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Patterns of Motor Impairment in Normal Aging, Mild Cognitive Decline, and Early Alzheimer's Disease

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In order to determine the relationship between cognitive dysfunction and motor behavior in older adults, 41 cognitively normal elderly (NL), 25 cases exhibiting mild cognitive impairment (MI), and 25 patients with mild Alzheimer's disease (AD) were examined using a broad array of motor/psychomotor and cognitive tests. Relative to the NL group, MI individuals (at risk for future decline to AD) performed worse on tasks involving fine and complex motor function (e.g., tracking and manual dexterity). AD patients also exhibited motor dysfunction on tasks assessing relatively more rudimentary motor control. Motor tasks were able to distinguish NL vs MI and NL vs mild AD individuals as effectively as cognitive tests of memory and language. These results indicate that motor impairment is an important aspect of cognitive decline in older adults. Motor/psychomotor assessments may be comparably sensitive to traditional tests of cognitive function in identifying persons affected by the earliest stages of AD pathology.

FROM normal aging through Alzheimer's disease (AD), a continuum of cognitive and functional capacity can be delineated. The extent to which this continuum is paralleled by a similar range of motor and psychomotor impairment is the focus of this report.

Clinical staging instruments such as the global deterioration scale (GDS; Reisberg, Ferris, de Leon, & Crook, 1982) and the clinical dementia rating (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982) have been used to classify elderly individuals as cognitively normal, mildly impaired, or demented. A GDS score of 1 or 2 and a CDR rating of 0 is reserved for subjects without clinical evidence for cognitive impairment. Mildly impaired subjects with subtle cognitive and functional deficits receive a GDS rating of 3 and a CDR rating of 0.5. Individuals so rated have also been referred to as minimally impaired, borderline, or questionably demented. A diagnosis of mild dementia (e.g., early AD) coincides with a GDS score of 4 and a CDR score of 1.

Recently, considerable clinical investigation has been applied to persons at GDS stage 3 or CDR stage 0.5. Such mildly impaired individuals show changes in cognitive test performance, especially with regard to memory and language function, and appear to be at increased risk for subsequent decline to AD (Flicker, Ferris, & Reisberg, 1991; Rubin, Morris, Grant, & Vendegna, 1989; Storandt, Botwinick, Danziger, Berg, & Hughes, 1984; Storandt & Hill, 1989). This observation suggests that the impairment experienced by many individuals at this stage is due to the presence of AD pathology. The topographic distribution of neuritic plaques and synaptic loss within the temporal, parietal, and frontal lobes in early AD supports the hypothesis that brain regions subserving motor/psychomotor as well as memory and language function may be affected.

Previous research provides some support for this contention. For example, while patients with mild AD manifest ideomotor dyspraxis, bradykinesis, and reflex changes (Edwards, Deuel, Baum, & Morris, 1991; Franssen, Reisberg, Kluger, Sinaiko, & Boja, 1991; Muller, Weisbrod, & Klingberg, 1991; Ott, Ellias, & Lannon, 1995), deep tendon hyperreflexia and frontal release signs can also be seen in nondemented elderly persons with a GDS rating of 3 (Franssen et al., 1991). In addition, performance on psychometric tasks incorporating a motor component (e.g., Digit Symbol Substitution and Trail Making) may also be impaired in mildly impaired (GDS = 3 and CDR = 0.5) subjects (Flicker et al., 1991; Reisberg et al., 1988; Storandt et al., 1984; Storandt & Hill, 1989). Moreover, when applied to nondemented individuals, tests of psychomotor function (Flicker et al., 1991; Flicker, Ferris, & Reisberg, 1993; Masur, Sliwinski, Lipton, Blau, & Crystal, 1994) and the presence of mild extrapyramidal signs (Richards, Stern, & Mayeux, 1993) have been useful in predicting the future development of dementia.

These considerations suggest that a comprehensive exploration of motor/psychomotor function in normal and cognitively impaired elderly persons is now indicated. Motor abnormalities account for some of the clinical heterogeneity observed in AD patients (Mayeux, Stern, & Sano, 1992; Rosser, Kennedy, & Newman, 1992) and may explain the variability in drug response demonstrated in AD (Forette, Bert, Breuil, & Boller, 1992; Levy et al., 1994). The emerging need to better characterize this heterogeneity will require a comprehensive examination of motor function in normal aging and AD. Furthermore, compared to traditional cognitive tests, motor measures may enhance the identification of individuals at risk for dementia by utilizing methods that are less dependent on levels of education. From a practical standpoint, the early detection of motor/psychomotor deficits among nondemented, mildly impaired and mildly demented elderly might serve to identify individuals at heightened risk for subsequent clinical decline in such areas as balance and gait, falling, operating a motor vehicle,

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and performance of activities of daily living (ADL). Deterioration in these important areas of motor function is associated with aging, exacerbated by cognitive decline, and is ultimately an invariable concomitant of AD (Reisberg et al., 1989).

The purpose of this study was to: (1) compare patterns of motor function observed in normal aging with those associated with mild cognitive impairment and mild AD; (2) assess the extent to which motor/psychomotor evaluations (especially those involving more complex motor control) can accurately distinguish normal elderly from mildly impaired individuals and patients with a clinical diagnosis of mild probable AD; and (3) examine the relationship of such evaluations to performance on tests of memory and language, performance on tests of more rudimentary aspects of motor function, and level of education.

METHOD

Participants

This study examined 91 healthy elderly individuals diagnosed in an outpatient setting at the New York University Aging and Dementia Research Center (NYU–ADRC) as cognitively normal (NL), mildly cognitively impaired (MI), or early AD, rated as GDS 1 and 2 (n = 41), GDS 3 (n = 25), or GDS 4 (n = 25), respectively (see Table 1). The NL group includes 4 individuals at GDS stage 1 and 37 subjects at GDS stage 2. Informed consent was obtained after the nature of the procedures had been fully explained. All cases were nonpaid volunteers and received comprehensive medical, physical, neurologic, and psychiatric examinations. This evaluation included full behavioral assessment and cognitive testing; routine laboratory testing that comprised blood chemistry, serum B_{12} and folate levels, thyroid function, and urinalyses; electrocardiograms; and either computed tomographic (CT) or magnetic resonance imaging (MRI) brain scans. Excluded from participation were subjects with Modified Ischemia Scale scores of 4 or greater (Rosen, Terry, Fuld, Katzman, & Peck, 1980); clinical or brain scan evidence of cortical or subcortical infarction, inflammation, infection, or neoplastic disease; or evidence of other medical, neurologic, or psychiatric conditions that could adversely affect cognitive or psychomotor function. The latter exclusions encompassed subjects with affective disorder, Parkinson's disease, normal pressure hydrocephalus, significant sensory impairment, peripheral neuropathy, or severe arthropathy. Additionally, none of the participants were taking medications or had other medical or physical conditions which could significantly influence motor or cognitive performance. Also excluded were any cases failing to complete, at minimum, all of the tests of complex motor and cognitive function. All cases diagnosed as mild AD fulfilled DSM-IIIR criteria (American Psychiatric Association, 1987) and the NINCDS-ADRDA criteria (McKhann et al., 1984) for a clinical diagnosis of probable AD. Subjects ranged in age from 54 to 86. As shown in Table 1, the three groups did not differ significantly ($p > .05$) in age, gender, or presence of white matter lesions on brain scans (as detected by nonspecific white matter hyperintensities on MRI or hypodensities on CT). The three groups had similar ($\chi^2 = 1.3; p > .50$) and relatively restricted distributions of education; only 2.4% of the NL, 8.0% of the MI, and 8.0% of the mild AD cases had less than 12 years of education. Results of a one-way analysis of variance (ANOVA) indicated that there was a significant difference in mean education ($p \leq .05$) among the three groups. Post hoc pairwise comparisons (Tukey HSD test) showed that although there was no difference in the average level of education between the NL and MI or between the MI and AD groups, the educational attainment of the AD group was lower than that of the NL group ($p \leq .05$).

Measures

The GDS (Reisberg et al., 1982) was used to divide our subjects into three cognitive severity groups: NL controls, MI individuals, and mild AD patients. These assignments were made following a semi-structured interview conducted by trained physicians (Reisberg et al., 1993). As part of the interview process, the clinician obtained information from both subjects and knowledgeable informants such as family members. The GDS is assigned based on the subject's overall level of cognitive and functional status in accordance with the published procedures. The GDS was assigned independent of knowledge of the subject's performance on the motor and cognitive tests examined in this study. Similarly, the motor and cognitive testing was conducted blind to

Table 1. Characteristics of the Normal (NL), Mildly Impaired (MI), and Mild Alzheimer's Disease (AD) Groups

	Normal[a] (n = 41)		Mildly Impaired[b] (n = 25)		Mild AD[c] (n = 25)	
Measure	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Age	69.9	(8.6)	73.9	(8.2)	71.6	(8.1)
Mini-Mental State Exam (MMSE)	29.2	(1.2)	27.6*	(3.1)	22.6***	(4.0)
Education (in years)	15.9	(2.6)	15.3	(2.9)	13.8*	(3.3)
Gender (percent males)	56.1%		56.0%		40.0%	
Percent with white matter lesions on neuroimaging scans	48.8%		48.0%		56.0%	

[a]Global Deterioration Scale (GDS) stage 1 or 2.

[b]GDS stage 3.

[c]GDS stage 4.

*$p \leq .05$; ***$p \leq .001$ (relative to normal group).

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the subject's GDS designation. The NL subjects (GDS = 1 and 2) show no manifest impairments on clinical evaluation. However, those NL subjects who are assessed at GDS = 2 do report subjective cognitive decline. The MI individuals (GDS = 3) manifest subtle observable cognitive deficits, which are not severe enough to meet clinical criteria for dementia; for example, they typically show mild memory and word-finding deficits while retaining competence in instrumental as well as basic activities of daily living. Dementia patients have GDS ratings of 4–7, spanning mild (early) through severe (end-stage) disease. The MI subjects in this study manifested a very mild degree of cognitive dysfunction. Their mean Mini-Mental State Exam (MMSE) score was 27.6, only 1.6 points lower than the mean for the NL group. However, previous studies have demonstrated that compared to normal controls, MI cases show greater than expected decline on age-sensitive cognitive tests (e.g., recent verbal memory) and are at increased risk (57%–72%) for developing AD after a 2–4 year follow-up interval (de Leon et al., 1993; Ferris et al., 1993; Flicker et al., 1991). In contrast, only 4 to 12% of the NL subjects decline to dementia at follow-up (de Leon et al., 1993; Flicker et al., 1991, 1993; Reisberg et al., 1994). It should be noted that although MI subjects are "as a group" at increased risk for future decline to dementia, some of these individuals are part of the low end of the normal distribution.

All subjects were administered motor/psychomotor tests and cognitive tests which are relatively motor independent (i.e., tests of immediate and recent memory and language). The motor tests, administered over two separate testing days, were part of a larger, comprehensive 5-hour motor/psychomotor battery that also included evaluations of gait, balance, and weight transfer; arm-electromyogram control; joint-position reproduction accuracy, etc. The cognitive assessments of memory and language were part of a one-hour cognitive screening battery given to all participants at the NYU–ADRC. Some of the motor/psychomotor tests selected for this study are well-known neuropsychological instruments, while others are specialized computer-based tests developed at the Department of Rehabilitation Medicine, NYU Medical Center (Gianutsos & Eberstein, 1987; Gianutsos & Notterman, 1987; Jarus, Wughalter, & Gianutsos, in press). The motor and cognitive tests are described in more detail below.

Manually administered motor/psychomotor tests. — The manual tests of motor function encompass nine tests, the first seven of which are manufactured by the Lafayette Instrument Company (P.O. Box 5729, Lafayette, IN 47903), including the (1) finger-tapping speed task using the Halstead-Reitan (Reitan & Davison, 1974) administration procedures, determining the maximum number of taps in five consecutive 10-second trials for each hand; (2) foot-tapping speed task, determining the maximum number of taps in two alternating 15-second trials per foot; (3) multihole steadiness test, in which time off center per 10-second trial for holes 1–8 is measured; (4) hand dynamometer test of grip strength, determined over three alternating trials per hand; (5) unimanual and bimanual peg placement tests from the Purdue Pegboard Test (Tiffin & Asher, 1948); (6) the unimanual placement of slotted pegs of the Grooved Pegboard Test (Klove, 1963; Matthews & Klove, 1964); (7) assembly test of the Purdue Pegboard (Tiffin & Asher, 1948), requiring asymmetric hand movements and construction ability; (8) Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), requiring the rapid drawing of appropriate symbols below randomly arranged numbers while referencing a number-symbol code. The number of correct symbols drawn in 90 seconds determines the score (Wechsler, 1981); and (9) the test of Alternating Hand Movements (Christensen, 1975), requiring rapid alternating hand movements (hands flat on table, one palm up, one palm down; then simultaneous turning of hands to reverse palm positions). The number of correct turns in 10 seconds is counted on each of two trials.

Computer-based tests of head positional tracking and head steadiness. — A computer-based system monitors and records the accuracy with which a cursor displayed on a video monitor is guided in tracking a stationary target also located on the monitor. Cursor and target position, as well as tracking error for each trial, are recorded and stored in computer memory. Assessment is conducted over blocks of 10 trials per task with task difficulty kept constant. Each trial is followed by post-trial knowledge of results. The time integral of error (cursor-target distance expressed dimensionally as the product of mm × seconds) is obtained for each trial. This measure represents tracking accuracy and is calculated by mathematically integrating cursor-target separation over time. The displacement between the cursor and target is tabulated for each sequential 5 msec epoch over the course of each 10-sec trial.

For assessment of head tracking control, the subject is seated facing a video monitor positioned at eye level. The video monitor displays a red, square-shaped target frame and a blue, square cursor (the position of which is controlled by the subject's head maneuvers). Preceding each trial, the red target frame is positioned in the center of the video screen and the subject initiates the start of each trial by centering the blue cursor inside the target. The "act of centering" immediately repositions the target frame to the upper right quadrant of the screen, and the subject is required to perform head maneuvers sufficient to reposition the cursor within the target. The cursor moves in response to head tilt transduced by a set of dual axis, gravity-referenced clinometers. The cursor is displaced upward or downward as the head pitches in a forward or backward direction, and laterally left or right with left or right rolling of the head. Tracking along the lateral and anterior-posterior (A-P) axes concurrently is required. When the head is maintained upright with respect to both the lateral and A-P axis, the cursor is positioned at the origin. Any shift in head orientation displaces the cursor off the origin. The subject must perform head-tilt maneuvers which result in positioning the moveable cursor within the stationary target frame. Head positional tracking is run under two conditions, *with on-line video feedback* and *without on-line video feedback*. The task is also conducted under conditions of both *compatible* and *incompatible* cursor movement. Compatible movement means that when the head is pitched forward (face down) the cursor concurrently moves down on the video screen, and

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when the head is pitched backward (face up) the cursor moves up. In the incompatible mode, moving the head forward (face down) causes the cursor to move up and vice versa (this mode requires more flexible, less stereotyped motor responses, compared to the compatible condition). These compatible and incompatible conditions are each carried out with on-line video feedback followed by a block of trials without on-line video feedback. Head steadiness is assessed on the same apparatus and display by requiring the subject to lock onto the stationary target positioned at the center of the screen and hold the cursor as steady as possible on the target. No displacement of target occurs and, thus, only a minimal amount of head tracking is required. The head steadiness task is run under the compatible condition with the presence of video feedback.

Cognitive tests of memory and language. — A set of eight tests were selected a priori to represent relatively motor-independent measures of memory and language function. The eight tests included assessments that have been shown cross-sectionally to differentiate elderly classified as NL from MI and/or mild AD and longitudinally to predict future cognitive status in nondemented elderly (Ferris, Crook, Flicker, Reisberg, & Bartus, 1986; Ferris et al., 1993; Flicker et al., 1991; Reisberg et al., 1988). Included were three representative tests of verbal and visual recent memory, the initial and delayed paragraph recall subtests, and the memory for designs subtest of the Guild memory battery (Crook, Gilbert, & Ferris, 1980; Gilbert, Levee, & Catalano, 1968); two tests of immediate memory and concentration, the digit span forward and backward subtests of the WAIS (Wechsler, 1955); and three tests of language function, the Vocabulary subtest of the WAIS (Wechsler, 1955), and the Category Retrieval test (Ferris et al., 1986) with "easy" (males first names) and "hard" category (items worn on the feet) conditions, based on published category norms (Battig & Montague, 1969).

Procedure

In order to reduce the number of variables entered in analyses, tests that a priori were deemed to be related to similar types of motor function were separated into three categories: (1) *tests of complex motor function* (motor control involving tracking in two or more planes of space, alternating patterns of movements, or rapid asymmetric, bimanual constructions); (2) *tests of fine motor function* (motor control involving rapid unimanual or symmetric bimanual placement of objects into precise locations, requiring eye-hand coordination); and (3) *tests of gross motor function* (motor control involving strength, steadiness, or rapid body movements that place minimal demands on visual guidance). These groupings of motor measures were used to construct a rough hierarchy, ranging from basic or gross to relatively complex motor function (see Table 2). It is recognized that gross motor speed does not require the same strategy or challenge of motor control involved in carrying out tasks of steadiness or strength. However, all three share a more rudimentary level of regulation than that involved in the more complex motor tests. In addition, certain tasks designated as complex tests like the Assembly Test of the Purdue Pegboard might also be grouped with the other tests of fine motor control because performance on all these tests is influenced by finger dexterity. In this case the Assembly Test was placed with the complex tests because of the added complexity of asymmetric bilateral control and dependence on constructional praxis, compared to the fine motor assessments. The relatively motor-independent *cognitive tests* were also grouped together, thus comprising a fourth test category for inclusion in the statistical analyses.

Table 2. Motor Battery

Gross Motor Function:
• Gross Motor Speed
Finger-tapping speed
Foot-tapping speed
• Steadiness
Hand steadiness
Head steadiness
• Strength
Hand dynamometer
Fine Motor Function:
• Purdue Pegboard (dominant, nondominant, bilateral)
• Grooved Pegboard (dominant, nondominant)
Complex Motor Function:
• Head Tracking (Two-dimensional)
With video feedback (compatible and incompatible movement)
No video feedback (compatible and incompatible movement)
• Assembly Test of Purdue Pegboard
• Digit Symbol Substitution Test (of WAIS)
• Alternating Hand Movements (Diadiokinesis)

Objective confirmation of our intuitively based "groupings" could be obtained through techniques such as principal components/factor analysis, and we employed these methods in a preliminary way to provide some justification for our a priori categorizations. Nevertheless, the relatively small sample size compared to the large number of test variables precluded us from utilizing factor analysis in a rigorous attempt to accomplish this goal. Definitive statistical confirmation will be possible when a sufficient number of additional subjects have been evaluated.

Statistical Analyses

In order to protect against adventitious significant results (i.e., group differences) in individual analyses, we conducted an omnibus multivariate analysis of variance (MANOVA) on all 24 performance tests contained in the four test categories. Subsequently, four separate MANOVAs were used to examine possible differences among the three groups of elderly (NL, MI, and AD), one for each of the sets of tests comprising the four constructs: complex motor function, fine motor function, gross motor function, and cognitive function. In addition, z-scores (relative to performance of a larger group of NL controls) were calculated for each test score subsumed within each of the four sets of functions. For each subject, a mean of the z-scores was determined for each set, and serves as a convenient composite summary score for each of the four categories

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of motor/cognitive function. Four separate one-way ANOVAs with follow-up Tukey HSD tests (using the Tukey-Kramer adjustment for unequal cell sizes) were performed on the mean *z*-scores for each set. These *z*-scores were also used to assess the relative independence of the complex tests of motor processing from the more rudimentary motor tests and tests of cognitive function. This was accomplished through the use of analyses of covariance (ANCOVAs). Discriminant function analyses (DFAs) with classification analyses were used to determine which sets of motor and cognitive measures best discriminated NL and MI as well as NL and mild AD individuals. Evaluation of the relationship of education to the motor and cognitive assessments was accomplished by means of Pearson correlations. All statistical analyses were conducted using the SYSTAT statistical system (Wilkinson, 1990).

RESULTS

Results of the omnibus MANOVA on all 24 performance tests indicted that the three clinically defined cognitive groups of elderly yielded statistically significant differences (Hotelling-Lawley Trace, $p \leq .001$). MANOVAs were then conducted on each of the four sets of tests.

Complex motor function. — A MANOVA indicated significant differences among the three clinically defined cognitive groups of elderly in performance on the set of five complex motor tests (Hotelling-Lawley Trace, $p \leq .001$). Pair-wise follow-up comparisons indicated that both the MI and mild AD groups performed more poorly on the set of five tests than the NL group. Test-by-test results using univariate analyses are shown in Table 3. All five individual tests comprising this set yielded statistically significant differences between the NL and MI cases; the same outcome was obtained with increased statistical confidence when the normal and mild AD cases were compared.

Fine motor function. — A similar MANOVA for the set of five tests of fine motor function yielded statistically significant differences among the three cognitive groups ($p \leq .05$). Follow-up analyses indicated that, compared to the NL group, the MI and mild AD groups performed more poorly on the set of tests as well as on each individual test (see Table 4).

Gross motor function. — A MANOVA for the set of six tests of gross motor function yielded statistically significant differences among the three cognitively defined groups ($p \leq .01$). However, follow-up analyses indicated that, compared to NL controls, *only* the mild AD group performed more poorly on the set of six tests. Furthermore, the MI cases performed more poorly on just one of the six individual tests and the early AD cases on only two of the six tests making up this set (see Table 5).

In order to assess possible differences among subcategories of gross motor activity, we conducted a more detailed exploratory evaluation of the gross motor measures by creating *subsets* comprising (1) gross motor speed (finger- and foot-tapping speed); (2) strength (hand dynamometer using dominant and nondominant hands), and (3) steadiness (hand and head steadiness). Three separate MANOVAs were run for each of the three subsets and showed that there were no differences between the NL and MI groups with respect to any of the three subsets, although a trend toward significance was evident for the steadiness set ($p \leq .10$). For both the gross motor speed and steadiness subsets, performance of the mild AD group was worse, relative to the NL group ($p \leq .01$). The set of strength measures failed to show statistically

Table 3. Performance of Subject Groups on the Set of Five Tests Involving Complex Motor Function

	Normal (n = 41)		Mildly Impaired (n = 25)		Mild AD (n = 25)	
Measure	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Head Tracking: with video feedback (error score)	9.6	(6.3)	13.6*	(7.1)	21.9***	(13.5)
Head Tracking: no video feedback (error score)	24.4	(8.5)	36.1***	(12.7)	46.3***	(14.0)
Purdue Pegboard: Assembly (no. of parts correct)	28.6	(6.2)	22.8**	(7.1)	15.8***	(7.6)
Digit Symbol Substitution Test (no. correct)	54.6	(10.0)	38.1***	(17.1)	23.9***	(16.0)
Alternating Hand Movements (per 10 sec)	29.1	(5.9)	22.9**	(8.4)	21.6***	(6.2)

*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$ (relative to normal group).

Table 4. Performance of Subject Groups on the Set of Five Tests Involving Fine Motor Function

	Normal (n = 41)		Mildly Impaired (n = 25)		Mild AD (n = 25)	
Measure	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Grooved Pegboard: Dominant Hand (seconds)	78.8	(15.3)	104.8**	(59.4)	131.5***	(71.6)
Grooved Pegboard: Nondominant Hand (seconds)	87.8	(21.5)	123.5**	(79.5)	146.7***	(89.6)
Purdue Pegboard: Dominant Hand (no. of pegs)	12.7	(2.0)	11.3**	(1.8)	11.0**	(2.1)
Purdue Pegboard: Nondominant Hand (no. of pegs)	11.7	(1.9)	10.6*	(2.5)	10.0***	(1.9)
Purdue Pegboard: Bilateral (no. of pegs)	9.7	(1.8)	8.4*	(2.1)	7.8**	(2.2)

*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$ (relative to normal group).

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significant differences in performance across all groups. Thus, representative indices of gross motor speed and steadiness but not of strength were affected by mild AD, suggesting that the more rudimentary types of motor control do not decline homogeneously.

Cognitive function. — As anticipated, a MANOVA employing a set of eight tests of immediate and recent memory and language function yielded statistically significant differences among the three cognitive groups ($p \leq .001$). Follow-up analyses indicated that the MI and mild AD groups performed more poorly on the set of eight tests than did the NL group. In addition, differences were apparent between the NL and MI cases on five of the eight tests comprising this set of cognitive tasks, whereas the NL and early AD cases differed on seven of the eight tests (Table 6).

The same pattern of results for the four sets of measures as well as for the three subsets of gross motor assessments were obtained when the analyses controlled for the effects of age, gender, presence of WMLs, and education. In addition, *z*-scores (relative to performance of a larger group of NL controls) were calculated for all tests subsumed within each of the four sets of complex motor, fine motor, and gross motor function and cognitive function. A mean of the *z*-scores was determined for each set to serve as a *composite summary score* for each subject for each category of motor/cognitive function. As will be evident in the analyses described below, these *z*-scores provide a convenient way of adjusting performance on complex motor tasks for the performance on relatively gross motor and on cognitive evaluations. Four separate one-way ANOVAs with follow-up Tukey HSD tests were performed on each of the mean *z*-scores. The results are depicted graphically in Figure 1 and confirm the pattern of group differences evidenced in the MANOVA analyses.

Figure 2 depicts a density plot displaying, for each case, performance on two of the tests comprising the set of complex motor measures, i.e., head tracking without video feedback and the Purdue assembly test. The plot shows that there is wide variability of scores among the MI (GDS 3) subjects, with some cases scoring more like the average NL controls (GDS 1–2) while others score more like patients with mild AD (GDS 4). The values of each of these individual motor scores or the composite *z*-scores collected at baseline might prove useful in predicting future cognitive/motor/functional status.

Figure 3 summarizes performance for the three subject groups on four subtests of the head tracking task (compatible vs incompatible movement both with and without video feedback). As the plots indicate, tracking performance under conditions of reduced feedback best distinguishes the cognitively NL from the MI cases. It appears that in order to accurately track and hold onto the target, mildly impaired subjects are more dependent upon the provision of extrinsic feedback, which may in part reflect a deficit in some aspect of motor memory. Figure 3 also reveals that the group

Table 5. Performance of Subject Groups on the Set of Six Tests Involving Gross Motor Function

	Cognitive Group[a]					
	Normal (n = 40)		Mildly Impaired (n = 24)		Mild AD (n = 24)	
Measure	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Finger-tapping speed	41.2	(5.5)	39.2	(6.2)	35.2***	(6.4)
Foot-tapping speed	50.7	(11.6)	50.4	(11.1)	49.9	(12.8)
Head steadiness (error score)	2.8	(2.7)	3.2	(1.4)	4.0	(2.0)
Hand steadiness (error: time off target)	1.2	(0.7)	1.7*	(1.0)	2.0**	(1.3)
Hand strength in dominant hand: Dynamometer (kgs)	25.8	(10.1)	22.8	(9.0)	21.4	(12.4)
Hand strength in nondominant hand: Dynamometer (kgs)	22.0	(10.0)	18.7	(8.2)	18.9	(9.8)

[a]One subject in each group had missing data on at least one of the tests of gross motor function and was not included in the analysis.
*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$ (relative to normal group).

Table 6. Performance of Subject Groups on the Set of Eight Tests Involving Cognitive Function

	Normal (n = 41)		Mildly Impaired (n = 25)		Mild AD (n = 25)	
Measure	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Initial recall of paragraphs (Guild)	8.7	(2.6)	5.1***	(2.5)	2.9***	(2.2)
Delayed recall of paragraphs (Guild)	9.9	(3.0)	4.9***	(3.7)	1.5***	(2.4)
Recall of designs (Guild)	5.7	(2.6)	3.2***	(2.1)	1.4***	(1.7)
Digit span forward (WAIS)	6.6	(1.3)	6.6	(1.2)	6.3	(1.2)
Digit span backward (WAIS)	5.4	(1.4)	4.7	(1.5)	3.8***	(1.2)
Vocabulary (WAIS)	68.7	(7.8)	60.6*	(13.8)	48.4***	(21.4)
Category retrieval (Easy)	18.9	(6.5)	15.5	(7.7)	11.7***	(4.7)
Category retrieval (Hard)	10.1	(3.2)	8.2*	(3.6)	6.2***	(2.0)

*$p \leq .05$; ***$p \leq .001$ (relative to normal group).

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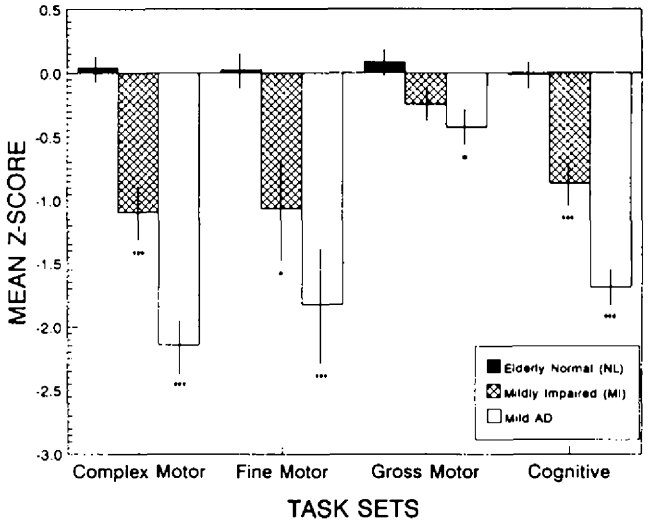

Figure 1. Group differences in performance on motor and cognitive tests. The mean of the *z*-scores (± *SEM*) for all tests in each task set for the three clinically defined groups, cognitively normal (NL), mildly impaired (MI), and mild Alzheimer's disease (AD). Comparisons are referred to values yielded by NL group. $*p \leq .05$; $***p \leq .001$.

differences are not easily explained by an underlying reaction/travel time deficit since the performance of both the MI and mild AD subjects asymptote at different levels up to 10 seconds after starting the trial. Since it takes most subjects less than 4 or 5 seconds to reach the general target area, the problems of locking onto the target encountered by elderly with mild cognitive impairment or mild AD during seconds 6–10 are indicative of deficits in executing subtle motor adjustments and readjustments around the target and are not easily attributable to a general motor slowing.

Classification of group membership. — Discriminant function analyses (DFAs) with classification analyses were used to determine which sets of motor and cognitive measures best discriminated NL and MI as well as NL and AD individuals. When the NL versus MI groups are considered, the set of five tests of complex motor function correctly classified 78.9% of the cases, while the set of eight cognitive tests correctly classified 80.3% of the cases ($p \leq .001$). Combining the sets of complex motor and cognitive tests correctly classified to 83.3% (specificity = 87.8% and sensitivity = 76.0%). Although the set of fine motor tests produced a significant DFA ($p \leq .05$), the accuracy of correct classification (65.2%) was not as high as that obtained with the complex motor or cognitive tests. Significance was not obtained by the DFA for the gross motor measures.

DFAs with classification analyses for cognitively NL versus mild AD groups revealed significant classifications when the complex motor, fine motor, gross motor, and motor-independent cognitive measures were used, thereby providing overall accuracies of group discrimination of 92.4% ($p \leq .001$), 74.2% ($p \leq .01$), 76.6% ($p \leq .001$) and 93.4% ($p \leq .001$), respectively. Thus the complex motor tests performed essentially as well as the cognitive measures

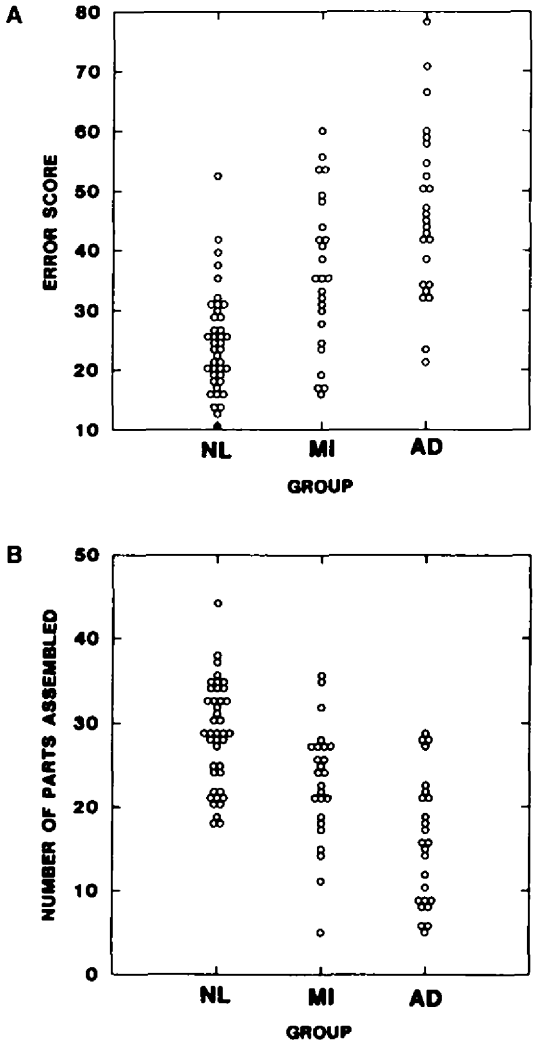

Figure 2. Density plot of case-wise performance with respect to two of the tests comprising the set of complex motor measures: **A**. head tracking without video feedback (collapsed across compatible and incompatible versions), and **B**. the Purdue Assembly Test.

in discriminating mild AD patients from normals. Combining the complex motor and the cognitive measures yielded an overall accuracy of 97% (specificity = 100% and sensitivity = 92%).

Relative independence of complex motor measures. — The results also provide evidence that the differences in performance on the tasks of complex motor function yielded by NL and MI elderly as well as between NL and mildly demented AD cases cannot be attributed to differences in performance on fine and gross motor measures or on motor-independent cognitive measures of memory and language. To examine this issue, an ANCOVA was conducted comparing performance of the NL and MI groups on the composite *z*-scores for complex motor ability. Even after the composite *z*-scores of fine motor, gross motor, and cognitive performance were controlled for, the MI group performed more poorly than NL controls on the complex motor tests ($p \leq .05$). Similar results

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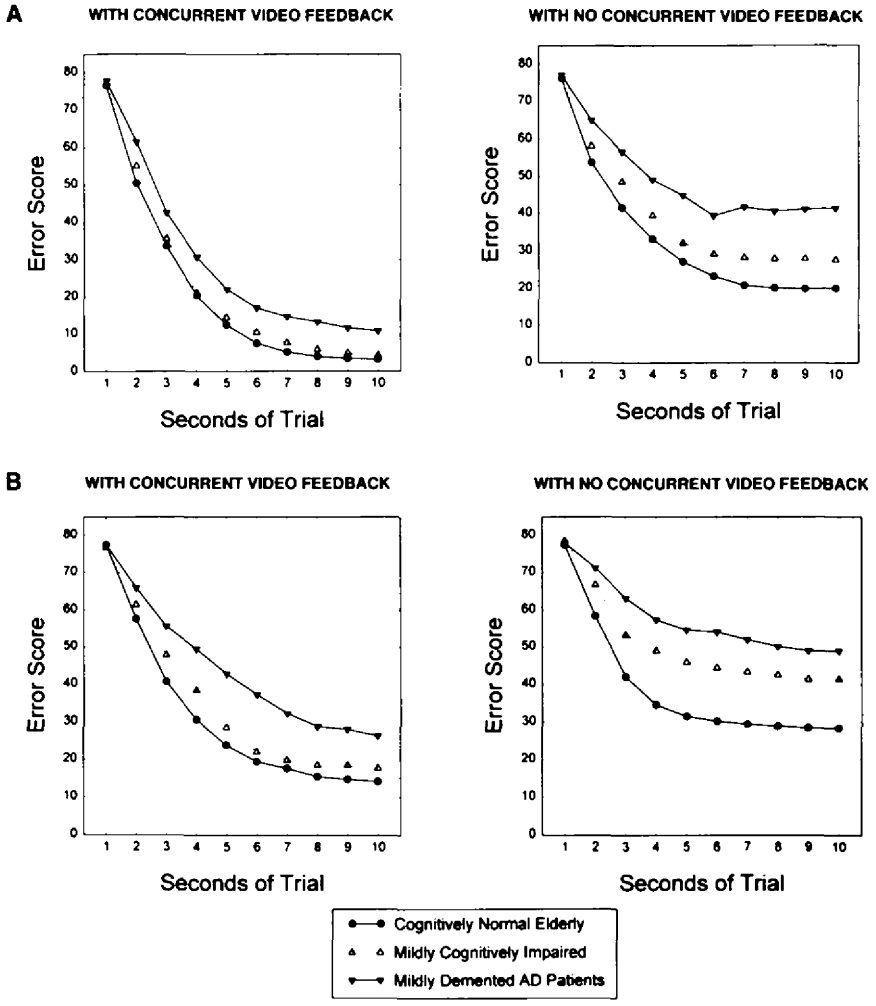

Figure 3. Task complexity is manipulated by requiring head movements that are either: **A**. head tracking: compatible movement, or **B**. incompatible with the movement of a cursor on a computer monitor (relative to a target). Control is performed in each condition, first with concurrent video feedback present and again with feedback removed. (Note that the head tracking scores depicted in Table 2 for the conditions with and without video feedback are collapsed across compatible and incompatible subtests.)

were obtained for the NL controls contrasted with the mild AD patients ($p \leq .001$). These findings indicate that the relationships observed between overall cognitive decline (as measured by the GDS) and performance on the complex motor measures cannot be adequately accounted for by differences in more rudimentary motor function or in motor-independent cognitive function.

Education and motor/psychomotor performance. — The results also imply that education is associated with both individual and composite motor-independent cognitive evaluations but *not* with motor/psychomotor tasks. In the NL elderly group ($n = 41$), the composite z-score of the eight cognitive tests and two individual cognitive tests, initial recall of Guild Paragraphs and WAIS Vocabulary, correlates significantly with education level, with r values of .35 ($p \leq .05$), .51 ($p \leq .001$), and .54 ($p \leq .001$), respectively. None of the composite z-scores or the individual tests of complex, fine, or gross motor function show a significant association with education (the r values ranged from only −.17 to .27).

DISCUSSION

The results of these cross-sectional analyses demonstrate a pattern of diminished motor control related to cognitive status in older adults. The association was observed for nondemented individuals who are mildly impaired as well as for patients with mild probable AD. This cross-sectional result suggests that as normal individuals decline cognitively to dementia, a loss of complex and fine motor control occurs before deficits of gross motor performance become evident. This conclusion requires longitudinal confirmation, work which is currently in progress. Even in the mild AD subjects examined in this study, some aspects of gross motor control such as foot-tapping speed and hand-grip strength show little evidence of decline. However, AD patients in more severe stages of impairment would be likely to show clear deficits on these measures as well (Reisberg, 1988; Reisberg et al., 1988). The group differences in motor and cognitive function persisted even after controlling statistically for age, gender, education, and presence of white matter lesions as detected through neuroimaging. The presence of white mat-

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ter lesions was necessary to control for, inasmuch as these lesions have been linked to motor decline in cognitively normal elderly (Golomb et al., 1995; Kluger, Gianutsos, de Leon, & George, 1988; Kluger et al., 1994) and in AD patients (George et al., 1986).

Our investigations have also revealed that MI and mild AD cases perform more poorly on motor tracking tasks of balance and weight transfer and certain tests of gait; these findings will be described in a separate report. We are compelled to conclude that motor/psychomotor decline represents an integral part of the earliest manifestations and stages of AD, especially dysfunction on motor tasks designated on an a priori basis as being complex. The motor tasks designated as complex constituted the best motor measures for correctly classifying NL from both MI and mild AD cases. The aspects of motor control contained in these complex tests include sensory-motor integration, motor choice, and planning and sequencing of movements as well as their temporal relation, and may be viewed as representing cognitive-motor behavior. These cognitive aspects of motor control as well as the level of manual dexterity required in many of the complex and fine motor tasks undoubtedly involve significant cortical/subcortical mediation.

The results of the present study indicate that the differences in complex motor control observed in the clinically determined subject groups are relatively independent of the influence of the more rudimentary aspects of motor control and of the memory and language aspects of cognition. The findings suggest that complex motor function is mediated by brain regions affected in incipient and early AD which are distinct from those areas involved in less complex motor control and in memory and language. Traditional views of the neuropathology of early AD have emphasized the appearance of plaques and tangles in the medial temporal lobe, a region clearly implicated in memory function (Golomb et al., 1994; Squire & Zola-Morgan, 1991). It is noteworthy that MI subjects show greater atrophy of medial temporal lobe structures (especially the hippocampal formation), as detected by MRI and CT scanning, and the presence of such atrophy has also proven to be an accurate predictor of future decline among such subjects (de Leon, George, Stylopoulos, Smith, & Miller, 1989; de Leon et al., 1993). Nevertheless, recent reports demonstrate that nondemented individuals with mild cognitive impairment (CDR = 0.5) typically harbor amyloid plaques within the frontal cortex, but cognitively normal persons of comparable age do not evidence such change (Morris et al., 1991). Furthermore, compared to normal controls, frontal cortex synaptic density is markedly decreased in AD (Scheff, DeKosky, & Price, 1990) and correlates highly with the magnitude of a patient's cognitive deficit (Terry et al., 1991). These observations suggest that frontal lobe dysfunction may occur early in the pathogenesis of AD, and combined with the importance of this area in motor control could provide a basis for our finding of motor/psychomotor change related to mild cognitive decline. Other candidate brain areas that could account for some of the motor decline include the parietal lobe (especially the posterior-inferior parietal association areas) and subcortical motor systems (especially the basal ganglia). The parietal lobes have been identified as important mediators of praxis and sensorimotor integration, and have been observed in AD to undergo atrophy (Brun, 1983) and to show metabolic deficits (Friedland, Brun, & Budinger, 1985; Jagust, Friedland, Budinger, Koss, & Ober, 1988; McGeer et al., 1986). The decline in metabolism of the parietal lobes is discernible in the earliest stages of the disease process (Smith et al., 1992). Subcortical structures and subcortical-cortical circuits important in motor control, including inputs into the basal ganglia, show changes in AD (Ditter & Mirra, 1987). The neural control of motor function is complex, involving the integration of many levels of the nervous system. The type of motor decline reported in this study does not lend itself to direct neuroanatomic explanation, but it may be possible in the future to relate relatively specific early AD-related brain changes to distinct facets of motor deterioration. It is also possible that the motor impairment observed in our subjects may partly relate to the presence of other conditions that sometimes overlap with AD, such as Parkinsons disease (Ditter & Mirra, 1987) and the Lewey body variant of AD (Hansen et al., 1990). Additionally, several previously published studies have reported impaired motor performance but intact motor skill learning in AD (Eslinger & Damasio, 1986; Gabrieli, Corkin, Mickel, & Growdon, 1993; Heindel, Salmon, Shults, Walicke, & Butters, 1989). These results could imply that motor deficits exhibited by patients with early AD are independent of motor skill learning processes. The relationship between motor learning and motor performance is a complex issue, and its exploration was beyond the scope of the present investigation.

Regarding the precision of classifying NL versus MI cases, we found similar overall accuracies for the set of complex motor (78.9%) and the cognitive (80.3%) tests. Neither the set of fine nor gross motor tests provided good discrimination of NL and MI cases. Combining both the complex motor and cognitive sets yielded an accuracy of 83.3%. This level of accuracy of group classification (i.e., 83.3%) may well be the best that can be obtained in differentiating NL (GDS stage 1 & 2) from MI (GDS stage 3) cases, given the inherent heterogeneity of the MI group (approximately 40% of cases classified as GDS = 3 are not destined to decline significantly over follow-up intervals as long as a decade [Reisberg et al., 1994]). Due to extensive overlap in psychometric performance, it apparently has been difficult to accurately differentiate mildly impaired (CDR = 0.5) elderly from normal controls (Storandt & Hill, 1989). We are aware of only one study that examined the results of classification analyses based on psychometric tests that discriminate between NL (CDR = 0) and MI (CDR = 0.5) elderly, reporting accuracies ranging from 77% to 84% (Robinson-Whelen & Storandt, 1992). These findings compare quite closely with the levels of accuracy we have obtained for distinguishing NL and MI individuals.

Several previous studies have attempted to use performance measures to differentiate normal from demented individuals. Based solely on motor tests, the accuracy of group classification between NL and mild AD cases, found in the present study, corresponds closely with results previously reported by others. For example, a measure of finger tapping (an assessment of gross motor speed) correctly

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classified 76% of relatively mild AD cases (mean MMSE of 19.9) versus normal elderly controls (Ott et al., 1995), and concurs with our finding that the gross motor set produced an accuracy of 76.6% for distinguishing NL individuals from mild AD patients (mean MMSE of 22.6). These NL versus AD classifications based on tests of gross motor function do not attain the high accuracy (92.4%) that we obtained using the set of complex motor/psychomotor tests.

When cognitive tests were previously used to classify demented versus normal elderly (often with a measure of psychomotor function included), accuracies ranging from 87% to 98% have been reported (Eslinger, Damasio, Benton, & Van Allen, 1985; Grober, Buschke, Crystal, Bang, & Dresner, 1988; Knopman & Ryberg, 1989; Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994; Storandt et al., 1984). A distinction between NL and very mild AD cases (mean MMSE of 25.0) has been drawn on the basis of memory tasks alone. In particular, a test evaluating delayed verbal recall produced the highest accuracy (i.e., 89.8% based on cutting scores 2 *SD*s above the NL mean) from among a set of memory measures which yielded an overall 91% accuracy, based on results of a DFA (Welsh, Butters, Hughes, Mohs, & Heyman, 1991). Our analyses indicate that the set of cognitive tests (excluding the motor measures) provided an accuracy of 93.4% for the NL versus AD differentiation. The best individual measure also proved to be an evaluation of delayed verbal recall, the Guild delayed paragraph recall subtest. The latter had an accuracy of 87.9%. It is noteworthy that an overall NL versus AD classification accuracy of 97% was obtained in the present study when our complex motor/psychomotor tests were combined with the cognitive tests.

Although we cannot entirely rule out the possibility in the present study that primary changes in sensory, muscle, or oculomotor function could have contributed to the observed group differences, they are unlikely to be significant factors given the strict inclusion and exclusion criteria and the mild degree of cognitive impairment manifested in these cases. Furthermore, performance on some of the complex motor measures that do not rely heavily on sensory (especially visual) information or on the integrity of eye tracking, such as alternating hand movements and headtracking in the absence of video feedback, still shows impairments related to mild cognitive impairment and early AD. This suggests that the motor deficits we have described cannot be easily explained by possible group differences in sensory or oculomotor function. Nevertheless, future studies of motor function in mildly cognitively impaired elderly should incorporate comprehensive assessments of sensory, muscle, and oculomotor function to evaluate the possible contributions of these factors. Similarly, group differences in attention and working memory could have contributed to our findings. Nevertheless, our analyses indicated that group differences in complex motor performance persisted after controlling for cognitive and gross motor performance. This observation suggests that aspects of complex motor function may be independent of attention and working memory processes that may be common to all tasks. But this issue should be addressed more directly in future studies of motor decline in the elderly.

Education has been identified as a possible risk factor for AD (Katzman, 1993; Mortimer & Graves, 1993; Stern et al., 1994). However, educational attainment is related to performance on cognitive tests that are used to define AD, making it unclear whether low education contributes directly to the development of this condition. Hence, the identification of assessments that are not associated with education but are related to presence and severity of dementia might help clarify the nature of the relationship between education and the development of AD. Analyses of the motor measures in NL elderly indicated a lack of correlation between performance on any of the motor variables and prior education. In contrast, some of the motor-independent cognitive measures of language and memory showed moderate relationships with education. This implies that the use of motor measures in predicting decline among individuals with varying degrees of education may improve the accuracy of prediction obtained when relying on cognitive tests alone. The certainty of our conclusion regarding a lack of association between the motor measures used in this project and education is somewhat limited by the relatively high education level of our subjects. It would be important in the future to evaluate the relationships between performance on these motor measures and educational attainment in elderly subjects having a broader range of educational background. However, it is also likely that the memory and language assessments would show substantially greater correlations with education in more diversely educated elderly than we found in these studies of primarily highly educated elderly persons. Thus, it is reasonable to conclude that the motor measures are relatively less related to educational attainment than the cognitive measures, and hypothesize that this difference will also pertain for more diverse subject populations.

It is well established that performance on a wide variety of cognitive tests is associated with educational background (Arbuckle, Gold, & Andres, 1986; Finlayson, Johnson, & Reitan, 1977; Kaszniak, Garron, Fox, Bergen, & Huckman, 1979). Although there are a number of studies showing significant relationships between education and psychomotor function, much of this work has examined tasks involving speeded manipulation of verbal symbols such as Trail Making (King, 1967) or reaction time/travel time measures (Era, Jokela, & Heikkinen, 1986; Houx & Jolles, 1993). These findings indicate that neuropsychological markers developed primarily on research patients with high levels of education may lose precision when applied to the broader group of elderly having more disparate educational backgrounds. However, a subset of our motor/psychomotor tests (e.g., motor-tracking), which emphasize accuracy of movement adjustment and readjustment around a target under varied conditions of task complexity and provision of external feedback, appears to be relatively less associated with education than tasks that are more directly dependent upon speed of processing, memory, and language.

In conclusion, we have shown that performance on complex motor tests can discriminate between normal elderly and nondemented individuals with mild cognitive decline who, as a group, are at increased risk for dementia. We believe that these tests may be useful in predicting longitudinal change in nondemented elderly. Furthermore, to the extent that these tests are educationally independent, they

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may have particular utility in the accurate detection of future decline in more poorly educated individuals. In addition, future studies examining age-related motor decline should consider assigning global clinical ratings of cognitive status to more clearly separate the effects of normal as opposed to pathologic aging on motor function. Finally, from a clinical standpoint, perhaps the examination of decline in motor function associated with clinically evident cognitive and functional decline in the elderly can help address a number of practical concerns such as risk of falling, driving competence, and efficacy of cognitive-enhancing drugs in nondemented as well as mildly demented elderly individuals.

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