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Validation of the NES2 in Patients With Neurologic Disorders

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WHITE, R. F., R. DIAMOND, M. KRENGEL, K. LINDEM, R. G. FELDMAN, R. LETZ, E. EISEN AND D. WEGMAN. *Validation of the NES2 in patients with neurologic disorders.* NEUROTOXICOL TERATOL **18**(4) 441–448, 1996.—Performance on the Neurobehavioral Evaluation System (NES) has been demonstrated to be affected by exposure to a variety of neurotoxicants. However, the relation of NES subtests to CNS function has not yet been documented in patients diagnosed with neurologic disorders known to implicate specific brain substrates. A validation study of the NES2 was carried out in patients with multiple sclerosis (MS) and Parkinson's disease (PD), disorders exhibiting neuropathology at loci (white matter in MS, basal ganglia in PD) believed to be the sites of action of several known neurotoxicants. The results indicated that performance on certain NES2 subtests was affected in expected ways in both types of patients. However, performance on many more subtests was impaired, relative to controls, in MS than in PD. The relative insensitivity to PD suggests that expansion and refinement of the battery are required if it is to serve well in detecting the effects of toxicants in subjects without frank physical symptoms. These are the goals of a new version of the instrument currently under development (NES3).

Computerized tests Neurobehavioral tests Neurologic disorders Multiple sclerosis Parkinson's disease Validation study

SEVERAL computer-based neurobehavioral test batteries have been developed for use in studies of occupational and environmental health (6,10,14,29,35) and related fields (8,30, 56). The advantages of computer-based batteries include standardized and precise presentation of test materials and efficient, objective, and accurate collection of response data. The Neurobehavioral Evaluation System (NES) (6) is at present the most widely used of these computerized systems in the fields of occupational and environmental health.

The primary purpose for which the NES was developed is investigation of the effects of potentially toxic substances on central nervous system (CNS) function. Psychometric issues bearing on the validity of the NES for this purpose have been addressed in several studies. Evidence that the NES shows an acceptable level of reliability comes from test–retest correlations in the range 0.6 to 0.9, obtained under both laboratory and field conditions (36). Selected NES subtests have correlated, albeit to a moderate degree, with the standardized tests to which they are related (7,24). Epidemiologic studies in healthy working populations have demonstrated orderly relations between subtle age-related declines in NES performance, consistent with expectations for a reliable instrument (5,19,42). Similarly, demographic variables such as sex and education have been found to be related to NES performance in expected ways.

Direct evidence that performance on the NES is related to exposure to neurotoxic substances has been obtained in both acute laboratory and chronic epidemiologic studies. Acute exposure to toluene (15) and ethanol (16,26) adversely affected performance on specific NES subtests. Several NES measures of psychomotor performance showed decrements following experimental administration of low doses of nitrous oxide (23,41) and a wider range of NES measures was affected by higher doses of that gas (41).

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Epidemiologic studies using the NES have shown that performance on many of the subtests of the battery is adversely affected by exposure to known toxicants, including solvents (4,5,11,19,25,28,34,39,53,54,61), lead (46,63), mercury (2,17, 33), and pesticides (42,55). Although these findings clearly implicate CNS involvement, full interpretation of results based on NES subtest performance requires knowledge of the brain–behavior relationships reflected in performance on particular NES subtests. A large literature has documented the relationships between performance on many traditional paper-and-pencil neurobehavioral measures and both specific neurologic syndromes and brain damage at known anatomic sites [e.g., (22,40,58)]. Although the various subtests of the NES derive from traditional neurobehavioral measures, they differ from those measures in many respects. Thus, a comparable level of knowledge remains to be developed with regard to the NES.

This report describes a validation study of the NES2 (37) with patients with two neurologic disorders: multiple sclerosis (MS) and Parkinson's disease (PD). [Patients with cortical focal lesions were also studied; those findings are reported separately (Diamond, R., White, R. F.; Krengel, M.; Lindem, K.; Feldman, R. G.; Palumbo, C.; Letz, R.; Eisen, E.; Wegman, D. Validation of the NES2 in patients with focal brain damage [unpublished data]).] The NES must be able to detect levels of impairment associated with clinically diagnosable disorders such as these neurologic syndromes if the battery is to be considered adequate to the identification of impairments at levels that might be seen in toxicant-exposed individuals who do not exhibit frank physical symptoms. The disorders chosen for study exhibit contrasting neuropathology: damage to the white matter in MS (1), and damage to the basal ganglia and dopaminergic system in PD (3). Several known neurotoxicants are believed to act upon these neuroanatomic sites: the development of white matter lesions has been described following exposure to toluene (20,52) and to mercury vapors (62); several neurotoxicants, including carbon disulfide, have been linked to basal ganglia dysfunction (32,43,47,48).

Specific hypotheses concerning the expected NES findings were made for the present study, based upon the traditional neuropsychological and neurobehavioral literature. Consideration of the neurobehavioral patterns described for MS patients [e.g. (50,60)] suggested that they would show deficiencies in motor speed and coordination, attention, visuospatial functioning, verbal learning, and visuospatial memory. MS patients were not expected to differ from controls in basic language/verbal functioning, as assessed by a test of word meanings. They were expected to show mood impairments, especially depression and fatigue. Descriptions of the performance patterns associated with PD on traditional tests [e.g., (51,59)] led to the expectation that patients with this disorder would show deficits in motor function, attentional difficulties, visuospatial impairments, and problems with visuospatial memory. Basic language/verbal functioning was expected to be intact. PD patients were expected to show elevated levels of confusion and fatigue.

METHOD

Subjects

Most of the patients were recruited from the in-patient and out-patient neurology services at the Boston Department of Veterans Administration Medical Center and the Boston University Medical Center; some MS patients volunteered in response to a request made in a publication of the Massachusetts Multiple Sclerosis Society. Spouses, other family members, and friends of the patients were enrolled to form a group to serve as age- and sex-matched controls. All procedures were approved by the IRB of the Boston Department of Veterans Administration Medical Center and the Boston University Medical Center. All patient groups were screened to exclude those with neurologic or psychiatric disorders predating or coexisting with the current disorder [e.g., closed head injury, seizures, cerebrovascular accident (CVA), brain tumor, encephalitis, history of learning disability, psychiatric diagnosis of affective or psychotic illness, current substance abuse]. Controls were screened for history of any neurologic disorder and for the remaining exclusion criteria applied to patients. All participants met inclusion criteria based upon three traditional neuropsychological tests used to screen for dementia (see below). Specific diagnostic criteria for the two patient groups were as follows

Multiple Sclerosis Group (MS). These patients met current diagnostic research criteria for this disorder (49). Clinical status, including a minimum of two exacerbations, was verified by the subject's neurologist. Magnetic Resonance (MR) scans confirmed the existence of multiple lesions with lesion sites in periventricular white matter (34.3%) and other subcortical white matter (49.0%) the most frequent.

Parkinson's Disease Group (PD). These patients carried a clinical diagnosis of idiopathic PD, provided by the subject's neurologist. Patients in stages 1 to 3 according to the modified Hoehn and Yahr staging (18) were included, with the majority (72%) at stages 2 and 2.5. Patients who exhibited phasic variation in functioning were tested in their "on" phase. Patients with generalized dementia (Mini-Mental State score < 23) and those with evidence of concurrent vascular or other neurologic disease were excluded.

Materials and Procedure

The subjects were first interviewed briefly to obtain information about birthdate, native language, education, occupation, history relating to learning disabilities, medical history, and current medications. Neuropsychological testing followed, comprising three traditional neuropsychological tests and the NES2, version 4.4 (37). The NES2 was administered to each subject individually and monitored by an examiner.

Traditional Neuropsychological Tests

Three traditional neuropsychological tests were administered: the Information and Picture Completion subtests of the WAIS-R (57), and the Mini-Mental State Examination (MMSE) (21). These instruments were used to screen for dementia. Subjects were required to obtain a minimum age-scaled score of 7 on at least one of the WAIS-R subtests. Subjects who could attempt all of the MMSE questions were required to attain a score of 23/30 (equivalent to a prorated score of 0.77) for inclusion in the study. The MMSE format was modified to accommodate subjects' motor disabilities. Subjects who could not hold a pen were asked to dictate a sentence instead of writing one; the design copying item was eliminated, and their score prorated relative to a possible total of 29 points (with a required minimum prorated score = 0.77). Subjects were not penalized for dysarthria on the item requiring repetition of "no ifs, ands, or buts."

NES Battery

The NES2 provides 17 subtests, intended for selection according to the purposes of particular investigations. To span

the entire range of cognitive functions while reducing the time required for testing, 14 subtests were selected for the present study. Standard set-up parameters (default values) were used for each subtest, as specified in the test manual (37). There are practice trials for each test and in several cases the examiner reinstructs the subject and repeats the practice trial if a criterion for administering the test trials has not been met. The subtests used are described briefly below, in the order in which they were administered. A more complete description of each test is given in the test manual. The software provided with the NES2 (the SUMM program) was used for the first level of data reduction and the output entered into SAS. The measure calculated by the SUMM program is indicated for each test.

Finger Tapping. A test of manual motor speed requiring key tapping with the index finger of the preferred, nonpreferred, and preferred and nonpreferred hands in alternation. Two large buttons mounted on a device separate from the computer keyboard were used for tapping. The measure is number of taps in 30 s in each condition.

Continuous Performance. A task measuring reaction time, omissions, and false-positive responses to a large target letter semirandomly embedded in a series of five single letters. There are five blocks of 1-min trials with 12 targets in each block. Stimulus duration is 50 ms with an ISI of 1000 ms. If more than five omissions or false positives occur in a block the subject is reinstructed and the block is begun again. Measures are latency, variability (SD), omissions, and number of false positives.

Hand–dash;Eye Coordination. A test of ability to control with the dominant hand (using a joystick) the vertical location of a cursor, the horizontal movement of which is preprogrammed, to keep it coincident with a sine wave pattern displayed on the screen. There are five trials. The measure is log root mean square error of the two best trials.

Paired Associate Learning. A verbal learning task in which seven names and occupations are presented for encoding in the form "Ken is a painter." Stimulus duration is 2000 ms with an ISI of 1000 ms. Then the statements are presented with a blank for the occupation to be selected from the on-screen list of seven. Feedback is provided after each response. Three learning trials are given. The measure is number correct on each trial; the total correct was used for data analysis.

Digit Span. An attention task in which large digits are presented successively for subsequent reproduction of the sequence by typing into a line of blanks. Stimulus duration is 600 ms with an ISI of 600 ms. Separate forward and backward spans are determined. Minimum spans presented are 4 forward and 3 backward; maximum spans presented are 10. At each span length, if the subject answers correctly the span is increased by 1; if the subject answers incorrectly a different sequence at that span length is presented. Testing ends if two successive trials are incorrect. The measures are maximum correct span length.

Grammatical Reasoning. A verbal reasoning task in which the subject must verify if an instance ("AB" or "BA") is concordant with a statement (e.g., "A follows B"). The statements vary in grammatical form (active vs. passive), verb ("follows" vs. "precedes"), in whether the statement is positive or negative, in whether the first item mentioned is "A" or "B," and in whether the statement is true or false. The measure used for data analysis was total number of errors.

Symbol/Digit. A psychomotor coding task in which the subject must find and enter from the keyboard the digit associated with each symbol in a key of symbols paired with nine digits. The pairing of symbols and digits changes randomly on each trial. There are five trials in which a semirandom array of symbols is presented with the subject required to fill in the digit code for each symbol in succession. Errors must be corrected before proceeding. The measure is average mean latency per digit for the two fastest trials.

Pattern Recognition. A pattern comparison task in which three matrices of 10×10 blocks are presented. Blocks are either light or dark. Two of the matrices are identical; the third contains three pseudorandomly chosen blocks that differ in value. The subject is asked to choose the pattern that differs from the other two. The measure is mean latency on correct trials.

Pattern Memory. A matrix similar to those in the pattern discrimination task is presented alone. 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 number correct and mean latency on correct trials.

Serial Digit Learning. A sequence of eight digits is presented repeatedly for learning. Stimulus duration is 600 ms with an ISI of 600 ms. A maximum of eight trials is given; the learning criterion is two successive correct trials. The measure is a weighted score reflecting the number of errors on each trial.

Horizontal Addition. The subject is asked to enter a two-digit sum of three one-digit numerals presented horizontally. There are 36 test trials. Stimulus duration is 50 ms with a 50 ms interval between response and the next stimulus. Measures are errors and latency of correct responses.

Vocabulary. A multiple-choice (four choices) recognition test of word meanings (used here to estimate native intellectual ability). There are 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 number correct.

Delayed Recall. A single trial of the seven names and occupations previously presented for paired associate learning is given once, in the format used for learning phase test trials, but without feedback. The recall test was given approximately 45 min after the conclusion of the learning trials. The measure is number correct.

Mood Scales. An inventory assessing self-report of degree of anger, confusion, depression, fatigue, and tension, for the preceding week. It is modeled on the Profile of Mood States (POMS) (44). Subjects are asked to indicate degree of endorsement (extremely, quite a bit, moderately, a little, not at all) of five descriptors for each scale, with the set of descriptors presented in a semirandom sequence. Each scale is scored for number of items endorsed, weighted for severity.

RESULTS

Demographic Data and Traditional Neuropsychological Tests

Table 1 gives demographic data for each of the subject groups along with their scores on NES Vocabulary (used here to estimate native intellectual ability) and on the traditional neuropsychological tests (MMSE, WAIS-R Information and Picture Completion subtests). PD patients were predominantly male (as about half of them were recruited from the Boston Veterans Administration Medical Center) and MS patients were predominantly female (in accordance with the known sex inequality in prevalence of this disorder). In correspondence with these differences in gender distribution, controls, who were most often spouses of the patients, were

TABLE 1
DEMOGRAPHIC DATA AND RESULTS FOR TRADITIONAL NEUROPSYCHOLOGICAL TESTS

	Normal Controls	Multiple Sclerosis	Parkinson's Disease
Number of subjects	67	61	73
Age*	56.5 (12.2)	46.0 (11.4)	61.6 (10.7)
% Male	42.4%	30.0%	80.8%
Education (years)*	14.5 (2.5)	15.1 (2.4)	14.3 (3.3)
NES Vocabulary*	20.9 (3.9)	20.9 (4.0)	19.0 (4.8)
MMSE*	28.8 (1.0)	28.1 (2.0)†	28.2 (1.3)‡
WAIS-R Information*	12.0 (2.4)	11.2 (2.8)	11.7 (2.7)
WAIS-R Picture Completion*	11.1 (2.2)	9.9 (2.8)‡	10.2 (2.4)†

*Entries are means (SD).
Significance levels are for differences from controls, after adjustment for age, gender, education, and NES vocabulary: †$p \leq 0.01$, ‡$p \leq 0.05$.

slightly older than MS patients and slightly younger than PD patients. As expected, the patient groups did not differ from controls on NES Vocabulary, indicating the suitability of this measure for use in estimating native intellectual ability. The Vocabulary data cohere with the similarity of the groups in education completed, a measure that also suggests that the groups were comparable in native intellectual ability.

Both patient groups scored lower on the MMSE at statistically significant levels relative to controls, as would be expected for this global measure of cognitive functioning. Neither patient group differed from controls on WAIS-R Information but both MS and PD patients were impaired on WAIS-R Picture Completion, in accordance with the problems in basic perceptual analysis that have been reported to occur in both of these disorders.

NES Subtests

Linear regression was used to estimate the mean difference for each test result between each of the two patient groups (MS and PD) and the controls. A separate model was fit to the results for each test outcome and the regression coefficient of a dichotomous group variable was interpreted as the mean difference in performance. The difference in test performance was adjusted for confounding by including age, gender, NES Vocabulary, and education as other independent variables in the model for each outcome. The adjustments reflect the fact that these variables affect performance on NES subtests.

An adjusted mean performance was estimated for each test in each patient group by adding the appropriate regression coefficient (with the appropriate sign) to the mean in the control group. The ratio of the adjusted mean to the control mean was calculated for each measure. After multiplying by 100, the ratios can be interpreted as an adjusted percent difference in performance between the patient group and controls. For measures in which a smaller score indicates better performance, such as latency, the percent in the patient groups would be expected to be greater than or equal to 100%. For measures in which a larger score indicates better performance, such as number correct, the percent in the patient groups would be expected to be less than or equal to 100%.

Results for the NES subtests are reported in Tables 2–5, grouped by neuropsychological domain or function. The tables give the mean and SD for the control group and the percentage of that mean achieved by patients in each group, calculated from the parameters in the linear model, as described above. The significance levels of the differences between patients and controls on each measure are also given. It should be noted that each comparison tests an independent a priori hypothesis that the patient group will differ from the controls.

Table 2 presents the results for tests of motor function. Both Finger Tapping and Hand–Eye Coordination were highly sensitive to the motor deficits expected in MS and in PD.

Table 3 presents the results for tests of attention/executive function. Continuous Performance scores revealed the attentional impairments expected in association with MS in latency, variability, and number of false positives. There were very few omissions in any group and patients did not differ from controls on this measure. Performance of the MS patients on Digit Span forward was impaired, although the more difficult backward span measure did not show a significant effect. Unexpectedly, neither Continuous Performance nor Digit Span identified the attentional deficits that have been reported to be associated with PD. As expected, both Serial

TABLE 2
PERFORMANCE ON TESTS OF MOTOR FUNCTION

Task	Normal Controls*	Multiple Sclerosis	Parkinson's Disease
Finger tapping			
Dominant hand	149.6 (27.2)	73.3%†	85.8%†
Nondominant hand	140.3 (23.9)	74.8%†	87.7%†
Alternating hands	196.3 (51.6)	69.5%†	71.5%†
Hand-eye coordination	2.3 (0.4)	108.7%†	108.7%†

*Mean (SD).
Percent of control scores after adjustment for age, gender, education, and NES Vocabulary: †$p \leq 0.01$ for differences from controls.

TABLE 3
PERFORMANCE ON TESTS OF ATTENTION/EXECUTIVE FUNCTION

Task	Normal Controls*	Multiple Sclerosis	Parkinson's Disease
Continuous performance			
Latency	352.1 (37.6)	123.0%†	104.9%
Variability	53.8 (16.1)	127.5%†	103.3%
False positives	0.0 (0.2)	3766.7%†	366.7%
Omissions	0.6 (1.0)	109.5%	88.9%
Digit span			
Forward	7.0 (1.6)	91.4%†	95.7%
Backward	5.5 (1.7)	92.7%	91.0%
Serial digit learning	2.8 (3.1)	146.4%‡	135.7%
Horizontal addition			
Latency	3.4 (1.1)	138.2%†	105.9%
Errors	1.1 (1.3)	127.3%	118.2%
Grammatical reasoning	7.5 (5.7)	101.3%	113.3%

*Mean (SD).
Percent of control scores after adjustment for age, gender, education, and NES Vocabulary: †$p \leq 0.01$, ‡$p \leq 0.05$, for differences from controls.

Digit Learning and Horizontal Addition (latency) were impaired in the MS group, but again, deficits in these measures that would be expected in the PD group did not emerge. Grammatical Reasoning did not detect the abnormal neurologic status of either the MS or PD patients, a result that may reflect the high variability on this test seen within all groups, including controls.

Table 4 presents the results for tests of visuospatial function and learning and memory. Symbol/Digit and Pattern Recognition, both of which are timed visuospatial tasks with a motor component, detected the expected deficits in the MS group but not in the PD group.

Performance on the verbal learning and memory task, Paired Associate Learning/Delayed Recall, was not impaired in either the MS or PD group. The NES test is much more difficult than are traditional paired associate tasks (on the NES test, controls answered only 11.5/21 items correctly during learning, or about 55%; on the traditional tests controls of this age answer approximately 19/24 items correctly, or 79%). Variability within all groups was very high. These factors may account for the failure of this subtest to detect a difference between patients and controls. In contrast, the test of visuospatial immediate memory, Pattern Memory, revealed the deficits expected to be associated with both MS and PD (in terms of number correct in both groups and in terms of latency as well, in the MS group).

Table 5 presents the results for the NES mood scales. The symptoms of depression and fatigue frequently seen in MS were detected, but dysphoria that has been reported to be associated with PD was not.

SUMMARY

The NES2 battery was generally effective in identifying the functional correlates of MS that have been reported in the neuropsychological literature. Of the 20 NES cognitive measures on which MS patients were expected to perform worse than controls, there were 14 on which these patients were impaired relative to controls at a conventional level of statistical significance. The positive findings included deficient motor function (Finger Tapping, Hand–Eye Coordination) and attention (Continuous Performance, Digit Span forward, speed of Horizontal Addition, Serial Digit Learning). Visuospatial function, on which MS patients were also expected to show

TABLE 4
PERFORMANCE ON TESTS OF VISUOSPATIAL FUNCTION AND MEMORY

Function and Task	Normal Controls*	Multiple Sclerosis	Parkinson's Disease
Visuospatial function			
Symbol/digit	2.7 (0.8)	133.3%†	107.4%
Pattern recognition	5.0 (1.1)	134.0%†	106.0%
Learning & memory			
Paired associate learning	11.5 (5.1)	90.4%	99.1%
Delayed recall	4.4 (2.2)	84.1%	104.5%
Pattern memory:			
Number correct	12.5 (1.6)	94.0%‡	91.2%†
Latency	6.1 (1.4)	123.0%†	103.3%

*Mean (SD).
Percent of control scores after adjustment for age, gender, education, and NES Vocabulary: †$p \leq 0.01$, ‡$p \leq 0.05$, for differences from controls.

TABLE 5
MEASURES OF MOOD

Mood Scale	Normal Controls*	Multiple Sclerosis	Parkinson's Disease
Anger	1.7 (0.6)	105.9%	94.1%
Confusion	2.2 (0.6)	109.1%	90.9%
Depression	2.0 (0.6)	115.0%†	100.0%
Fatigue	2.7 (0.7)	125.9%†	107.4%
Tension	2.7 (0.8)	103.7%	96.3%

*Mean (SD).
Percent of control scores after adjustment of age, gender, education, and NES Vocabulary: †$p \leq 0.05$, ‡$p \leq 0.01$, for differences from controls.

deficits, was impaired, as assessed by Symbol/Digit and Pattern Recognition. However, because both of these tests are timed and require a motor response, the degree to which these findings are specific to visuospatial capacities as such, may be questioned. MS patients showed the expected difficulties with memory for visuospatial material (Pattern Memory). In addition, these patients indicated, as anticipated, impaired mood on scales of depression and fatigue. Unexpected findings for the MS group included relatively normal performance on Digit Span backward and on new learning of verbal material (Paired Associate Learning).

The behavioral patterns seen in PD patients on the NES2 subtests were congruent with the neuropsychological literature in several respects. Of the 20 cognitive measures examined, PD patients differed from controls on 5. The deficiencies in motor function expected for this group were seen on Finger Tapping and Hand–Eye Coordination. As predicted, PD patients showed problems with memory for visuospatial material (Pattern Memory, number correct). However, attentional difficulties expected in PD were not evident at a statistically significant level. The NES tests also failed to detect an impairment in visuospatial ability (Pattern Recognition) that has been found in groups of PD patients with the use of other tests (9,12,27,45). Elevated levels of confusion and fatigue, also frequently reported for PD patients, were not identified.

DISCUSSION

Many of the NES2 subtests appear to meet the gold standard criterion for neuropsychological tests, that is, the ability to detect the abnormal neurologic status of these patient groups. The exceptions were Grammatical Reasoning and Paired Associate Learning/Delayed Recall, both of which failed to differentiate patients from controls at a statistically significant level. Notable, however, was a marked difference in the ability of the subtests to detect deficits expected in MS as opposed to those expected in PD, with much greater sensitivity to MS. Many tests failed to differentiate PD patients from controls, and several tests were performed more poorly by MS patients than by PD patients. Because the MS patients were younger, better educated, and had higher NES Vocabulary scores, selection bias yielding an intellectually inferior group of MS patients cannot be invoked to explain these differences. Scores on the standard neuropsychological tests (MMSE, WAIS-R Information and Picture Completion) were similar in the two patient groups. Thus, their differences on the NES measures cannot be explained on the basis of a more profound "general dementia" affecting the MS group more than the PD group.

Additionally, a subset of the PD patients included in the present study was presented an abbreviated battery of traditional neuropsychological tests. Many of the functional deficits expected on the basis of the literature but not detected by the NES2 subtests were, in fact, observed on the traditional tests given (31). This implies that the results in the present study are not attributable to an unrepresentative sample of PD patients.

The results suggest that the neuropathological consequences of MS (especially white matter lesions) affect attention, visuospatial function, and mood, as measured by the NES2, more profoundly than do the neuropathological consequences of PD (dysfunction of the basal ganglia, especially the substantia nigra). Thus, the NES2 may be considered adequate for the detection of cognitive and affective impairments associated with white matter lesions, and therefore potentially sensitive to the results of exposure to neurotoxicants with this site of action. In contrast, the relative insensitivity of the battery to PD suggests that impairments consequent on exposure to neurotoxicants affecting the basal ganglia and dopaminergic system may be poorly identified. This finding has particular import for toxicant research. Whereas the PD patients tested showed obvious clinical evidence of basal ganglia dysfunction, cognitive deficits in subjects exposed to toxicants affecting the basal ganglia could be expected to be more subtle, especially in individuals without evidence of clinical disease on physical examination.

Several omissions are evident in the NES2. Attention is probed only in the visual modality and only with letters and numbers: the addition of auditory presentation and the inclusion of more complex stimuli would extend the range of attentional demands. Incorporation of tasks requiring complex tracking and strategy development (aspects of executive function) would increase the likelihood of detecting the more subtle impairments often reported to be associated with damage to subcortical grey matter structures (as in PD). Formal language processing tasks (such as naming) are not represented in the current battery. Deficits in verbal learning and memory, known to be associated with MS, were not detected by the single NES2 test representing this domain (Paired Associate Learning/Delayed Recall). List learning tasks have been developed that permit the analysis of several distinct components of verbal learning and memory not readily evaluated from paired associate data, suggesting the usefulness of incorporating an instrument of that type. The visuospatial tasks included in the NES2 require a timed motor response; the addition of a task not imposing this requirement would be informative of the effects of neurotoxicants on basic visuospatial processing. Finally, memory for visuospatial material could be assessed by a production task as well as by the current (recognition) task, adding greater difficulty and perhaps greater discriminability. These and other refinements are currently being developed for incorporation in a new version of the NES, NES3 (38). Administration of the new instrument to suitable groups of patients with neurologic disorders will be an important step in its validation.

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