Positron Emission Tomography in Evaluation of Dementia
Regional Brain Metabolism and Long-term Outcome

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Context Deficits in cerebral glucose utilization have been identified in patients with cognitive dysfunction attributed to various disease processes, but their prognostic and diagnostic value remains to be defined.

Objective To assess the sensitivity and specificity with which cerebral metabolic patterns at a single point in time forecast subsequent documentation of progressive dementia.

Design, Setting, and Patients Positron emission tomography (PET) studies of $[^{18}F]$fluorodeoxyglucose in 146 patients undergoing evaluation for dementia with at least 2 years’ follow-up for disease progression at the University of California, Los Angeles, from 1991 to 2000, and PET studies in 138 patients undergoing evaluation for dementia at an international consortium of facilities, with histopathological diagnoses an average of 2.9 years later, conducted from 1984 to 2000.

Main Outcome Measures Regional distribution of $[^{18}F]$fluorodeoxyglucose in each patient, classified by criteria established a priori as positive or negative for presence of a progressive neurodegenerative disease in general and of Alzheimer disease (AD) specifically, compared with results of longitudinal or neuropathologic analyses.

Results Progressive dementia was detected by PET with a sensitivity of 93% (191/206) and a specificity of 76% (59/78). Among patients with neuropathologically based diagnoses, PET identified patients with AD and patients with any neurodegenerative disease with a sensitivity of 94% and specificities of 73% and 78%, respectively. The negative likelihood ratio of experiencing a progressive vs nonprogressive course over the several years following a single negative brain PET scan was 0.10 (95% confidence interval, 0.06-0.16), and the initial pattern of cerebral metabolism was significantly associated with the subsequent course of progression overall ($P < .001$).

Conclusion In patients presenting with cognitive symptoms of dementia, regional brain metabolism was a sensitive indicator of AD and of neurodegenerative disease in general. A negative PET scan indicated that pathologic progression of cognitive impairment during the mean 3-year follow-up was unlikely to occur.

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their cognitive and behavioral symptoms. The assessment is conducted with a combination of diagnostic tools, including history and physical examination, mental status testing, a detailed neurologic examination, common laboratory tests, structural neuroimaging (computed tomography [CT], magnetic resonance imaging [MRI]) in many instances, and specialized tests (eg, electroencephalography, cerebrospinal fluid examination) in selected patients.\textsuperscript{5,6} Numerous studies have found that AD and other neurodegenerative diseases can produce significant alterations in brain metabolism detectable with positron emission tomography (PET), including at very early stages of the disease, as has been extensively reviewed.\textsuperscript{7-12} The actual sensitivity and specificity of PET for the evaluation of dementia, however, has been difficult to assess, as data from few cases of dementia patients who underwent both PET and autopsy of the brain (the criterion standard for diagnosis of AD) have been previously available. The most recent, and largest, series to be published comprised 22 cases\textsuperscript{13}; while seemingly reasonable estimates of the diagnostic accuracy of PET were derived from the data, the small sample size limited the statistical confidence associated with those estimates,\textsuperscript{14} particularly with respect to specificity, as the study involved only 6 patients without AD. To further address this problem, we have forged an international collaborative effort to pool and analyze brain PET and histopathologic data from multiple centers. We also examined the prognostic value of regional brain metabolic data, for predicting when a progressive course of dementia is likely to prevail regardless of specific diagnosis, by comparing the patterns of cerebral metabolism revealed by PET with long-term clinical follow-up or presence of any inexorably progressive neurodegenerative disease verified by autopsy.

**METHODS**

A total of 284 patients presenting with symptoms of dementia were evaluated at neurology, psychiatry, and PET facilities affiliated with 8 academic centers: University of California, Los Angeles (UCLA); National Institutes of Health, Bethesda, Md; University of California, Davis, in association with Lawrence Berkeley National Laboratory, University of California at Berkeley; Duke University, Durham, NC; University of Pennsylvania, Philadelphia; Université de Liège, Liège, Belgium; New York University, New York, NY; and Max-Planck-Institut für Neurologische Forschung, Köln, Germany. Two groups of patients were included: (1) those studied with PET, followed longitudinally for at least 2 years (n = 146, UCLA), and (2) those studied with PET whose disease status was later confirmed histopathologically (n = 138, all institutions). All patients prospectively enrolled at UCLA provided written informed consent and were studied in accordance with a protocol approved by the UCLA institutional review board. The portion of the investigation involving study of autopsy cases sent from outside institutions was exempt from UCLA institutional review because it only involved inspection of postmortem records. The methods of study pertaining to each group will be described in turn.

**Study of Patients Undergoing Brain PET and Long-term Clinical Follow-up**

Patients underwent PET at UCLA between 1991 and 1998 after being referred to the Nuclear Medicine Clinic for symptoms of cognitive decline or behavioral change (Table 1). Cerebral uptake of intravenously administered \textsuperscript{[18F]}2-fluoro-2-deoxy-D-glucose (FDG, 10 mCi or 370 MBq) occurred while patients lay with eyes open in a dimly lit, quiet room. Emission scanning commenced 40 minutes following the injection of FDG, using (prior to October 1996) a Siemens/CTI ECAT 831 or 931 scanner or (beginning in October 1996) a higher resolution Siemens ECAT EXACT HR or HR+ scanner (CTI PET Systems Inc, Knoxville, Tenn). Emission images were obtained with the canthomeatal plane of each patient’s head set parallel to the plane of the ring of detectors. Images were reconstructed using a calculated attenuation correction algorithm and displayed in axial and coronal orientations as contiguous planes of brain tissue. Each scan was read on the day of its acquisition by a faculty member certified by the American Board of Nuclear Medicine and serving as the attending physician of the nuclear medicine facility at the UCLA Center for Health Sciences. Thus, readers were blinded to clinical follow-up data at the time of report of scan findings.

Patients were followed up for an average of 3.2 years after PET (range, 2.0-9.4 years). Questionnaires were sent to patients’ referring or most recent managing physicians, requesting clinical data pertaining to details of their functional, behavioral, and cognitive status (including dates and findings of neurologic and psychiatric examina-
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...ions and associated standardized scales of impairment). Additional information was obtained from UCLA medical records, including patient date of birth, handedness, sex, date of PET, indication for scan, medications at time of PET, severity of dementing symptoms at time of scan, and CT/MRI findings (when available). Data pertaining to individual patients were kept confidential.

Prognostic value was assessed with respect to the ability of regional metabolism to predict progression of neuropsychological problems (with memory, language ability, visuomotor skills, and personality and/or behavioral changes). This assessment was made for all patients undergoing PET in the Nuclear Medicine Clinic at UCLA for evaluation of dementia between 1991 and 1998 for whom clinical follow-up information permitted clear evaluation of whether progressive dementia was present (146 [35%] of 418 total). To meet this criterion, neuropsychiatric data had to be available for at least 2 years following initial PET. Exceptions to this requirement were made for 6 cases with compelling unambiguous clinical data obtained sooner (ie, reversal of symptoms of normal pressure hydrocephalus after ventriculoperitoneal shunting, established diagnosis of Huntington disease). Outcome data were independently reviewed by 2 board-certified internists who, blinded to PET findings, classified patients into 1 of 2 categories: (1) progressive cognitive impairment (ie, memory, language, or functional abilities that progressively diminished at a pace faster than would be expected to occur as a consequence of normal aging processes), or (2) cognitive impairment that was nonprogressive over a period of at least 2 years (eg, mild short-term memory deficit typical for patient’s age and state of general physical health), other than changes clearly associated with CT/MRI–documented advancement of cerebrovascular disease. Interrater concordance of independent determinations of a progressive vs nonprogressive course was 92.5% (135/146), and the remaining cases were rated after discussion to reach consensus.

Study of Patients Undergoing Brain PET and Subsequent Neuropathologic Examination

Patients at each center underwent PET scans between 1984 and 1998 as part of research protocols designed to compare clinical and neuroimaging evaluations with results of neuropathologic examination. Instrumentation and scanning procedures were autonomously determined at each PET facility, and thus varied somewhat between facilities; images similar to the types of images collected at UCLA were acquired at all sites. More recent scans tended to be acquired on instruments capable of higher spatial resolution, but all instruments produced scans with adequate resolution to allow visual recognition of metabolic patterns characteristic of neurodegenerative disease. Questionnaires were sent to all contributing sites, requesting the following clinical data: patient date of birth, handedness, sex, date of PET, indication for scan, medications at time of PET, severity of dementing symptoms at time of scan, CT/MRI findings (when available), date of autopsy, pathology-based diagnosis, and any other noted brain abnormalities.

Autopsies were performed between 1984 and 2000, an average of 2.9 years after PET (range, 0.1–9.5 years). Histopathologic findings were established by neuropathologists at each contributing site, by the methods and criteria standard for each institution at the time pathologic examination was conducted. For 1 case, in which the patient’s brain tissue had been sampled by biopsy and autopsy with discordant results, diagnosis was based on autopsy results. For the purpose of this analysis, findings for each patient were classified as positive or negative for presence of neurodegenerative disease in general, and AD specifically. Accepted research criteria for pathologic diagnosis of AD were followed at all sites, although the specific set of applied criteria varied.

Each site was instructed to provide the scan findings obtained blinded to autopsy data. At the site of central coordination for this investigation, clinical, PET, and autopsy information was received and recorded after names had been redacted, replaced by code numbers at the contributing sites. Of all cases with PET-based diagnosis and histopathologic examination, 36 have been previously described,13,15,16 while the remaining 102 (74%) of pathologically verified cases (and 100% of the 146 longitudinally verified cases) are being presented for the first time.

Analysis of Brain Metabolic Data

For all cases in this study, scan results were classified by a nuclear medicine physician blinded to all pathological and clinical information except age, sex, and (when available at the time PET had been performed) CT and MRI reports, as indicative of a progressive or nonprogressive clinical course based on the image findings originally reported, according to the following criteria established a priori: progressive scans had (1) focal cortical hypometabolism in parietal, temporal, and/or frontal lobes, or (2) diffuse hypometabolism in associative cortex with relative sparing of sensorimotor cortex, or (3) a pattern of cerebral metabolism pathognomonic for a known neurodegenerative disease associated with progressive cognitive decline (ie, severe bilateral hypometabolism of caudate and lentiform nuclei seen in Huntington disease), with neither 1 nor 2 accounted for by matched findings on CT or MRI indicative of cerebrovascular disease, in those instances (n = 145) in which structural imaging data had been obtained. Nonprogressive scans had no abnormal findings or had only abnormal findings that did not meet the definition of progressive (eg, generalized cerebral atrophy with associated globally decreased metabolism, without sparing of sensorimotor cortex). For pathologically verified cases, based on the scan findings originating from each facility, patterns of cerebral metabolism were classified not only as being positive or negative for presence of any progres-
sive neurodegenerative dementia (eg, AD, dementia with Lewy bodies, frontotemporal dementia, Creutzfeldt-Jakob disease, progressive subcortical gliosis), but also for presence or absence of AD, specifically, by criteria established as described above and in the legend for Table 2.

To assess interrater variability, PET findings of the first 100 longitudinally followed cases analyzed were independently classified by a second nuclear medicine physician who was blinded to clinical information as above. To more closely parallel the application of this method in a nonresearch setting, this second physician was given no prior training and relied only on a half page of written instructions (corresponding to the criteria above) on evaluating the scans. Assigned PET classifications were concordant in 94% of cases, and overall correspondence to subsequent clinical course was nearly unchanged (84% vs 82%). Original images for half of the autopsy cases (68/138) also were available for examination at the central coordinating site. Diagnostic categorization (AD, neurodegenerative disease without AD, or no neurodegenerative disease) by a nuclear medicine physician blinded to all previous readings and to all clinical information other than patient’s age and sex was concordant with originally provided information in all but 1 case.

Statistical Analysis
Significance of differences between continuous variables across subject groups was assessed by 2-sided t test. Strength of association of categorical variables with clinical outcome results was assessed by χ² test, and associations were regarded as significant if P<.01, to adjust the more commonly used criterion of P<.05 for the multiple (4) categorized patient characteristics that could be tested for possible associations. Estimates of the sensitivity, specificity, accuracy, relative risk, and likelihood ratios were calculated by standard methods, and 95% confidence intervals (CIs) were calculated on the basis of assuming approximation of a normal distribution.\(^{17}\)

**RESULTS**
For the longitudinally followed patients, basic demographic characteristics are shown in Table 1. While 97% of the patients were experiencing cognitive problems at the time of PET, only 8% were noted to have altered personality or behavior at presentation. Among patients with cognitive complaints, memory deficits were most common, followed by difficulties with visuomotor and language skills. For the 108 patients whose handedness had been recorded, 98 (91%) were right-handed. The most uniformly available measure of cognitive function that could be identified across the subjects was the Mini-Mental State Examination (MMSE),\(^{18}\) obtained for the majority (85/146) of longitudinally confirmed cases. The mean (SD) of the MMSE scores of longitudinally followed patients measured near time of PET was 24 (6), of 30 total possible points. Initial MMSE scores of more than three fourths of the patients were at least 20, and most had scores ranging from 26 to 30.

For the pathologically verified patients, lack of uniformity of procedures among contributing sites for collection of demographic information prevented meaningful pooling of some of the analogous information. However, 59% of the patients in that group were male, the mean (SD) age (67[10] years) was similar to that of the longitudinally followed group, and a standardized rating of severity of dementia (as questionable, mild, moderate, or severe) obtained for 79 of 138 pathologically confirmed cases revealed that 70% of patients with documented severity ratings also had questionable or mild dementia near time of PET (17 questionable, 38 mild, 13 moderate, and 11 severe cases).

The predictive value of PET was examined by comparing the pattern of regional metabolism, visualized at time of initial evaluation, with each patient’s subsequent course (FIGURE). In the group with longitudinal clinical follow-up, a progressive course was documented in 59% (86/146) of the cases. PET correctly predicted an ensuing progressive course with a sensitivity of 91% (78/86; 95% CI, 85%-97%) and correctly predicted a nonprogressive course with a specificity of 75% (45/60; 95% CI, 64%-86%). The mean 3.2-year (SD,
1.7) clinical follow-up period for longitudinally followed patients was similar for those with positive (3.10 years) and negative (3.36 years) scans.

In the group with pathologically confirmed diagnoses, AD was identified in 70% (97/138) of histopathologically examined cases (Table 2). PET correctly identified the presence or absence of AD in 88% (95% CI, 82%-93%) of the cases, with a sensitivity of 94% (91/97; 95% CI, 89%-99%) and a specificity of 73% (30/41; 95% CI, 60%-87%). As the ability to make an accurate diagnosis is most clinically relevant in the earlier stages of disease, we additionally analyzed the subset of data representing the 55 patients with ultimate pathologic diagnosis who were documented to have questionable or mild dementia at time of PET. For this group, 41 (75%) of whom had AD, overall accuracy of PET was 89% (95% CI, 81%-97%) (ie, as high as it was for the whole group), with

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**Figure.** Positron Emission Tomography (PET) Patterns and Occurrence of Progressive Disease in 284 Patients Undergoing Evaluation for Dementia

PET scans typical of each of 6 categories of cerebral metabolic patterns (designated N1, N2, N3, P1, P2, and P3) are shown. The darkness of each point in each PET scan is directly proportional to the concentration of radiopharmaceutical located there, providing a map of cerebral metabolism. 

- **N1** shows the normal metabolic pattern at high (upper image) and mid-level (lower image) axial planes through the brain. At comparable levels, the N2 images display generalized atrophy and associated hypometabolism.
- **P1** images display bilateral parietal (arrows in upper image) and temporal (arrows in lower image) hypometabolism.
- **P2** images show extensive frontal hypometabolism.
- **P3** images show hypometabolism of both caudate and lentiform nuclei.

Images displaying **N1**, **N2**, and **P3** patterns were acquired with a Siemens ECAT EXACT HR+ scanner (CTI PET Systems Inc, Knoxville, Tenn); those displaying **N2**, **N3**, and **P2** patterns were acquired with a Siemens ECAT 931 scanner (CTI PET Systems Inc). The upper **N3** image was acquired using a GE Signa 1.5-T MRI scanner, repetition time=2100 milliseconds, echo time=80 milliseconds. 

*3 (Alzheimer disease) AD, 1 AD+progressive supranuclear palsy, and 3 Creutzfeldt-Jakob cases.
†86 AD, 4 AD+Lewy bodies, 1 AD+Parkinson disease, 1 AD+ cerebrovascular disease, 1 AD+Lewy bodies+cerebrovascular disease; 7 frontotemporal, 6 Lewy bodies, 3 subcortical gliosis, 2 Creutzfeldt-Jakob disease, 1 progressive supranuclear palsy, and 1 lipofuscinosis Kufs disease case.
sensitivity (95%; 95% CI, 89%-100%) and specificity (71%; 95% CI, 48%-95%) remaining comparable. Finally, PET detected the presence of neurodegenerative disease of any kind with a sensitivity of 94% (113/120; 95% CI, 90%-98%), specificity of 78% (14/18; 95% CI, 59%-97%), negative likelihood ratio of 0.075 (95% CI, 0.035-0.16), positive likelihood ratio of 4.2 (95% CI, 1.8-10.1), and overall accuracy of 92% (127/138; 95% CI, 88%-97%).

An overall measure of the prognostic value of PET was obtained by pooling the data across the longitudinally and neuropathologically studied groups (Figure). Of 210 patients with brain PET findings considered indicative of a progressive demencing process, 191 (91%) were subsequently documented to have progressive disease, either through longitudinal follow-up or histopathologic identification of a neurodegenerative dementia. In contrast, of 74 patients with PET findings considered negative for a progressive demencing process, only 15 (20%) exhibited evidence of progressive disease. Thus, symptomatic patients having areas of focal cortical hypometabolism not accounted for by cerebrovascular changes (identified by MRI in a total of 20 cases) had a progressive dementia with a 4.5-fold greater frequency than those with unsuspicous metabolic patterns. With regard to (prevalence-independent) test performance measures, of 206 patients with progressive disease, 191 had initial PET findings indicative of a progressive dementia, yielding a prognostic sensitivity of 93% (95% CI, 89%-96%); among the 78 patients without progressive disease, negative scan findings were reported in 59 cases, corresponding to a prognostic specificity of 76% (95% CI, 66%-85%). Overall accuracy was thus 88% (250/284; 95% CI, 84%-92%). The negative likelihood ratio (1/[1-sensitivity]/specificity) was 0.096 (95% CI, 0.06-0.16), while the positive likelihood ratio (specificity/[1-sensitivity]) was 3.8 (95% CI, 2.6-5.6). χ² Analysis confirmed that initial pattern of cerebral metabolism was significantly associated with subsequent course of progression (P<.001).

**COMMENT**

The measurement of regional brain metabolism in patients with symptoms of dementia has been under study since the early 1980s and has been extensively reviewed in recent years. The best studied application of this type is the use of PET with FDG to evaluate AD. Assessment of the diagnostic accuracy of PET even for this application, however, has been hindered by the rarity with which such studies involve patients undergoing longitudinal follow-up or subsequent histopathologic examination, as the approach used in most previous clinical series has been the comparison of PET findings to clinical assessments performed near the time of PET. The current investigation provides a clinical series that is not only among the largest yet reported for longitudinally assessing patients undergoing PET for dementia evaluation, but further, offers data for a quantity of previously unpublished PET studies of histopathologically diagnosed cases of dementia that substantially exceeds the sum total found in the previous published literature. It thereby provides a sample size that for the first time allows for statistically meaningful estimates of the diagnostic value of PET.

Based on MMSE (mean [SD], 24 [6]) and other severity data (eg, 70% with questionable or mild dementia), the patients evaluated in this study generally represented a mildly impaired population, in the context of the dementia neuroimaging literature: those articles stratifying patients by severity typically define an MMSE score of 20 as the cutoff for “mild” or “early stage” disease, and in a recent analysis of the usefulness of PET in “very early” dementia, the mean MMSE score was 25. Patterns of brain metabolism predicted whether these patients would likely have a clinical course marked by progressive dementia. Accuracy was particularly high with respect to prognostic sensitivity (93%), indicating that when a patient presents with cognitive or behavioral symptoms due to a progressive neurodegenerative process, sufficient cortical degeneration has usually already occurred to detectably diminish metabolism of some areas of the cortex. On the other hand, 9% of the patients with such metabolic deficits remained free of clinically or histopathologically evident neurodegenerative disease in our study, indicating that processes other than those poised to cause cognitive deterioration can produce areas of focal hypometabolism discernible by PET. It is thus important to bear in mind that while a negative scan offers considerable reassurance, a positive scan should not in itself be interpreted as a forerunner of certain progression.

Other potential limitations of the data deserve mention. For the longitudinally followed group, a minimum of 2 (and an average of 3) years of stable cognitive status after the time of PET was required for a patient to be deemed to have a nonprogressive postscan course. Some patients may have developed signs of progressive dementia after the period of follow-up included in this study. If these patients had a negative PET scan, then they would have been categorized as true negatives when in fact they were false negatives, so the sensitivity reported would have been falsely elevated. If patients had an abnormal PET scan with no progression detected during follow-up (but progression evident on longer follow-up), they would have been classified as false positives when in fact they were true positives, and the specificity reported here would be lower than the true specificity. Previous literature indicates that regional cerebral hypometabolism detectable by PET is highly sensitive to changes associated with neurodegenerative disease, including to changes occurring years before the emergence of overt symptoms, making the latter scenario seem more likely than the former.

Finally, for patients who were in fact free of progressive dementia at the time of scanning but subsequently ac-
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required a dementing illness, the conclusions reached here would not be affected. It needs to be emphasized, however, that the predictive ability of PET reported has been established only for the 2 to 3 years following the time of PET. A similar limitation exists for the neuropathologically diagnosed group: as there was no standardized periodic clinical evaluation of patients across centers, and as the interval between PET and histopathologic examination was variable, it is possible that some patients actually developed dementia during that interval without such disease having been present at the time of scanning, leading to some scans to be wrongly classified as true positive and others to be wrongly classified as false negative. In that case, the impact on our results would be that actual sensitivity is higher, and actual specificity is lower, than the values reported here. Since these changes are opposite in direction to those in the longitudinal arm of the investigation, the overall effect of all of them might be at least partly mitigated in our pooled analysis.

It was not within the scope of this article to attempt to quantitatively relate specific FDG-PET scan parameters to the rate of cognitive decline. We recently reported, however, that the magnitude of decline in performance of certain memory tasks over a 2-year period, among a small group of prospectively recruited cognitively intact subjects at genetic risk for development of AD, was proportional to the degree of hypometabolism in specific brain regions affected by AD.27 Another study, of a group of patients presumed to have AD, mostly with presenile onset,28 also found that the degree of cerebral hypometabolism correlated with subsequent deterioration.

A final potential limitation, regarding the degree of generalizability of the current results, needs to be considered. Most patients (including all those in the longitudinally followed group) were referred for PET evaluation on clinical grounds rather than recruited into a research protocol. Nevertheless, whether these results apply in other settings and populations with similar specificity and sensitivity remains to be determined. However, specialized equipment and staff were not required; readings were obtainable with simple visual analysis of scans acquired under standard clinical protocols by nuclear medicine clinical staff with no special neurologic expertise.

Although many of the relatively infrequent causes of dementia symptoms (thyroid disease, nutrient deficiencies, neurosyphilis, electrolyte imbalances) can be excluded on the basis of readily obtained laboratory analyses of blood samples, the most common causes—such as AD, cerebral vascular dementia, and depression, which together comprise the vast majority of cases—cannot be excluded or diagnosed on that basis. Nor can brain tumors or many other serious but less common causes (eg, frontotemporal dementia, dementia with Lewy bodies, Creutzfeldt-Jakob disease, Parkinson disease with dementia, corticobasal degeneration) be excluded that way. These latter entities, like AD, however, are inexorably progressive, as documented by straightforward longitudinal monitoring over several months to years following symptomatic presentation. The greatest clinical difficulty lies, therefore, in accurately identifying neurodegenerative disease at the time of presentation of early symptoms. This study was not designed to assess what role PET should play in the diagnostic evaluation of dementia. Rather, it addressed the more modest objective of providing basic data pertinent to determining the sensitivity and specificity of brain metabolic patterns, acquired and interpreted in a fashion attainable with clinical use of PET, for forecasting cognitive decline. Such data offer an informed basis for determining the value of PET in the clinical management of patients with early AD and other forms of dementia. The current findings provide evidence that the use of PET for evaluation of an appropriate population permits sensitive identification of future decline associated with AD and other neurodegenerative disease.

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Pets are the air of science. Without them you never can fly.
—Ivan Pavlov (1849-1936)