsychiatric effects may be more sensitive than medical examinations in detecting early, chronic effects of toxicant exposure. Even with no clinical signs of poisoning, an exposed group of workers scored significantly lower on standardized clinical tests that measured speed, vigilance, and manual dexterity compared to non-exposed workers. Those workers with clinical signs such as nerve conduction slowing performed even worse. The "latent" poisoning described by Hanninen, i.e. subjects demonstrating psychological impairment who had not been diagnosed with a chemical intoxication, has since been referred to as "subclinical encephalopathy" (Baker et al., 1985a; Baker and White, 1985b; White and Feldman, 1987). A diagnostic system has been developed to differentiate toxic encephalopathy on the basis of the permanency and severity of behavioral change (Baker and White, 1985b; Johnson, 1987; White et al., 1992). The disorder may be acute or chronic, but generally follows a progression of severity and permanency, i.e. the higher the exposure dose and the longer the exposure duration, the more impairments observed and the more likely they are irreversible. A

clinical diagnosis of toxic encephalopathy is based on a thorough neuropsychological evaluation by a trained neuropsychologist which includes an interview, review of the individual's exposure and medical history, and extensive neuropsychological testing with an appropriately designed clinical test battery (White and Proctor, 1992). In this study, a documented history of exposure was a requirement for all cases. This information was most often obtained and confirmed by the referring occupational health physicians.

In epidemiologic studies, one of the limitations to employing clinical neuropsychological tests is that they are time consuming and require a number of trained personnel to administer the tests (Baker et al., 1985c). Hence, the development of several computer-assisted systems of administering a battery of neurobehavioral tests has occurred (e.g., Baker et al., 1985c; Camerino 1985). The Neurobehavioral Evaluation System (NES) is one computer-assisted test battery that has undergone an extensive process of validation throughout the progression of its development. Specific tests in the NES have been shown to be sensitive to exposure to toluene, nitrous oxide, and alcohol in acute, experimental studies (Greenberg et al., 1985; Mahoney et al., 1988; Hooisma et al., 1988; Echeverria et al., 1989) and in field studies, specific subtests of the battery discriminated an occupational solvent-exposed group from non-exposed controls (e.g. Fidler et al., 1987a, Baker et al,. 1988).

There are several other important criteria, however, besides sensitivity to exposure to neurotoxicants to consider when selecting a test battery for epidemiologic studies (White and Proctor, 1992). Two of these criteria include sensitivity to CNS dysfunction and ability to examine theoretical constructs. These criteria require that tasks included in a battery be known to be sensitive to brain damage and be able to test specific brain-behavior relationships. In the case of the NES battery, whose tests are adapted from standard neuropsychological tests, it follows that the validation process would include comparing NES test performance to that on associated standard ones as well as testing patients with diagnosed cerebral diseases to determine if predicted functional deficits are observed also with the NES. In prior studies, the NES scores on several subtests have been shown to correlate moderately well ($r=0.42$-0.76) with scores on standard clinical neuropsychological tests (Baker et al., 1985d). A recent study has assessed the relationship between performance on the NES2 test battery and specific types of brain damage in neurological patients with specific cerebral disorders (e.g. Parkinson's Disease, multiple sclerosis, and focal lesion patients (PI: RF White, PhD; NIOSH grant # 1R01OH02767). Results indicated that some existing NES2 tests were relatively insensitive to deficits in some cognitive domains (i.e. executive function, visuospatial ability, and memory) (White et al., 1996; Krengel et al., 1996).

The goal of this study was to examine whether predicted functional deficits observed in central nervous system damage due to neurotoxicant exposure (based on standard neuropsychological tests) are observed by testing patients with diagnosed toxicant encephalopathy with the NES2/3 test battery.

B. Specific Aims

The NES is a battery of computer-administered tests designed for use in epidemiologic investigations of the neurobehavioral effects of suspected or known chronic environmental and/or occupational neurotoxicant exposure (Baker et al., 1985d; Letz and Baker 1986). The NES is based on standard neuropsychological tests well characterized in terms of brain-behavior relationships. To date, performance on specific NES 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 exposure to solvents, pesticides, and

mercury exposure in field studies of exposed groups (Baker et al., 1988; Fidler et al., 1987a; Albers et al., 1987; Hrychorczuk et al., 1987; Letz et al., 1990; Spurgeon et al., 1992; Langworth et al., 1992; Steenland et al., 1994). However, although the NES tests were designed to detect subclinical group effects rather than identify clinical cases, the NES has not been studied in persons with a clinical diagnosis of toxicant encephalopathy (TE) to determine if the specific test sensitivity observed in prior exposure studies is indicative of subtle toxicant encephalopathy.

The present study investigated the validity of the NES2/3 test battery in patients with diagnosed toxic encephalopathy based on World Health Organization criteria (Johnson, 1987). Subjects were asked to complete the NES2/3 test battery as well as some selected standard neuropsychological tests (total time 4 hours).

Specifically, there were three major aims (and a fourth more exploratory) to the investigation:

- To determine if hypotheses regarding expected patterns of performance in solvent encephalopathy are observed on specific subtests of the NES in patients diagnosed with solvent encephalopathy compared to controls.
- To determine if hypotheses regarding expected patterns of performance in lead encephalopathy are observed on specific subtests of the NES in patients diagnosed with lead encephalopathy compared to controls.
- To compare performances on computerized tests with performance on the associated standard neuropsychological tests in both patients and controls.
- To determine if the impaired performances associated with lead and solvent encephalopathy are different as hypothesized and whether one can discriminate between the lead and solvent encephalopathy groups based on NES test performance.

Related to the specific aims of the study, the present study explored several hypotheses concerning the sensitivity of NES subtests to detect hypothesized brain-behavior functional deficits in patients diagnosed with toxic encephalopathy. It is predicted that, when compared to controls, patients with toxic encephalopathy would score poorly on specific subtests of the NES. Also, it was hypothesized that the pattern of functional impairments observed in patients with solvent encephalopathy will be somewhat different than that observed in patients with lead encephalopathy.

Solvent encephalopathy. Patients with solvent encephalopathy have shown deficits in executive function (cognitive tracking and flexibility) and attention, visuospatial abilities, short-term memory, and mood (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 Sort Test, Digit-Symbol Substitution Test, Delayed Recognition Span Test, Visual Reproductions, and Profile of Mood States (POMS) (Echeverria et al., 1991; 1995; White et al., 1992; Anger 1990) compared with non- (or less) exposed workers. It was predicted that, when compared to controls, the patients with solvent encephalopathy would score more poorly on specific subtests of the NES that were designed to test the same functional domains as the traditional tests (e.g., Continuous Performance Test, Pattern Memory, List Learning and delayed recall, Digit Symbol Test, and Mood scales).

Lead encephalopathy. Patients with lead encephalopathy have shown deficits in attention, motor skills, visuospatial abilities, short-term memory, verbal ability, and mood (White et al., 1992). In epidemiological studies of lead-exposed workers employing standard neuropsychological tests, impaired performances have been observed in Santa Ana, backwards

Digit Span, Digit- Symbol Substitution Test, Visual Reproductions, Embedded Figures, Paired Associate Learning, WAIS-R Vocabulary Test, WAIS-R Similarities, and POMS (Hanninen et al., 1978; Baker et al., 1984; Yokoyama et al. 1988; Anger 1990) compared with non- (or less) exposed workers. Thus, it was predicted that, when compared to controls, the patients with lead encephalopathy will score more poorly on specific subtests of the NES (e.g., Hand-Eye Coordination, Finger Tapping, Vocabulary, List Learning and delayed recall, Digit Symbol Test, and Mood scales).

There is evidence that suggests that a somewhat different pattern of functional deficits may be demonstrated in solvent encephalopathy compared to lead encephalopathy (Anger, 1990). It was hypothesized that performance on tests of attention, visual memory, language skills and specific mood states will discriminate between lead and solvent encephalopathy. However, due to the revised study design because of fewer number of solvent and lead TE patients available for recruitment (see further description below in **Methods section**), we were not able to examine the more exploratory specific aim and hypothesis about whether solvent and lead TE patients demonstrate a clear difference in their patterns of functional deficits.

C. Methods and Procedures

This study was conducted using a case-control design. 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 demographic characteristics and questions about medical and occupational histories. Then, the NES2/3 test battery and set of traditional neuropsychological tests (see below for description) were administered to each subject individually by a qualified examiner trained appropriately in all test administration procedures. The examiner was blind to whether the subject was a case or control.

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 being diagnosed with solvent and lead encephalopathy that were being following at the university 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):

i. Evidence of toxicant exposure(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. For most of the lead TE cases, objective evidence of elevated exposure from physiological measures was available. A documented history of exposure in the medical records (obtained and confirmed by the referring occupational health physicians) was a requirement for all cases.

ii. 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 the prior clinical neuropsychological evaluation. Performance

deficits on an appropriately designed clinical neuropsychological test battery (White and Proctor, 1992), in a pattern which meets the definition of mild to severe toxicant encephalopathy (Baker et al., 1985a; White et al., 1992; White and Proctor, 1997), were evaluated to identify cases.

iii. 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 as the reported chemical exposure or could possibly modify the chemical's effect, particularly with solvents (Sato et al., 1980; Katz, 1985). Also, premorbid cognitive deficits (such as occur in persons with residual developmental learning disabilities) and psychiatric disorders (such as personality disorders and affective/anxiety disorders) (White et al., 1992) were examined.

One of the Co-Investigators (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 others in referred patients. Furthermore, we focused on locating and recruiting TE cases that had either exclusively a mixed solvent or a lead exposure history. For clearer interpretation of results, we did not recruit TE cases with overlapping neurotoxicant exposure histories, that is, persons who had exposure to other neurotoxicants such as pesticides, carbon monoxide, and other metals. A total of nine solvent TE and eleven lead TE cases met the above criteria and consented to participate in the study. All cases had chronic exposure to either of these neurotoxicant groups. Some of the solvent TE cases were exposed via hobbies or non-work 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 to exclude persons with CNS or psychiatric disorders that affect cognitive function or ability to work (e.g., closed head injury, epilepsy, stroke, bipolar disorder). Also, potential controls were screened regarding past environmental and occupational exposures and excluded if they had significant toxicant exposures in the past. 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 determined that although not usually able to provide an absolute estimate of past exposure, information so collected can provide useful relative information about exposure. 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 for screening purposes.

A total of 50 control subjects were recruited and 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.

As mentioned above, the number of solvent and lead TE cases who completed the study was less than originally planned. This was due to several factors: fewer numbers of new TE cases being diagnosed and followed in Boston area occupational clinics and the relatively stringent diagnostic criteria that excluded persons with multiple neurotoxicant exposures and

comorbid diagnoses. For example, out of the 146 persons referred to Dr. White's clinic between 1993-98, only 11 were diagnosed with either solvent or lead encephalopathy (the majority of recent patients being referred to Dr. White's clinic have been given a psychiatric diagnosis or multiple chemical sensitivity). To date, one has died, two refused to participate, three were not located in order to contact, and one lives out of the New England area (Iowa). Four of them participated in this study. Power calculations indicate that the study (given the above smaller sample sizes: 10 patients and 50 controls) does have adequate power (≥80%) to detect differences in the NES subtest means in the range of 15-21% of normal values. A difference of 20% of normal is generally considered to be of clinical neurological significance. To acknowledge the multiple testing issue, power calculations are based on the two-tailed alpha = 0.01 significance level.

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 collectively in this study as the NES2/3 test battery), and a traditional neuropsychological test battery. A list of the NES2/3 tests and the traditional tests is presented in **Table 1**.

To address several of the concerns raised by the earlier validation studies, the five newer NES3 tests were designed and made available in 1996 (Letz et al., 1996) for administration on a pen-based laptop computer with audio commands using digitized speech. (The original administration formats of this neurobehavioral test battery (referred to as NES or NES2) 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), the presentation and administration of neurobehavioral tests can now be more easily updated to more appropriate modalities thus allowing the integration of new tests closer in design to the traditional tests.

The NES2/3 battery used in this study was presented on a pen-based laptop computer, operating with Windows 3.1 software, with an external keyboard [2] and took about 1 hour to complete; the traditional test battery took subjects 75-90 minutes to complete.

NES2/3 Battery:

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

[2] When this study was designed, it was anticipated that the pen-based laptop computer design would be continued by IBM and Compaq computers. Thus, Dr. Letz spent considerable time in developing the five newer NES3 tests in order to be installed onto two laptop computers available and/or purchased for this study, although only the Compaq computer was compatible with the joystick needed for the Hand-Eye Coordination test. However, in the fall of 1996, Dr. Rick Letz was informed that pen-based laptops were not going to continue to be supported by IBM or Compaq, and thus, he felt that he could not easily put all the proposed new NES3 tests on the laptop set-up, as he had originally thought in 1995 when my grant was funded. He decided to switch and work to put the NES3 test battery on a desktop PC environment (operating under Windows 95 and with a Touch Screen monitor). However, to do that he estimated would take him approximately 10 more months or until early 1998. At that point, I decided to go ahead with my project and use the NES2/3 test battery as it was. (The complete NES3 battery, operating under Windows 95 on a desk top PC, is now available through Dr. Letz at neurobehav@mediaone.net.)

Also, during the course of this project, the Compaq laptop computer was stolen so we were no longer able to administer the Hand-Eye Coordination test.

(trials #1-3). Then, a single interference trial is given with a new orally presented 12-item list (trial #4). The number of items correctly answered for trials #2-4 were analyzed, using trial #1 as a practice trial. 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 is a computerized version of the Trail-Making Test in which a subject alternates between number and letter sequences. After a practice trial, where 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 where 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.

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 trial, 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 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 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 trials (an additional trial is given for practice and is not scored).

Traditional Test Battery:

The following tests were included in the traditional 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 and it has been well validated in numerous neurologic patient groups as well as in normal control populations who were asked to feign 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 and computer-assisted tests considered to measure cognitive function in the same behavioral domain were determined.

D. Results

Demographic Data and Traditional Neuropsychological Tests. 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), TOMM, and NES Vocabulary. 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 the lower education levels. However, after adjustment for age, education, and gender differences between the groups, the mean scores for these WAIS-R tests remained significantly lower for the lead TE cases. Additionally, NES 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.

On traditional neuropsychological tests (after adjustment for age, education, and gender differences), significant performance differences on Trail-Making Test, Finger Tapping test, Verbal Paired Associate Learning, and CVLT were observed between solvent TE cases and controls (**Table 3**). Similarly, after controlling for age, education and gender, performance differences were observed between lead TE cases and controls on WAIS-R Digit Span, WMS-R Visual Spans and Visual Reproductions, Trail-Making Test, Wisconsin Card Sorting Test, and CVLT. On the POMS, 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 Test Battery. Results for the NES2/3 tests are reported in **Table 4** grouped by neuropsychological function or 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. 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, that combines a timed visuospatial task with an attentional component, 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, delayed recognition of the List Learning task, was impaired in the solvent TE group. The performances were impaired in the lead TE group for the last test trial 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.

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 Traditional Neuropsychological Tests. Moderate (0.40 to 0.59) to relatively high (above 0.60) correlations between the NES and standard neuropsychological test scores (**Table 5**) 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 only modestly correlated (0.14-0.35). However, there was a moderate correlation between the NES backward visual span test and the 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.

E. Discussion

Significant performance differences between cases and controls were observed in predicted domains on NES test battery, but were more robust in solvent TE cases with predicted deficits observed in tasks involving motor, attentional and tracking, visuospatial, and memory abilities, as well as mood. Moreover, significant performance differences between TE cases and controls were noted on standard neuropsychological tests in predicted domains, as expected. Interestingly, lower NES Vocabulary scores were observed in the solvent TE cases compared to controls, although there were no 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 intellectual ability ('hold' test) in studies of neurotoxicant effects. This question has been suggested by several studies that report that the results of vocabulary tests are influenced by solvent (Bolle et al., 1996; Michelsen and Lundberg, 1996; Viaene et al. 1998) and lead exposure (Baker et al., 1984). Similarly, performance on the NES Vocabulary test has been associated with increased overtime work, after controlling for other covariates (Proctor et al., 1996). 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 rather 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.

Overall, the correlations between standard and NES tests from the same functional domains were moderate. The computer and standard 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. 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 less well-correlated pairs of tests included complex tracking of visually presented information (forward spans on the NES3 Visual span test, NES2 Pattern Memory) and the learning trials of the NES List Learning test. There may be several explanations for these discrepancies. Similar to that

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. Additionally, different levels of test difficulty are being compared as the NES3 Sequences A and the List Learning tasks involve simpler processing skills compared to Trails A and the 16-word learning trials of the CVLT.

It is recognized that one limitation of this study is the relatively small sample of TE cases. However, we did have adequate power to detect clinically significant differences (greater than 15-20%) in test performances between case and control 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 group differences in test performances. Familiarity with computers was also examined when comparing the solvent TE cases to controls, but it did not affect the results presented (67% of the solvent TE and 82% of the controls reported familiarity with computers). It is possible that other factors not addressed could potentially accountable for group differences (i.e., socioeconomic status).

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 NES 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 computer-based test assessment methods for native intellectual ability is planned. As part of a follow-up project, subjects will be given a short battery of NES2/3 tests and all will undergo XRF to measure bone lead (supervised by Howard Hu, MD, ScD) in order to examine whether a dose-response relationship between bone lead and NES2/3 test performance can be observed. (See the abstract describing the follow-up project on page 18 of this Report.)

F. Conclusions

In conclusion, the new 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. The hybrid test battery of selected NES2 and newer NES3 tests used in this study 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 or lead exposure.

Development and study of the newer administration and response modalities in conjunction with additional NES3 tests is ongoing (White et al., 1999). Thus, NES3 validation studies are continuing on various patient groups (such as those with specific neurologic and/or psychiatric disorders).

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Publications

Presentations:

Proctor SP, White RF, Letz R, James K, Marans K, Lindem K, Diamond R. NES3: Validity studies in toxicant-exposed subjects. Presented at the Seventh International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health, Stockholm, Sweden; June 1999.

White RF, Letz R, James K, Marans K, Vasterling J, DeLaney R, Krengel M, Rose F, **Proctor SP**. NES3: A computer-based system for clinical neuropsychological assessment. Presented at the Seventh International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health, Stockholm, Sweden; June 1999.

Manuscripts (submitted):

Proctor SP, Letz R, White RF. Validity of a computer-assisted neurobehavioral test battery in toxicant encephalopathy. Manuscript submitted to NeuroToxicology.

Follow-up project:

Boston University Faculty Research Development Grant: ***Evaluation of a Computer-Assisted Neurobehavioral 'Hold' Test as a Measure Basic Academic Ability.*** PI: Susan P. Proctor, DSc; project period: 1/1/2000-12/31/2000; $7,500.

Abstract

Having an appropriate and valid neurobehavioral test battery is essential in order to examine the cognitive effects of chemical exposures in occupational and environmental settings (White and Proctor, 1992). Recent work by the Principal Investigator (Proctor et al., manuscript submitted) has addressed the validity of a computer-assisted neurobehavioral test battery, the Neurobehavioral Evaluation System (NES; Letz and Baker, 1986), and its ability to detect differences in test performance between patients diagnosed with toxicant encephalopathy (resulting from lead or solvent exposure) and controls. One criterion for neurobehavioral test batteries (whether the battery consists of traditional or computer-assisted tests) is that they include a 'hold' test to provide an estimate of pre-morbid abilities (White and Proctor, 1992; Lezak, 1995). However, results from several recent epidemiological studies suggest that a vocabulary test may not be an adequate measure of native intellectual abilities in persons with significant neurotoxicant exposure (Bolle et al., 1996; Michelsen and Lundberg, 1996; Viaene et al. 1998). This conclusion was also suggested in the recent study by the PI as significantly lower NES vocabulary scores were observed in patients diagnosed with solvent encephalopathy compared to controls, but no differences in education level and WAIS-R Information scores were noted. There are several potential explanations for this observation: basic verbal abilities are affected by neurotoxicant exposure; or other covariates not being controlled for could explain the difference (such as motivation levels). Another hypothesis, specifically pertaining to the computer-oriented vocabulary test, is 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 rather represents a test additionally involving attention (a domain affected by neurotoxicant exposures).

The primary objective of the proposed study is to examine the utility of the NES Vocabulary test as a 'hold' test by administering a brief (50 minutes) test battery that will additionally include two traditional 'hold' tests (WAIS-R Information and Vocabulary) and a test of motivation. Subjects for this study will also have X-ray fluorescence (XRF) measurement of bone lead (Hu, 1998) so that we can address whether a dose-response relationship between bone and blood lead and cognitive test outcomes is present.

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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 (S's)*: latency; # false positives & non-responses (NES2) CPT (Animals): latency; # false positives & non-responses (NES3) Digit Symbol: latency (NES3)	WAIS-R Digit-Symbol Substitution Test (Wechsler, 1981) WAIS-R Digit Spans (Wechsler, 1981)
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: 3 learning trials, delayed recognition (NES3)	WMS Verbal Paired Associate 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

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)
NES Vocabulary	15.5 (6.9)	- -	20.5 (3.6)
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%

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

TABLE 3. RESULTS FROM COMPUTER-ASSISTED TEST BATTERY (Adjusted means (SE)).

	Solvent cases	Lead cases	Controls
MOTOR			
Finger Tapping:			
Preferred hand	111.4 (8.4) **	152.5 (7.5)	158.9 (3.5)
Nonpreferred hand	104.8 (6.7) **	143.4 (6.0)	147.8 (2.8)
ATTENTION			
Continuous Performance (S's):			
mean latency	510.2 (25.7) *	- -	434.1 (8.6)
number of false positives #	0.84 (0.31)	- -	0.65 (0.09)
number of non-responses #	1.1 (0.3) +	- -	0.24 (0.09)
Continuous Performance (Animals):			
mean latency	578.0 (19.1)	572.5 (17.0)	553.3 (7.9)
number of false positives #	0.81 (0.22)	1.2 (0.20) +	0.56 (0.09)
number of non-responses #	1.3 (0.2) **	0.72 (0.19) *	0.08 (0.09)
Digit Symbol:			
latency	73.1 (3.3) **	65.6 (2.9) *	59.2 (1.4)
ATTENTION/EXECUTIVE FUNCTION			
Sequences A&B:			
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 (0.17) +	0.30 (0.07)
VISUOSPATIAL FUNCTION/MEMORY			
Pattern Memory:			
number 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:			
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:			
trial 2: number correct	10.3 (0.4)**	11.7 (0.4)	11.8 (0.2)
trial 3: number correct	10.4 (0.4)**	11.6 (0.3)	12.0 (0.2)
trial 4: number correct	8.5 (0.6)**	9.6 (0.5)*	11.0 (0.2)
delayed recall: number correct	9.9 (0.4)**	10.7 (0.4) +	11.6 (0.2)
MOOD			
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)

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

TABLE 4. RESULTS FROM THE STANDARD CLINICAL BATTERY (Adjusted means (SE)).

	Solvent cases	Lead cases	Controls
MOTOR			
Finger Tapping:			
Preferred hand	43.0 (3.1) *	47.1 (2.7)	50.2 (1.3)
Nonpreferred hand	40.0 (2.3) +	42.9 (2.1)	44.5 (0.96)
ATTENTION			
WAIS-R Symbol-Digit Substitution	47.4 (4.3)	48.2 (3.4)	53.7 (1.6)
WAIS-R Digit Span	14.3 (1.4)	13.6 (1.3) *	16.6 (0.59)
ATTENTION/EXECUTIVE FUNCTION			
Trail Making Test:			
A, latency	35.0 (3.7)	34.8 (3.3)	30.3 (1.5)
A, errors #	0.03 (0.09)	0.28 (0.08) *	0.06 (0.04)
B, latency	98.3 (12.5) +	96.3 (11.2) +	73.5 (5.2)
B, errors #	0.19 (0.16)	1.35 (0.14) **	0.37 (0.06)
Wisconsin Card Sorting Test:			
%-ile (# correct/trials)	71.8 (4.4)	69.3 (3.9) +	77.1 (1.8)
VISUOSPATIAL FUNCTION/MEMORY			
WMS Visual Reproductions:			
Immediate recall, %-ile	86.4 (4.7)	58.6 (5.2) **	83.1 (2.0)
Delayed recall, %-ile	76.3 (7.3)	52.3 (8.1) *	77.7 (3.0)
WMS-R Visual Spans:			
Forward span	5.5 (0.43)	4.7 (0.56) *	6.0 (0.16)
Backward span	5.2 (0.32)	4.4 (0.42) *	5.5 (0.12)
VERBAL MEMORY			
Verbal paired Associate Learning:			
Easy items, immediate recall	10.8 (0.5)	10.5 (0.4)	11.2 (0.2)
Easy items, delayed recall	4.0 (0.06)	4.0 (0.05)	4.0 (0.03)
Difficult items, immed. recall	5.4 (1.1) +	5.4 (0.89) *	7.5 (0.42)
Difficult items, delayed recall	2.6 (0.36) *	3.0 (0.31)	3.5 (0.14)
California Verbal Learning Test:			
Trial 2, # correct	8.3 (0.78) +	8.3 (0.69) +	9.8 (0.32)
Trial 3, # correct	9.5 (0.82) *	9.1 (0.73) *	11.5 (0.34)
Trial 4, # correct	10.4 (0.86) +	10.1 (0.77) *	12.1 (0.36)
Trial 5, # correct	11.1 (0.79)	10.6 (0.71) *	12.4 (0.33)
Tues. list, # correct	6.2 (0.60)	4.7 (0.54) **	6.9 (0.25)
Short, delayed recall	9.3 (0.96)	8.3 (0.85) *	10.9 (0.40)
Long, delayed recall	9.3 (0.96) *	8.4 (0.86) *	11.3 (0.40)
MOOD			
Tension	46.9 (2.5) *	45.5 (2.1) *	37.9 (1.0)
Depression	45.1 (2.0) *	41.5 (1.7) +	38.3 (0.78)
Anger	49.2 (2.8) *	48.2 (2.4) *	42.9 (1.1)
Fatigue	54.9 (2.9) *	52.4 (2.5) *	46.2 (1.1)
Confusion	49.2 (2.5) *	47.8 (2.1) *	40.9 (0.97)

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

TABLE 5. CORRELATIONS BETWEEN SELECTED NES AND TRADITIONAL TESTS

FUNCTION	NES TEST	TRADITIONAL TEST	CORRELATION
Motor	NES2 Finger Tapping, preferred hand	Finger Tapping Test, preferred	0.59
	nonpreferred	nonpreferred	0.53
	NES3 CPT latency (Animals)	NES2 CPT latency (S's)	0.65
Motor/Attention	NES3 Digit Symbol	WAIS-R Digit-Symbol Substitution Test	0.70
Attention/ Executive Function	NES3 Sequences A&B	Trail-Making Test A & B latency	A: 0.44 B: 0.60
		A & B errors	A: -0.06 B: 0.18
Visual functioning/ Memory	NES3 Visual Spans: F, B	Visual Reproductions, immediate recall	F: 0.20; B: 0.35
	NES3 Visual Spans: F, B	delayed recall	F: 0.35; B: 0.56
	NES2 Pattern Memory	Visual Reproductions, immediate recall	0.14
	NES2 Pattern Memory	delayed recall	0.25
Verbal ability/ Memory	NES3 List Learning (over 3 trials)	CVLT (range over trials)	0.20-0.41
	NES3 List Learning delay	CVLT, short & long delay	short: 0.38 long: 0.43
	NES3 List Learning delay	Verbal PAL: difficult items	
		immediate recall	0.44
		long delayed recall	0.51
Mood	NES2 Mood (range over subsets)	POMS (range over subscales)	0.76-0.81
Academic/ Verbal Knowledge	NES2 Vocabulary	WAIS-R Information	0.45

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

APPENDICES

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7th International Symposium on Neurobehavioral Methods and Effects
in Occupational and Environmental Health, June 20-23, 1999

NES3: A computer-based system for clinical neuropsychological assessment

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A computer-based neurobehavioral evaluation system (NES3) has been expanded for use in routine neuropsychological evaluations. The tests in the expanded system include 1) the previously developed NES3 screening battery tests: List Learning, Visual Spans, Sequences, Digit Symbol, and List Learning Delayed Recognition, 2) new versions of some NES2 tests
3 Finger Tapping, Continuous Performance Test (Letters), Continuous Performance Test (Animals), Tracing, Pattern Comparison, Pattern Memory, Vocabulary and Mood Scales, and 3) adaptations of some non-computer-based tests: Auditory Digit Spans, Line Orientation, Paced Auditory Serial Addition Test (PASAT), Diamond Naming, Incomplete Figures and Visual Analogue Profile of Mood States. All instructions are given by the computer using digitized speech. Most responses are made by the subject on a touch screen. Some responses are made using buttons on a joystick box. Most of the tests are computer-administered but some (e.g., Incomplete Figures and Naming) require that an interviewer press a key when the subject makes a correct response. The software runs under Windows 95, and all data are written into a Microsoft Access database.
This battery has been administered to more than 200 patients referred to the neuropsychology services of four Veterans Administration hospitals in the U.S. All patients who met criteria for study inclusion received a full traditional neuropsychological examination as well as the NES3. Diagnostic outcomes were determined at two levels using the traditional neuropsychological data. First, the neuropsychologist determined whether existence of neuropsychological impairment could be identified. For patients identified as being impaired, specific neuropsychiatric diagnoses were then made. Retests using the NES3 battery were performed on 10% of the sample after a period of one week to one month. Feasibility and patient acceptance of the tasks was identified for all of the NES3 subtests except PASAT. Test-retest correlations ranged from high (>.8) to modest. Changes in the administration of the tests with modest test-retest reliability will be discussed. Preliminary data analyses suggest that some of the NES3 subtests show good sensitivity to diagnosis of cognitive impairment. NES3 may provide a standardized approach to clinical neuropsychological assessment of patients suspected of toxicant-induced cognitive impairment. When further validated, the NES3 may contribute additional tasks with high sensitivity to neurological impairment for use in screening batteries of subjects with toxicant exposures in occupational and environmental epidemiology.

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NES3: Validity studies in toxicant-exposed subjects

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Prior work in our laboratories has shown that the NES2 subtests are very good at identifying behavioral impairment in subjects with neuropathology involving the white matter of the brain (in subjects with multiple sclerosis) but not the basal ganglia (in subjects with Parkinson's disease). Because many neurotoxicants act on the basal ganglia, we were concerned about the sensitivity of the NES2 to detect subtle effects of neurotoxicant exposures. For this reason, additional computer-based tasks that more closely approximate the stimulus and response characteristics of traditional neuropsychological tests with known sensitivity to basal ganglia and other types of cerebral dysfunction were developed and implemented into a screening NES3 battery composed of tasks known as List Learning, Visual Spans, Sequences, Digit Symbol and List Learning Delayed Recognition. These tasks use touch screen response mechanisms and were evaluated for sensitivity to diagnosis of toxicant-induced encephalopathy.

The study used a case-control design. Cases were clinically diagnosed patients with chronic toxicant-induced encephalopathy (due to exposure to lead or mixed solvents) using these criteria: 1) evidence of toxicant exposure(s) to lead or solvents in a temporal pattern related to development of behavioral complaints, 2) evidence of central nervous system dysfunction on traditional neuropsychological tests and 3) elimination of other primary diagnoses as explanations for the CNS dysfunction through differential diagnosis. Control subjects were recruited through the general medical services of two academic teaching hospitals and among family members and acquaintances of the case subjects. Selection of control subjects enrolled ensured a categorical matched sample similar in age (+/- 5 years) and gender distribution to the cases. Controls were screened and excluded if they had significant toxicant exposures in the past. All subjects had at least 8 years of education. The NES3 screening battery was administered along with the following NES2 tasks: Fingertapping, Pattern Memory, Continuous Performance Test (Animals), and Mood States. All subjects completed a battery of selected traditional neuropsychological tests.

Performance on the NES battery by persons diagnosed with solvent encephalopathy and with lead encephalopathy was compared to that of controls. In both cases and controls, performance on the NES3/2 tests were also compared to performance on the neuropsychological tests assessing similar functional domains (e.g., Trail-Making Test and NES3 Sequences).