

dependency in patients with Alzheimer disease

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Abstract—Objective: To determine whether specific cognitive deficits can predict the progression of Alzheimer disease (AD). **Methods:** Two hundred fifty-two patients with AD enrolled in the Predictors Study were followed at 6-month intervals for up to 4.5 years with neurologic, cognitive, and psychiatric examinations. Neuropsychological functions were assessed by the Modified Mini-Mental State Examination (mMMSE). Items of mMMSE were divided into five cognitive domains: temporospatial orientation, short-term memory, long-term memory, language, and visuoconstructive functions. Loss of autonomy was assessed by both the Dependency Scale (DS) and the Equivalent Institutional Care (EIC) rating. Cox proportional hazards models, adjusted for age, sex, estimated duration of illness at entry into the study, and presence of extrapyramidal signs and behavioral disturbances, were used to determine the predictive value of each neuropsychological domain on dependency outcomes. **Results:** Global mMMSE, temporospatial orientation, and short-term memory scores were associated with a greater relative risk of moderate or severe dependency. The visuoconstructive score predicted the development of severe dependency. Long-term memory and language scores were not predictive of the EIC or DS endpoints. **Conclusions:** The presence of certain neuropsychological deficits at a patient's initial visit, such as short-term memory, temporospatial orientation, and constructive apraxia, predict more rapid dependency in patients with Alzheimer disease. Neuropsychological items have different weights in term of predictive power, and these effects are independent of the influence of age and disease duration at baseline.

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In recent years, interest in factors that predict rate of functional decline in patients with Alzheimer disease (AD) or time to reach specific outcomes has increased. It has primarily focused on demographic data such as age at onset,^{1,2} educational level,³ presence of clinical signs such as extrapyramidal signs^{2,4} (EPSs) and behavioral symptoms,^{5–7} and global cognitive deficit measured by the Mini-Mental State Examination (MMSE).^{8,9}

Although the most prominent feature of AD is the decline in cognitive functions, the influence on functional decline of specific cognitive deficits has not been frequently studied. Longitudinal analysis of the Predictors Study showed that a higher total score of the Modified Mini-Mental State Examination (mMMSE) was predictive of reaching nursing home entry or death more slowly.¹⁰ A recent study showed that baseline level of cognition was not related to mortality, but high rate of annual global cognitive decline increased the risk of mortality.¹¹

In fact, cognitive decline is not a uniform process. It involves alterations in different neuropsychological domains, each of them supported by specific neu-

ronal networks. It is now well established that a deficit in episodic memory is the earliest and most prominent cognitive manifestation of AD, reflecting the precocious involvement of mesial temporal structures.¹² Aside from memory, patients may also demonstrate early impairment in aspects of attention and executive functions,¹³ visuo-perceptual functions,^{13,14} expressive and receptive language, and the ability to plan and organize activities.¹⁵ These disorders are consistent with the secondary extension of lesions to the neocortical associative areas.

The aim of this study was to assess the sensitivity of specific neuropsychological parameters obtained at the first visit for predicting levels of dependency in AD. Patients with AD were enrolled in the Predictors Study and followed longitudinally at 6-month intervals for up to 10 years. Patients were assessed with the mMMSE and with the Dependency Scale (DS) at each visit. Items of the baseline mMMSE were grouped into five cognitive domains: temporospatial orientation, short-term memory, long-term memory, language, and visuoconstructive function. We used Cox proportional hazards models to deter-

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mine which of these domains were predictive of reaching specific dependency endpoints. Specific functional outcomes were assessed by both the DS and the Equivalent Institutional Care (EIC) rating.

Methods. Subjects. Subjects were members of the Predictors Study cohort.¹⁶ Two hundred fifty-two patients with probable AD were recruited into the study at three different sites: Columbia University, Johns Hopkins University School of Medicine, and Massachusetts General Hospital. Details of inclusion and exclusion and recruitment methods have been previously described.¹⁶ In summary, each patient recruited had to meet National Institute of Neurological and Communication Disorders and Stroke/Alzheimer Disease and Related Disorders Association criteria for probable AD except for the allowance for lesions on neuroimaging described below. Intellectual impairment was documented by neuropsychological testing using the standard clinical batteries of each institution. Although diagnostic test batteries differ somewhat at each center, they all included tests of memory, orientation, abstract reasoning, language, attention, and construction. Patients had to be maintained off antipsychotic medications for at least 1 month before their initial evaluation.

Exclusion criteria were history or current clinical evidence of substance abuse, schizophrenia, schizoaffective disorder, or major affective disorder prior to the onset of intellectual decline; any electroconvulsive therapy treatment within 2 years of recruitment or ≥ 10 lifetime electroconvulsive treatments at any time; and history or clinical signs of stroke or a Hachinski Ischemic Scale score ≥ 5 . Patients with small subcortical lesions on CT or MRI scans that were clinically and historically silent and were judged to be < 2 cm in diameter were included, as were those with diffuse symmetric periventricular lucencies. Patients with cortical lesions of any size or location or with focal cortical atrophy in a specific vascular distribution were excluded.

This project was approved by the institutional review board at each participating institution, and all patients or their proxies provided written informed consent.

Procedures. All patients were seen at 6-month intervals and underwent the following procedures.

Onset dating and features. At the initial visit, the physician estimated the disease duration based on interview of the patient and the informants. Disease onset was also estimated using a standardized onset interview technique that systematically queries the earliest date of manifestation of specific disease symptoms as well as the latest point at which these symptoms were not present.¹⁷

Neurologic examination. Clinical neurologic examination included selected items from the Unified Parkinson's Disease Rating Scale described in a previous article.⁴ Rated EPSs included tremor, rigidity, bradykinesia, gait, posture change, and facial appearance. For all statistical analyses that used EPSs, patients who had at least one sign rated as mild to moderate (rated score 2) were considered to have EPSs.

Neuropsychological assessment. Cognitive function was examined using the mMMSE.^{18,19} This instrument included all items from the standard MMSE²⁰ plus the Wechsler Adult Intelligence Scale-revised Digit Span Subtest²¹ and additional attention/calculation and general knowledge, language, and construction items. The maximum score on the mMMSE is 57. Test-retest reliability is high ($r = 0.95$), and correlations with the original MMSE ($r = 0.89$), the Blessed Memory Information Concentration Test ($r = 0.93$), and Full-Scale IQ ($r = 0.66$) are indicative of adequate validity.²² For the current analysis, the items on the mMMSE were grouped to define five major cognitive domains: temporospatial orientation, short-term memory, long-term memory, language, and visuoconstructive domains. Items assessing temporospatial orientation were those of the standard MMSE and led to a maximum score of 10. Short-term memory consisted of immediate recall of three words, Forward and Backward Digit Span Subtests, and attention/calculation items with a maximal score of 20. Long-term memory consisted of delayed recall of three words (10-minute delay recall) and general knowledge items (names of the five previous presidents). Maximum score of long-term memory was 8. Language was assessed by items from the standard MMSE and confrontation naming of 10 items from the Boston Naming Test, for a maximum score of 17. Visuoconstruc-

tive abilities were assessed by copying two figures and were rated from 0 to 2.

Functional assessment. Functional capacity was rated with Parts 1 and 2 of the Blessed Dementia Rating Scale (BDRS), whose reliability and validity have been established.²³ Moreover, it has been shown useful in evaluating longitudinal changes in function.

Dependency assessment. Level of dependency was assessed by the DS, which rates the patient's need for care.²⁴ It is based on interview data and summarizes the interviewer's impression of the care the patient received and required, regardless of location. Maximum score is 5. The EIC was established from the second section of the DS. Categories include limited home care, adult home (a supervised setting with regular assistance in most activities), and health-related facility. Maximal score is 3. Previous studies have demonstrated the robust validity of these scales.^{11,25}

Data analyses. Cox analysis. Cox analyses focused on the five cognitive domains evaluated by the mMMSE. The outcomes of severity of the disease were defined by two stages of clinical dependency in every day life. Moderate dependency was defined as reaching a score of 2 on the EIC (patient needing a supervised setting with regular assistance in most activities) and a score of 3 on the DS (patient needing to be watched when awake). Severe dependency was defined as reaching a score of 3 on the EIC (patient needing health-related facility) and a score of 4 on the DS (patient needing to be dressed, watched, and fed). For each combination of predictor and outcome, we calculated a Cox proportional hazards model that used months from the initial visit as the time variable. All Cox analyses were adjusted for estimated duration of illness, sex, and education level. In addition, as preliminary analyses revealed that age and EPSs influence survival, Cox analyses were also adjusted for these variables.

Comparisons of initial cognitive performance between the group of patients that did and did not reach dependency. We defined a group of patients that did not develop moderate dependency (score below 3 on the DS) and a group that reached this endpoint at 1 and 2 years. We compared their cognitive performance at the initial visit. One hundred three patients at 1 year of follow-up and 57 patients at 2 years were not dependent; although 116 patients at 1 year and 121 at 2 years were moderately dependent.

Results. Clinical characteristics at baseline. At study entry, mean patient age was 72.8 ± 8.9 (mean \pm SD) years with a sex ratio (M/F) of 41/59. Education level was 13.1 ± 3.6 years. At the baseline visit, the mean estimated duration of illness was 2.3 ± 2.2 years. Score on the DS was 2.3 ± 0.8 and on the EIC 1.5 ± 0.6 . Mean scores of the BDRS were 3.3 ± 1.4 on Part 1 and 0.5 ± 0.9 on Part 2. All patients ($n = 252$) were followed for at least 6 months, 219 for ≥ 1 year, 178 for ≥ 2 years, 159 for ≥ 3 years, and 125 for ≥ 4 years. Mean mMMSE score at inclusion was 37.1 ± 6.2 . Temporospatial orientation score was 6 ± 2.3 (maximum = 10), long-term memory score 1.9 ± 1.6 (maximum = 8), short-term memory score 14.8 ± 3.3 (maximum = 20), language score 13.6 ± 2.4 (maximum = 17), and visuoconstructive score 0.9 ± 0.8 (maximum = 2).

Cox analysis. Analysis of the data was performed on the four major endpoints assessing moderate and severe dependency.

Moderate dependency. Global cognitive efficiency, measured by total score of the mMMSE, was associated with an elevated risk of reaching moderate dependency as defined by the EIC (table 1). Temporospatial orientation and short-term memory scores were associated with nursing home care. Long-term memory, language, and visuoconstructive scores were not associated with an elevated relative risk (RR) of reaching this endpoint.

Global cognitive efficiency, measured by the total score of the mMMSE, was associated with elevated risk of reaching moderate dependency as defined by the DS score. The

Table 1 Cox proportional hazard analysis predicting moderate dependency

Predictor	Moderate dependency		Severe dependency	
	Institutional care rating	Dependency	Institutional care rating	Dependency
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Total mMMSE	1.59 (1.28–1.97)*	1.45 (1.22–1.74)*	1.38 (1.16–1.63)†	1.44 (1.21–1.70)*
TS orientation	1.82 (1.23–2.70)†	1.93 (1.36–2.74)†	1.57 (1.13–2.18)‡	1.68 (1.20–2.36)†
Long-term memory	1.37 (0.89–2.11)	1.26 (0.86–1.86)	1.15 (0.81–1.65)	1.01 (0.70–1.44)
Short-term memory	2.4 (1.56–3.69)*	1.96 (1.36–2.74)†	1.66 (1.18–2.33)†	1.65 (1.18–2.31)†
Language	1.25 (0.82–1.93)	1.32 (0.93–1.88)	1.30 (0.93–1.82)	1.37 (0.97–1.92)
Construction	1.26 (0.78–2.03)	1.14 (0.78–1.68)	1.61 (1.10–2.35)‡	1.61 (1.10–2.36)‡

Analysis was adjusted for age, duration of illness, sex, presence of extrapyramidal signs; and education level.

* $p < 0.0001$.

† $p < 0.005$.

‡ $p < 0.01$.

RR = relative risk; mMMSE = Modified Mini-Mental State Examination; TS = temporospatial.

same cognitive domains that were predictors for the nursing home care endpoint proved to be significant for the DS. Temporospatial orientation and short-term memory scores were associated with higher occurrence of dependency. Long-term memory, language, and visuoconstructive scores were not associated with an increased RR of reaching this endpoint.

Severe dependency. Global mMMSE, temporospatial orientation, and short-term memory scores were robust predictors of reaching severe dependency as defined by the EIC and were also robust predictors of severe dependency defined by the DS (see table 1). In addition, the visuoconstructive score was a predictor of severe dependency, as defined by the EIC and the DS. Long-term memory and language scores were not predictive of the EIC or DS endpoints.

Comparisons of initial cognitive performance between groups that did and did not develop dependency. We compared neuropsychological scores at the initial visit between patients who developed moderate dependency 1 year later ($n = 116$) and those who did not ($n = 103$) (table 2). The two groups differed in scores on the mMMSE, temporospa-

tial orientation, and short-term memory. The other neuropsychological scores (in particular, long-term memory, language, and visuoconstructive scores) did not differ between the two groups. At 2 years of follow up, we found the same pattern of results: The two groups (121 “dependent” patients and 57 “nondependent” patients) differed in scores on the mMMSE, temporospatial orientation, and short-term memory, while the other neuropsychological scores did not differ.

Discussion. Several strengths of the study should be noted. The cohort was large and followed at regular intervals for a long period of time. Patients were recruited from different medical centers, diminishing the risk of a center effect both for the diagnostic procedure and for the identification of predictors. Dependency was assessed with valid scales. Using nursing home care as a study endpoint was more useful than using the entry into a nursing home itself.¹⁰ The DS measures the amount of assistance that patients with dementia require to perform daily

Table 2 Comparisons of initial cognitive performance between groups that did and did not develop dependency

Initial score	1 year of follow-up			2 years of follow-up		
	Dependency +	Dependency -	p	Dependency +	Dependency -	p
	Total mMMSE	35.8 ± 5.0	39.6 ± 6.1	<0.0001	37.5 ± 5.7	40.8 ± 6.2
TS orientation	5.7 ± 2.2	6.5 ± 2.2	0.0002	6.2 ± 2	7.2 ± 2	0.01
Long-term memory	1.5 ± 1.3	2.1 ± 1.7	NS	2.3 ± 1.7	2.4 ± 1.9	NS
Short-term memory	14.4 ± 3.7	15.8 ± 3.9	0.04	14.4 ± 3.5	16.2 ± 4.4	0.01
Language	13.5 ± 2.0	14.1 ± 2.3	NS	14.1 ± 2.1	14.5 ± 2.4	NS
Construction	0.8 ± 0.7	1.0 ± 0.8	NS	0.8 ± 0.9	1.2 ± 0.7	NS

Analysis was adjusted for age, duration of the illness, sex, presence of extrapyramidal signs, and education level.

Dependency + = patients who had developed moderate dependency; Dependency - = patients who had not developed moderate dependency; mMMSE = Modified Mini-Mental State Examination; TS = temporospatial.

activities.²⁴ The EIC rating, used as an endpoint in this study, was based on several measures of activities of daily living that reflect the real needs of patients at home. Whereas the neuropsychological data were not as comprehensive as in more detailed neuropsychological studies, they reflect the kind of data available to practicing neurologists and therefore constitute more practical information for them.

As previously described, the level of global cognitive impairment was a risk factor for dependency and placement.^{4,9} Furthermore, this study showed that the various cognitive domains had different weights in terms of predictive power. A lower score in temporospatial orientation and in short-term memory was associated with a higher risk of reaching moderate and severe dependency sooner, and a lower score in visuoconstructive function was also associated with a higher risk of reaching severe dependency. By contrast, language and long-term memory performance were not predictive of dependency. These findings are in agreement with the fact that differences in the rate of progression of neuropsychological deficits are directly related to the progression of the underlying cerebral lesions. Indeed, spatial and temporal progression of AD neuropathology is directly responsible for the emergence of cognitive and behavioral changes, which can be linked to the decline of functional capacity.

The fact that long-term memory score was not predictive of dependency is not surprising. Long-term memory is the central core of the disease and occurs in its early stages.²⁶ An amnesic syndrome of the "hippocampal" type is highly suggestive of AD.²⁷ This is consistent with the precocious involvement of mesial temporal structures, as demonstrated by postmortem evidence²⁸ and by morphometric MRI in mildly affected patients^{29,30} or in patients with mild cognitive impairment who subsequently developed AD.³¹ As a consequence, long-term memory performance has a rapid floor effect in follow-up studies, as been previously noted with the delayed recall score of the MMSE and the Mattis Dementia Rating Scale.³² This precocious involvement of mesial temporal structures may also explain why long-term memory is a robust predictor of dementia in patients with mild cognitive impairment^{2,33} and in nondemented elderly subjects.^{33,34}

Lower short-term memory score at first visit was predictor of moderate and severe dependency. It does not seem to result from the relative weight of the short-term memory items in mMMSE (maximal score of 20/57) because language evaluation has approximately the same weight (17/57) and no predictive power. The role of short-term memory as a predictive factor might result from the fact that it involves attentional resources that are considered to represent the central executive component within the theoretical framework of working memory.³⁵ Patients with mild AD are impaired in the functioning of the central executive component of working memory, particularly when patients are required to per-

form two concurrent tasks simultaneously, a common feature of everyday activities.³⁶ This may explain why impairment in short-term memory implies more functional consequence in routine activities of daily living than language or visuospatial impairment.

Temporal and spatial disorientation was associated with a high risk of reaching dependency. Previous studies showed that this neuropsychological deficit occurs early in the course of the disease^{33,37,38} and probably reflects a degeneration of the pathways linking the hippocampus with the superior parietal and posterior cingulate cortex.³⁹ Autonomy, defined by the capacity to act without assistance, directly depends on the ability to refer oneself spatially and temporally. Temporospatial orientation therefore plays an important role in everyday activities, and when it deteriorates, caregivers' assistance is required. These results suggest that temporospatial orientation should be more carefully studied in the future as it may be relevant in terms of risk of dependency.

The visuoconstructive score, assessed with only one component of visuoconstructive ability (figures copy), predicted severe dependency. Disturbances of visuospatial constructive functions are well recognized in AD and closely related to the pathologic changes in posterior temporoparietal and occipital associative areas and to the reductions in regional cerebral perfusion and regional metabolic changes in these same cortical areas.^{29,40-42} Our results fit well with a previous study showing that constructive apraxia was a predictor of accelerated cognitive decline.⁴¹ This suggests that, more than language (which is not a predictive factor), visuoconstructive abilities provoke a severe dependency outcome because the integrity of visuospatial and praxic functions, which both rely on parietal lobe function, is involved in daily activities.

In future research on a larger sample, it would be beneficial to better understand the combined effects of all predictors described in AD to inform and help family to prepare for care.

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