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Fluorodeoxyglucose positron emission tomography of mild cognitive impairment with clinical follow-up at 3 years

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Abstract

Background: Alzheimer's disease (AD) is the most common dementing illness. Development of effective treatments directed at AD requires an early diagnosis. Mild cognitive impairment (MCI) often heralds AD. Thus, characterizing MCI is fundamental to the early diagnosis of AD.

Methods: 19 MCI patients referred from a memory loss clinic and 27 healthy subjects, all followed up for 3 years. Metabolism scans (MCI minus controls) were compared voxel-wise after anatomic normalization and were examined both visually and with a computerized classifier.

Results: Agreement between raters as to whether the individual scans were normal or abnormal was high. Agreement between raters of the eventual clinical diagnosis and baseline metabolic pattern was poor. A computerized classifier was unsuccessful at classifying MCI from normal; however, its performance improved when using only prototypic AD-like MCI scans, indicating the classifier worked well when shared patterns existed in the data. Outcomes on follow-up were nine of 19 AD, five of 19 remained MCI, and five of 19 developed dementias other than AD. Both MCI cases of early Lewy body dementia (LBD) showed an AD-like metabolic pattern.

Conclusions: Visual inspection proved reliable in determining normal from abnormal scans, but it proved unreliable at predicting diagnosis on follow-up. Computerized classification of MCI by using an AD-like metabolic template (such as derived from the averaged MCI images) showed potential to identify patients who will develop AD. However, the metabolic pattern in early LBD did not differ from that in AD.

Keywords: MCI; PET; Support vector machine; Brain metabolism; Diagnosis; Alzheimer, Frontotemporal dementia; Lewy body; Aging; Classification

1. Introduction

Mild cognitive impairment (MCI) is considered a transitional phase between healthy cognitive aging and Alzheimer's disease (AD). It is diagnosed when a patient (1) has memory complaints, (2) shows a decline greater than 1.5 standard deviations from the age- and education-adjusted mean in declarative memory scores as assessed by neuropsychological testing, (3) has intact general cognition, (4) shows normal activities of daily living, and (5) does not have dementia [1]. From the initial emphasis on verbal memory, now termed amnestic MCI, the concept has been extended to include multiple-domain MCI and single-domain, nonamnestic MCI [2]. Approximately 20% of individuals older than the age of 70 years have MCI, with the incidence rising to almost half of those 80 years or older.

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Pharmaceutical agents to prevent or treat AD are under development. Such drugs have the greatest opportunity to treat AD before the disease has progressed to the stage in which extensive brain damage has occurred. The diagnosis of MCI is a frequent inclusion criterion for such drug studies. It is assumed to represent a prodrome to AD. Therefore, structural and functional characterization of MCI is important for the early diagnosis of AD.

MCI can be distinguished both structurally and functionally from healthy aging. For example, MCI patients show loss of gray matter and enlarged ventricles [3]. The greatest change occurs in the hippocampus and medial temporal cortex, but it can also include medial prefrontal cortex, posterior cingulate cortex (PCC), orbitofrontal cortices, insula, uncus [4], and others. Functionally, hypometabolism localizes to the PCC and parietal cortex as well as to the medial temporal lobe [5–13]. In contrast, gray matter density declines during normal aging in the dorsal prefrontal and parietal cortices [14]. The major decline in brain metabolism with age in healthy subjects localizes to the anterior cingulate cortex and adjacent regions [15].

Although the changes in MCI differ clearly from healthy aging, MCI patients share many features with AD. At the most basic level, the neuropathology of MCI appears to be that of AD [16,17]. In addition, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) studies have shown that those MCI patients who later develop probable AD show metabolic reductions similar to those found in AD. For example, eight MCI patients who later converted to probable AD showed reduction in the PCC and cinguloparietal cortices at their baseline evaluation [8]. Impaired baseline metabolism in the left parietotemporal region of MCI patients predicted those who progressed during a period of 3 years [18]. During the examination of 30 MCI patients for 16 months, 13 patients showed an AD pattern of hypometabolism; 11 of these converted to AD, whereas 16 of the 17 patients without the AD pattern remained stable [13]. Likewise, in a large series of 284 patients undergoing evaluation for dementia, the pattern of hypometabolism had predictive power. FDG-PET was able to predict deterioration during a 3.2-year follow-up period, with a sensitivity of 91% and a specificity of 75% [19]. These studies suggest that MCI patients with AD-like metabolic changes tend to progress and convert to AD.

The clinical course of MCI is variable. Overall, MCI patients have greater cognitive decline than normal subjects and show less decline than AD patients [1]. Although 1% to 2% of normal elderly convert to AD per year, approximately 10% to 15% of MCI patients convert to AD per year. Therefore, MCI represents at least a group at high risk of converting to AD. It is important to note that the original criteria for MCI are based on a clinical sample, ie, those presenting to clinicians with memory complaints. These criteria do not perform as well in population-based studies in which interviewers ask subjects about memory complaints [20,21]. The diagnosis appears unstable in such studies, with as many as 25% of MCI subjects reverting to normal during a follow-up interval of 10 years [22].

Imaging studies suggest metabolic heterogeneity within MCI itself. With FDG-PET, only 43% of MCI patients exhibited a pattern consistent with AD [13]. A large multicenter study with 114 MCI patients and 110 healthy elderly subjects found an AD pattern by FDG-PET in 79% of multiple-domain MCI patients but only 31% of amnestic MCI patients [7]. Amyloid deposition and hypometabolism as assessed by PET showed concordance in 54% of MCI cases [23]. Similarly, only half of MCI patients showed detectable amyloid deposition or microglial activation as assessed with PET [24].

The present study compared FDG-PET images in MCI patients referred from a memory loss clinic with a control, normative database of carefully screened subjects. The objective was to determine whether MCI patients could be reliably classified from healthy controls, and, if so, could the follow-up diagnoses be determined by the baseline findings. The MCI and control images were interpreted visually and also processed through a support vector machine (SVM). SVM uses a kernel function to map the data into an infinite-dimensional space, in which a hyperplane can be used to do the separation. This allows SVM models to perform separations even when the boundary between the classes is very complex, and even when classes with few samples or samples have high-dimensionality feature vectors. The patients were followed up for 3 years after the PET scan.

2. Methods

2.1. Human subjects

The characterization of the control subjects has been described previously [15]. Briefly, they were recruited from the community and underwent extensive medical and laboratory examination. They were assessed free of lifetime history of psychiatric disorders by using a structured diagnostic interview. All magnetic resonance images were considered normal for age.

The MCI patients were referred for imaging from the memory loss in the Geriatric, Research, Education, and Clinical Center at the Minneapolis Veterans Affairs Medical Center (MVAMC) in Minneapolis, MN. The diagnosis of MCI was made according to the criteria of Petersen et al [1] after an extensive evaluation including neuropsychological testing and medical evaluation. All but one woman were white male veterans. The ages ranged from 54 to 85 years (mean, 80).

All subjects gave informed consent approved by the Institutional Review Board of both the VAMC and the University of Minnesota. The MVAMC's Radiation Drug Committee also evaluated the protocols and dosimetry for consistency with food and drug administration guidelines.

Because of the possibility that control subjects were incorrectly classified as normal controls and could later become symptomatic for AD [25], all controls were reevaluated at ~2 to 3 years after the scan by using the Minnesota

Cognitive Acuity Screen [26]. All of those screened as cognitively impaired at 2 to 3 years were removed from the control data set. The final normal control data set consisted of 27 subjects (12 women) with ages 41 to 94 years (mean, 72).

2.2. PET imaging

The methods have been described previously [15]. Briefly, after an overnight fast, subjects received an intravenous injection of ^{18}F-FDG at a dose of 5 mCi/70 kg, as they reclined with eyes closed and ears open in a quiet dark room. After a 30-minute uptake period, they were transferred to an ECAT 953B or ECAT Exact scanner (Siemens, Knoxville, TN). Attenuation was measured. No arterial catheters were used for absolute quantitation.

2.3. PET scan processing and analysis

PET scans were adjusted to a whole-brain mean activity and stereotactically normalized by using Neurostat (S. Minoshima, University of Washington, Seattle, WA). This software has been validated [27–29] and has been used in several studies of aging and AD [7,8,13,15]. Each patient's scan was compared voxel-wise with the normative data set after age regression to generate difference images. Each control subject's scan was compared with the remainder of the control scans by using the leave-one-out method with replacement. The color scale for viewing the data ranged from purple (minimum hypometabolism displayed, t = −2) to white (maximal hypometabolism displayed, t = −6). One blinded reader (J.V.P.) examined the scans by using only the transverse sections. The other blinded reader (M.A.K.) used iiV [30] to examine the images. This program displayed all perspectives (coronal, sagittal, and transverse) containing a point of interest selected by the user.

The patterns of metabolic change were identified visually by the readers according to criteria reported widely [5–13]. The AD pattern was identified by hypometabolism in the medial parietal cortex and lateral parietal regions. The medial parietal involvement could include posterior cingulate, retrosplenial cortex, or precuneus. The lateral parietal regions included mostly inferior parietal regions (supramarginal gyrus), with extension into superior parietal cortex and lateral temporal cortex. The frontotemporal dementia (FTD) pattern was identified by hypometabolism in anterior/superior temporal cortex and mesial/lateral prefrontal cortex, particularly with greater involvement in the left than in the right sides. Because there is no pathognomonic feature for early Lewy body dementia (LBD), no attempt was made to classify it unless occipital hypometabolism was present, which occurred in no one.

2.4. Support vector machine

These analyses were done on the first 13 MCI cases and 15 controls. The SVM classifier was run on SVMLight [31] by using a radial basis function. The parameters for the function were chosen through cross-validation by using a toolkit called LIBSVM [32]. Feature selection was accomplished by using the FSELECT tool that measures the f-score, a simple calculation used to measure the discrimination between two sets of numbers [33]. The entire brain was resampled into 3 × 3 × 3 cubic voxels (voxel dimension, 2.25 mm^3) to minimize computation time. Two features, lobe and cluster, were defined. The lobar features came from the Talairach Daemon (Research Imaging Center, UTHSCSA, San Antonio, TX), yielding 12 regions, six in each hemisphere [34]. A brain lobe was labeled as MCI or normal if ≥50% of the cubes had the label MCI or normal, respectively. The cluster feature used a template based on the average image of the MCI subjects (Figure 1). Each cluster or connected region was identified by using a t threshold of 2. Each sample cube gave seven first-order statistics on the counts observed: sum, maximum, minimum, mean, median, standard deviation, and variance. Additional second-order features included entropy, energy, contrast, and homogeneity [35]. Classification used a cluster-by-cluster approach as well as a whole-brain approach and leave-one-out cross-validation.

3. Results

3.1. Baseline and follow-up diagnoses of MCI patients at 3 years

Table 1 shows the baseline clinical diagnoses of all MCI patients as well as their diagnoses at 3 years. As noted, 11 of 19 subjects had amnestic MCI, with four of these having deficits in multiple domains. On follow-up at 3 years, nine of 19 (47%) MCI patients converted to probable or possible AD. Two of 19 (∼10%) patients converted to probable LDB, one of which was autopsy-verified. Another two cases converted to probable FTD. Case pL0083 converted to dementia, not otherwise specified. Five of 19 (26%) remained labeled as MCI. During the 3 years, four deaths occurred involving one probable AD case, one definite LBD case (autopsy-verified), one FTD case, and pL0083 (dementia, not otherwise specified).

3.2. Visual inspection of the difference images

The two independent blinded raters experienced in PET assessed each difference image as normal or abnormal and, if abnormal, whether having an AD or FTD pattern. This would be the most straightforward approach in a clinical setting. Figure 1 shows the average of all MCI patients minus the average of all normal subjects. This average corresponds to the typical AD-like pattern in the literature. However, heterogeneity in metabolic patterns was evident in individual cases. For example, Figure 2 shows baseline examinations of three MCI subjects, with one showing the AD-like pattern, one without any pattern, and another with an FTD-like pattern. Table 2 shows the agreement between different rater's classifications. The agreement (κ) between the initial diagnostic label and the observed PET pattern was low for both

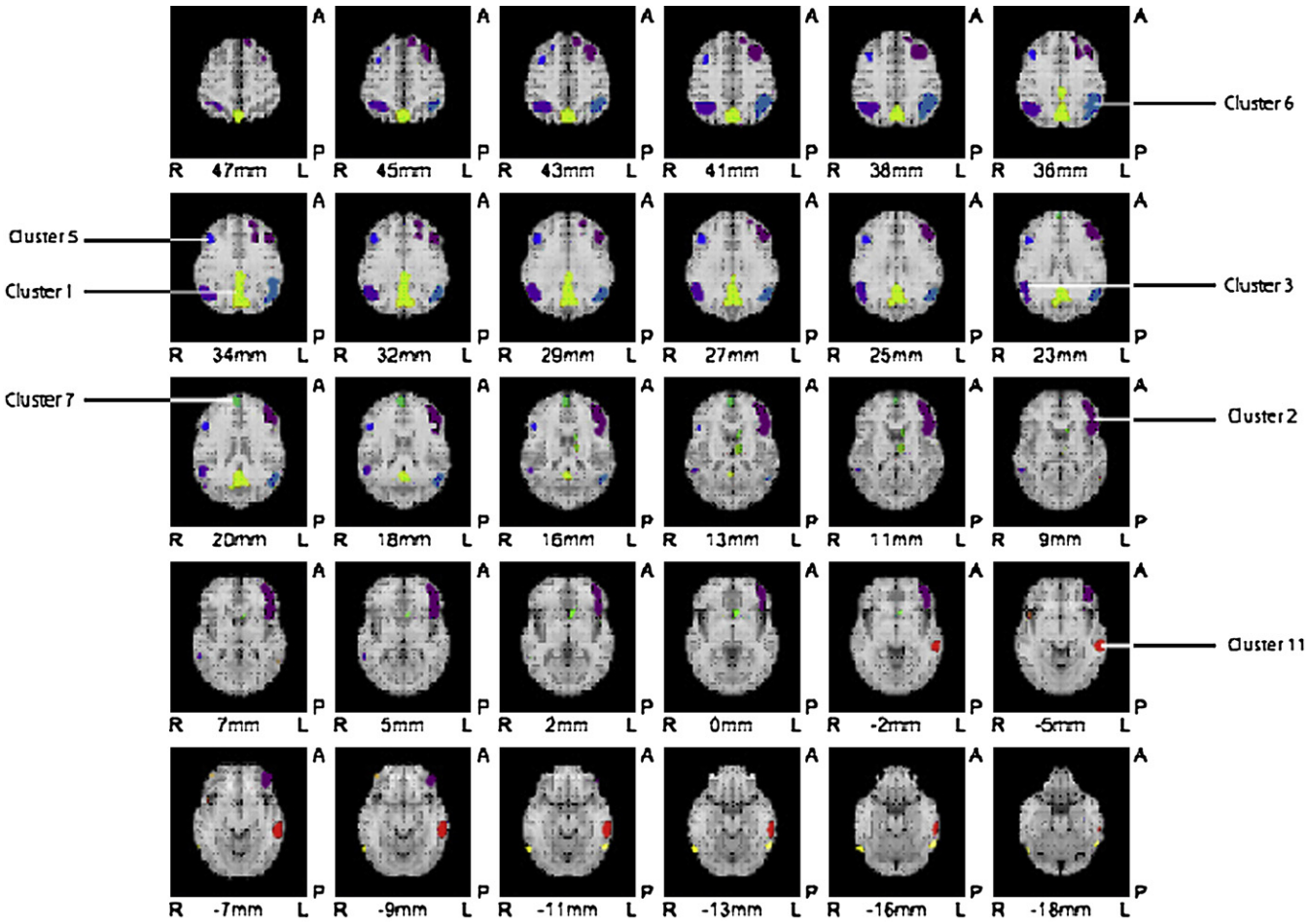

Fig. 1. Cluster division for SVM based on the subtraction of ^{18}FDG-PET scans of healthy controls from all MCI patients after age regression (ie, MCI template). Note the similarity to AD pattern. Top of image is anterior; image left is patient's right side. Each cluster has been colorized to aid in identification.

raters (J.V.P.: $\kappa = 0.40$, standard error [SE] = 0.14, $P < .006$ [versus $\kappa = 0$]; M.A.K.: $\kappa = 0.55$, SE = .13, $P < .001$ [versus $\kappa = 0$]). The inter-rater agreement for classifying images as normal or not normal was high, despite each rater using slightly different approaches to examine the data (J.V.P. versus M.A.K. for the rating of all normal subjects as normal versus not normal: $\kappa = 0.86$, SE = 0.08, $P < .001$; ie, agreement on 43 of 46 normal subjects); (J.V.P. versus M.A.K. for the rating of all MCI subjects as normal versus not normal: $\kappa = 0.66$, SE = 0.17, $P < .002$; ie, agreement on 16 of 19 MCI patients).

To address the issue of whether baseline classification predicted outcome at 3 years, Table 1 shows the baseline classification by both raters along with the clinical diagnosis at 3 years of follow-up. Seven of 19 cases (pL0047, pL0078, pL0093, pL0094, pL0100, pL0102, and pL0106) showed agreement across both raters. Of these, three cases (pL0094, pL0102, and pL0106) were classified as normal but on follow-up were diagnosed as probable or possible AD. Cases pL0078 and pL0093 were classified by both raters as AD, but on follow-up they were diagnosed as definite LBD and probable LBD, respectively. Case pL0100 was classified by both raters as FTD, and the follow-up diagnosis was FTD. Therefore, baseline classification of MCI scans by visual analysis did not reliably predict outcome at 3 years, particularly in trying to differentiate early AD from early LBD.

3.3. Support vector machine

The clusters were defined on the basis of the average t-image between all MCI (N = 19) subjects contrasted with normal controls (N = 27) to provide an MCI template. Figure 1 shows the individual clusters from this averaged difference image. The first classification experiment used the clinical diagnosis (MCI, normal) to label each scan. By using $3 \times 3 \times 3$ cubes, whole-brain and lobar analysis yielded overall sensitivity of 62% and specificity of 83%. Analysis with individual clusters did not work well; each brain was classified as normal.

The second classification approach used training labels based on the pattern in the image, not on clinical diagnosis. Because MCI criteria might result in a heterogeneous group of patients, the next classification used prototypic examples. All difference images of each MCI patient versus controls

Table 1
Initial PET findings and diagnoses of MCI patients at 3 years of follow-up

Scan no.	Initial diagnosis	Reading (J.V.P.)	Reading (M.A.K.)	Diagnosis on follow-up
pL0024	MCI, amnestic	AD	FTD	Probable AD*,†
pL0025	MCI, amnestic	HC	AD	MCI, amnestic*
pL0043	MCI, amnestic	AD	HC	Probable AD
pL0046	MCI, amnestic	HC	FTD	Probable AD
pL0047	MCI, amnestic	AD	AD	MCI, amnestic
pL0078	MCI, nonamnestic, multi-domain	AD	AD	Definite LBD*,†
pL0083	MCI, nonamnestic	AD	HC	Dementia, NOS*,†
pL0093	MCI, NOS	AD	AD	Probable LBD†
pL0094	MCI, amnestic, multi-domain	HC	HC	Probable AD
pL0099	MCI, amnestic, 1 domain	HC	AD	Probable AD
pL0100	MCI, NOS	FTD	AD/FTD	Probable FTD†
pL0102	MCI, amnestic	HC	HC	Possible AD
pL0103	MCI, nonamnestic	HC	AD	MCI, nonamnestic, stable
pL0106	MCI, amnestic, multi-domain	HC	HC	Possible AD
pL0111	MCI, nonamnestic, multi-domain	HC	AD	Probable FTD
pL0112	MCI, nonamnestic, 1 domain	HC	AD	MCI, nonamnestic, 1 domain
pL0113	MCI, amnestic, multi-domain	Artifact	AD	Probable AD
pL0115	MCI, amnestic, multi-domain	HC	AD	Probable AD
pL0116	MCI, nonamnestic, multi-domain	HC	FTD	MCI, nonamnestic, multi-domain

Abbreviations: NOS, not otherwise specified; HC, healthy control.
*AD-like pattern used for SVM analysis.
†Deceased.

were reviewed visually. The control images were selected on the basis of their having no significant differences (ie, $t < 2$) from the rest of the controls (N = 15/27). The MCI images were selected as AD-like on the basis of their having hypometabolism in the PCC and in at least one unilateral parietal lobe (Figure 1; N = 5/19; pL0024, pL0025, pL0078, pL0083, and pL0093). The average image of the preselected MCI scans minus preselected controls showed only one right parietal focus large enough to use as a cluster (Figure 1, cluster #3, 176 valid cubes). This cluster showed an overall classification accuracy of 90%, with 100% sensitivity and 86% specificity. Whole-brain classification with lobar segmentation yielded accuracies in the range of 85% to 90%. Because of the small number of MCI prototypic scans, a low

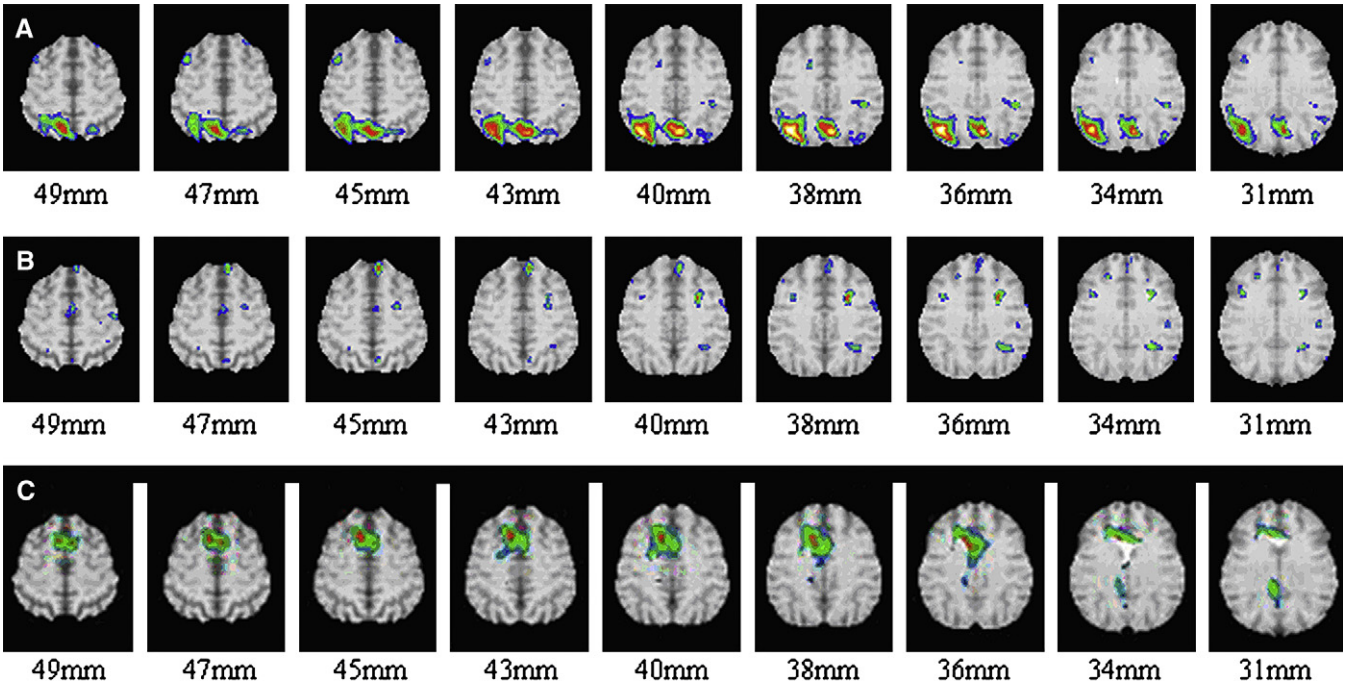

Fig. 2. Examples of ^{18}FDG-PET difference images between different individual MCI patients versus controls showing examples of presence (A) and absence (B) of an AD -like pattern as well as one with an FTD pattern (C). The numbers indicate millimeters above the anterior and posterior commissural plane. Orientation is same as in Fig. 1.

Table 2
Concordance of classification by two blinded raters of ^{18}FDG-PET difference images (MCI patient minus controls)

Interpreter	Initial diagnostic classification	Sample size, N	Normal PET	AD-PET	FTD-PET
J.V.P.*	MCI	19	11	6	1
M.A.K.	MCI	19	5	10	4
J.V.P.	Normal	27	22	2	3
M.A.K.	Normal	27	22	3	2

*One subject's scan rated as artifactual.

sensitivity was observed when two of five cases were misclassified. These results might be improved with more cases for training.

4. Discussion

4.1. Clinical outcomes at 3 years

As expected, the most frequent outcome was AD (47%) or MCI (26%). Probably with continued follow-up, more of the MCI cases would have converted to AD. Given the age range of the sample, the frequencies of conversion to FTD (~10%) and LBD (~10%) are not inconsistent with other prevalence estimates [36].

4.2. Visual classification of MCI versus normal FDG-PET scans

There was good inter-rater agreement of FDG-PET scans classified by visual inspection as normal versus not normal. Assuming that most neuropsychiatric disorders have signal-to-noise ratios in the image similar in magnitude to that seen in MCI patients, a clinician could be informed as to whether any specific patient has or does not have a normal scan. This might be helpful when there are no clues to diagnosis or evidence for pathology without other findings. Patients with negative scans are unlikely to progress. However, in the present series, both raters identified three of 19 MCI patients as showing the healthy control pattern, yet at 3 years, these patients progressed to probable or possible AD.

There was poor agreement for both raters between diagnosis at 3 years and baseline FDG scans identified by the initial label (MCI versus normal) and classified as PET pattern (normal, AD, and FTD). This suggests that labeling scans as MCI or normal did not produce a population with consistent patterns in the FDG-PET images. Indeed, 26% of the MCI sample on follow-up at 3 years had probable dementias other than AD. When others have used the AD pattern as a template, a considerable fraction of MCI patients do not show the AD pattern.

The large number of MCI patients who did not convert to AD or did not show the AD hypometabolic pattern appears counterintuitive, given the predominant finding that the pathology of MCI is that of AD [16,17]. The follow-up interval in this study was short, and more cases of conversion to AD would be expected with time. We used diagnoses as end points, in which longitudinal cognitive scores could show progressive deterioration despite persistence of the MCI diagnosis. Also, clinicians might have referred cases with more complex or atypical presentation; this series was not serial. However, this sample was also different from those studied for pathology. The study by Morris et al [16] used clinical dementia rating 0.5 rather than MCI criteria. The equivalence of these two diagnostic approaches is unclear. In the study by Markesbery et al [17], control subjects with Braak stages III or higher were excluded, which could bias the differences between AD and controls. Also, the mean time between diagnosis and death for MCI cases was 2 years. Only four of the cases presented here died during the subsequent 3 years. Therefore, MCI is clearly enriched in those who will convert to AD, but patients fitting these criteria can develop other dementias. Differences between MCI groups probably reflect differences in the recruitment method and definitions.

4.3. SVM classification

SVM classification on the basis of the clinical diagnosis of MCI does not produce a population with a consistent pattern in FDG-PET scans. The highest accuracy achieved by cluster classification was 67%, and the highest whole-brain classification was 76%. No model produced both high sensitivity and high specificity.

This conclusion is consistent with other published literature. For example, Drezega et al [13] found only 43% of MCI patients had PET scans suggestive of AD pathology. The study also showed that 85% of those with the hypometabolic AD pattern converted to AD with a mean follow-up of 16 months, whereas those without such a pattern remained largely stable at follow-up (94%). Similarly, a more recent, large multicenter study found 76% of multi-domain MCI showed the AD pattern, whereas only 31% of amnestic MCI showed the pattern [7]. The greater prevalence of the AD pattern in the multiple-domain MCI group is consistent with its more aggressive course compared with purely amnestic MCI [37].

Using structural atrophy as quantitated by gray matter density from structural magnetic resonance images from the AD neuroimaging initiative data set, Fan et al [4] used three groups: AD, MCI, and normal subjects. They trained an SVM classifier to optimally separate AD from normal subjects. With this classifier, they found that one of three MCI patients did not have the AD pattern of atrophy. The AD-like MCI patients showed greater change scores in the Mini-Mental State Examination than did the MCI patients without the AD structural pattern. No follow-up was reported. Their approach differed from ours in that the present study did not use AD patients to generate a template but attempted to initially classify MCI from normal controls directly. The improved classification on the basis of separation of AD from controls [4] when compared with

separation of MCI from controls (the case here) suggests the AD pattern is the dominant feature in MCI. In other words, there is no other metabolic signature in MCI patients.

Indeed, the selection of prototypes from the present data set helped SVM to classify MCI from normal controls. When MCI images were preselected, showing at least some prototypic AD-like patterns as well as control images that were clearly void of any signals when compared with the other controls, the best performing models had accuracies of 90% with either lobar or cluster feature analysis, even with the limited number of scans after selection. This confirmed that SVM was in fact working properly. The right parietal cluster was the sole feature in the cluster analysis. However, the very small number of images produced by the preselection of prototypes yielded poor sensitivities and specificities. The loss of so many images suspicious for artifacts or other signals in selecting prototypic images underscores the importance of preventing motion during scanning, which can be particularly difficult for elderly patients (especially because many current scanners do not have list mode capabilities, ie, collection of data in sequential blocks of time enabling recovery of data when motion occurs). In addition, accurate anatomic standardization becomes more important in the face of increased ventricular and sulcal volumes.

4.4. Limitations of the study

The sample size of 19 MCI patients and 27 control subjects might limit the generalizability of the results. Larger samples would improve computerized classification based on machine learning from exemplars. The MCI subjects were recruited from a memory loss clinic in the Geriatric, Research, Education, and Clinical Center program at a VA Medical Center. All MCI subjects but one were male. Both the source of the subjects and their gender might limit generalizability of the results to other types of clinics or female subjects. Intersubject registration methods and machine learning algorithms are rapidly evolving and might provide improved signal-to-noise ratios in the processed images. Selection of other SVM parameters and software might improve the robustness of the classification. However, the present implementation worked fine with the selected a priori prototypic images. The results of this study depend also on the technology used for imaging. More modern PET scanners with higher resolution might decrease partial volume effects that directly affect the metabolic data and would likely improve the detectability of medial temporal changes. Finally, elderly patients often take many medications and have comorbid illnesses, both of which could affect the brain metabolic data.

4.5. Conclusions

FDG-PET scans from subjects who were normal or diagnosed with MCI could be classified visually as normal or not normal with good inter-rater agreement. However, classification of the scans from the MCI group into normal, AD, or FTD was less reliable. SVM was unsuccessful at classifying MCI patients from normal subjects. Most likely, the heterogeneity seen at follow-up could account for this. In this sample of MCI patients, 25% developed dementias other than AD during a 3-year follow-up. Therefore, no metabolic signature arose in MCI other than the AD-like pattern. SVM was most successful when using only prototypic normal images or AD-like images from MCI patients, indicating that SVM could succeed when there were consistent patterns. The right parietal cortex provided the best classification between MCI scans with AD-like pattern from normal controls. With either whole-brain or cluster analysis, the accuracy was about 90%. The designation of MCI enriches a sample that will develop AD, but a significant number of cases will also develop other dementias. Identifying baseline scans as AD or FTD met with only partial success when compared with the follow-up diagnoses at 3 years. These results suggest that drug trials targeted at AD pathology should preselect enrollees with AD-like patterns. Nevertheless, patients with LBD showed typical AD patterns that would contaminate the sample unless they were also responsive to the treatment under investigation.

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