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Objective: To compare assessment of regional cerebral metabolic changes with [11C]dihydrotetrabenazine (DTBZ)–positron emission tomography (PET) measurement of regional cerebral blood flow (K₁) and fludeoxyglucose F18 (FDG)–PET measurement of regional cerebral glucose uptake (CMRglc) in a clinically representative sample of subjects with mild dementia and mild cognitive impairment (MCI).

Design: [11C]Dihydrotetrabenazine-PET K₁ and FDG-PET CMRglc measurements were performed.

Setting: University-based cognitive disorders clinic.

Participants: Fifty subjects with either mild dementia (Mini-Mental State Examination score ≥ 18) or MCI. Their results were compared with those of 80 normal control subjects.

Main Outcome Measures: The DTBZ-PET regional K₁ and FDG-PET CMRglc measurements were compared with standard correlation analysis. The overall patterns of DTBZ-PET K₁ and FDG-PET CMRglc deficits were assessed with stereotaxic surface projections (SSPs) of parametric images.

Results: The DTBZ-PET regional K₁ and FDG-PET CMRglc measurements were highly correlated, both within and between subjects. The SSP maps of deficits in DTBZ-PET regional K₁ and FDG-PET CMRglc measurements were markedly similar. The DTBZ-PET K₁ SSP maps exhibited a mild decrease in sensitivity relative to FDG-PET CMRglc maps.

Conclusions: Both DTBZ-PET K₁ and FDG-PET CMRglc measurements provide comparable information in assessment of regional cerebral metabolic deficits in mild dementia and MCI. Blood flow measures can assess regional cerebral metabolism deficits accurately in mild dementia and MCI. Blood flow assessments of regional cerebral metabolic deficits can be combined with tracer binding results to improve utility of PET imaging in mild dementia and MCI.

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The present approach to diagnosis of dementia relies on clinical characterization, psychometric evaluation, and application of standardized clinical criteria. There is overlap in clinical criteria for the 3 major forms of degenerative dementia—Alzheimer disease (AD), Lewy body dementia (LBD), and frontotemporal dementias (FTDs)—and clinical diagnosis has relatively poor specificity. Differentiation is particularly difficult in individuals with early, mild dementia. Positron emission tomography (PET) is a useful technique for evaluation of dementias. Fludeoxyglucose F18–PET (FDG-PET) assessment of the regional cerebral metabolic rate for glucose (CMRglc) is the most widely studied PET method for evaluation of dementias. Fludeoxyglucose F18–PET is useful in determining whether individuals have an underlying cerebral problem, differentiating types of dementia, identifying cerebral abnormalities in individuals with mild cognitive impairment (MCI), predicting the likelihood of progression from MCI, and predicting the rate of progression of dementia.

Fludeoxyglucose F18–PET identifies characteristic patterns of regional cerebral metabolic changes in AD, LBD, FTDs, and vascular dementia. Positron emission tomographic methods identifying characteristic pathologic features of dementias are being explored. Diminished dopaminergic nigrostriatal terminals are a feature of LBD. Single-site studies and a recent multicenter clinical trial indicate that PET or single-photon
emission computed tomographic methods measuring nigrostriatal dopaminergic terminal density are useful in establishing a diagnosis of LBD.\textsuperscript{40-42} Tracers binding to characteristic histopathologic features of dementias, such as the amyloid ligand 2-(4-methylaminophenyl) benzothiazole (Pittsburgh Compound B), may provide an in vivo analogue of histopathologic diagnosis.\textsuperscript{43-52} Determining patterns of altered regional cerebral metabolism and abnormal retention of tracers aimed at characteristic pathologic features should provide complementary information. This can be accomplished by studying patients with FDG-PET and a second PET study using one of the nigrostriatal dopaminergic terminal ligands or \textsuperscript{[11C]} Pittsburgh Compound B.\textsuperscript{53} This approach requires at least 2 scans with accompanying increased expense, radiation exposure, and demands on patients.

Regional cerebral metabolism and regional cerebral blood flow are tightly coupled.\textsuperscript{54-56} Data analysis for some PET tracers allows determination of the regional cerebral tracer blood-to-brain transport rate (K\textsubscript{1}) as a measure of regional cerebral blood flow. We reported previously that assessment of regional cerebral K\textsubscript{1} of the dopaminergic terminal ligand \textsuperscript{[11C]} dihydrotetrabenazine (DTBZ) produced results closely comparable with measurement of CMR\textsubscript{glc} with FDG-PET.\textsuperscript{57} Our prior study was a retrospective analysis of subjects drawn from a well-characterized research cohort not representative of clinical practice. These subjects had moderate AD (mean Mini-Mental State Examination [MMSE] score=15), LBD (mean MMSE score=17), and FTD (mean MMSE score=23), contrasting with subjects with early, mild dementia/ MCI, in whom accurate clinical diagnosis is most difficult. To confirm the utility of K\textsubscript{1} assessments, we report the comparison of FDG-PET assessment of CMR\textsubscript{glc} with measurements of DTBZ-PET K\textsubscript{1} in a prospective series of representative subjects undergoing initial characterization of mild dementia and MCI.

### METHODS

#### SUBJECTS

Fifty subjects were recruited through the Michigan Alzheimer Disease Research Center as part of an ongoing project studying the utility of PET imaging in early dementia and MCI. Subjects were drawn from the Cognitive Disorders Clinic at the University of Michigan. Subjects were excluded if their MMSE score was lower than 18 or if they had a confounding neurologic or psychiatric disorder that prevented establishment of a clear diagnosis of dementia or MCI. Subjects were also excluded if clinical evaluation (including routine structural imaging) indicated a diagnosis of vascular dementia. While this is not a population-based cohort, subjects enrolled for this study are representative of patients seen for initial evaluation in tertiary referral cognitive disorders clinics. There is no overlap in subjects between those enrolled in this study and our prior study of DTBZ K\textsubscript{1} and FDG-PET CMR\textsubscript{glc}.

All subjects underwent standardized clinical and psychometric evaluations. Clinical evaluations consisted of a history and standard neurologic examination performed by a neurologist experienced in evaluating dementias. All subjects underwent evaluation for treatable causes of dementia with recommended serum and structural imaging studies.\textsuperscript{58} Psychometric evaluation included the Alzheimer Disease Research Center Unified Data Set measures (Digit Span, Category Fluency, Trails Test, Digit Symbol, Wechsler Memory Scale–Revised Logical Memory Story A, 30-item Boston Naming Test, Geriatric Depression Scale, and Neuropsychiatric Inventory Questionnaire) plus additional standard measures of memory, executive function, attention, language, visuospatial function, mood, and anxiety. Clinical and psychometric data were abstracted into a standard form stripped of identifiers by 1 of the authors (J.F.B.). Standardized data forms were reviewed in a consensus conference by 3 authors (R.L.A., K.A.F., and B.G.) to assign a consensus diagnosis. Standard criteria were used to assign diagnoses of AD, LBD, and FTD.\textsuperscript{58-60} For diagnosis of MCI, standard clinical and psychometric criteria were applied.\textsuperscript{61} Subjects with MCI were classified as having single-domain MCI (amnestic or nonamnestic) or multidomain MCI. All subjects underwent PET imaging within 3 months of initial evaluation. Scans of 80 age-matched, normal subjects studied previously in our center were used as control data (supplementary table at http://sitemaker.umich.edu/albinsuppldata).

#### PET IMAGING

All subjects underwent DTBZ- and FDG-PET either in the same imaging session or on consecutive days if they were not able to tolerate the 4-hour procedure. The DTBZ scans were performed on a Siemens ECAT Exact HR+ scanner (Siemens, Knoxville, Tennessee), while FDG scans were performed on a Siemens Biograph Classic PET/CT scanner. Subjects were awake and supine in a quiet, dimly lit room with their eyes open. For DTBZ, a mean dose of 666 MBq (SD, 66 MBq [mean, 18 mCi; SD, 1.8 mCi]) of DTBZ was administered intravenously. An equilibrium protocol was used, infusing 33% of the dose for 30 seconds, followed by continuous infusion of the remaining 45% for 60 minutes.\textsuperscript{62} The FDG studies were performed as a single 20-minute scan acquired 30 minutes after intravenous injection of a mean dose of 296 MBq (SD, 29 MBq [mean, 8.0 mCi; SD, 0.8 mCi]) of FDG. All scans were acquired in 3-dimensional mode. Measured attenuation correction was performed using a 5-minute 2-dimensional transmission scan followed by segmentation and reprojection. Scatter correction was performed on all scans. After Fourier rebinning of the 3-dimensional projection sinograms into 2-dimensional data sets, images were reconstructed using ordered subset expectation maximization, with 4 iterations and 16 subsets with no additional smoothing, providing both in-plane and axial image resolution of approximately 5.5-mm full-width at half-maximum.

#### IMAGE PROCESSING AND DATA ANALYSIS

The single 20-minute FDG image acquired starting 30 minutes postinjection provided an index of CMR\textsubscript{glc}. For the DTBZ scan, the average of the first 4 minutes of uptake provided our index of ligand transport, K\textsubscript{1}. The PET images for both measures for each subject were reoriented to a common coordinate system based on the stereotactic atlas of Talairach and Tournoux.\textsuperscript{63} After reorientation, all images underwent linear scaling and nonlinear warping.\textsuperscript{64} A single transformation based on the individual’s summed FDG and DTBZ K\textsubscript{1} images was calculated for each subject and then applied to both image sets. All transaxial levels of the Talairach and Tournoux atlas have been digitized, and a set of standardized cortical and subcortical volumes of interest (VOIs) was defined on the atlas images.\textsuperscript{65} A subset of 34 cortical VOIs (17 per hemisphere) was selected for analysis and applied automatically to all images for all subjects with mild dementia and mild MCI and the 13 control subjects for correlation analysis of DTBZ K\textsubscript{1} and FDG CMR\textsubscript{glc}.
This set of regions included cortical areas hypothesized to provide the best differentiation between groups. We expected frontal regions, particularly medial, to be affected more in FTD than AD or LBD and posterior parietal/posterior cingulate regions to be more affected in AD and LBD than FTD. We expected the occipital region to be more affected in LBD than AD or FTD and to be the region that best differentiates LBD from AD. Sensorimotor cortex was included as a cortical region likely to be least affected in these dementias. The FDG and DTBZ K1 images were normalized to the mean VOI value obtained from the pons and cerebellar vermis. These 2 regions were selected as the normalizing factor because they are structures known to be minimally involved in these disorders, enhancing the ability to detect regional cortical deficits by removal of the more variable global factor in these measures.

STATISTICAL ANALYSIS

Both within-subject and across-subject correlations were performed. Within-subject correlations were calculated for each of the 50 subjects with mild dementia or MCI and 15 controls who received both FDG and DTBZ scans. The VOI FDG CMRglc and DTBZ K1 normalized values were correlated for all 34 selected cortical regions. Across-subject correlations were calculated for each of the 34 regions separately for the 50 subjects with mild dementia or MCI and 15 controls.

STEREOTACTIC SURFACE PROJECTIONS

The use of stereotactic surface projections (SSPs) is a standard method for processing FDG CMRglc data to produce easily interpretable parametric images. In this voxel-based method, gray matter activity is projected to the cortical surface in an anatomically standardized manner. The resulting map of brain activity is compared with a database of appropriate matched subjects to generate a z-score map of deviations from normal. The z-score maps permit ready visual interpretation of CMRglc deficit patterns. We used the Neurostat program and a control database from 68 subjects of similar age without clinical evidence of any neurologic disease. These 68 individuals were studied previously in our center using the same scan protocol used in this project.

RESULTS

SUBJECTS

Fifty subjects with dementia or MCI participated. Their mean age was 70 years (SD, 10 years; range, 51-91 years; 28 women; 22 men). There were 19 subjects with AD, 5 with LBD, and 9 with FTD. Sixteen subjects were classified as having MCI, with 9 subjects with amnestic MCI, 4 with nonamnestic MCI, and 3 with multidomain MCI. One subject refused psychometric evaluation and was classified as indeterminate. Of the 80 control subjects scanned, 27 received FDG (mean age, 71 years; SD, 9 years; range 55-88 years; 13 women, 14 men), and 68 received DTBZ (mean age, 68 years; SD, 8 years; range, 55-86 years; 38 women; 37 men). Fifteen control subjects received both FDG and DTBZ scans (mean age, 70 years; SD, 9 years; range 55-86 years; 8 women; 7 men).

FDG CMRglc AND DTBZ K1 CORRELATION ANALYSIS

There was excellent correspondence between regional cerebral metabolism assessed with FDG and regional cerebral blood flow assessed with DTBZ K1. Regional deficits averaged across all subjects with mild dementia or MCI, reported as percentage of the control mean, were similar for the 2 PET measures in most regions examined (Figure 1). Frontal cortical regions did exhibit slightly greater deficits in FDG than in DTBZ K1, reaching significance both laterally and medially. In other regions, both the magnitude of the declines and the variability of the deficits were comparable.
Within-subject correlations of the measures, the magnitude of the deficits correlated highly. The range of values, averaging 0.78 (SD, 0.08; range 0.64-0.88). The much broader range of data values.

Across-subject correlations between FDG and DTBZ 

K1 (across the regions examined) averaged 0.88 (SD, 0.07) for the 50 subjects with mild dementia or MCI (range, 0.73-0.96; Figure 2). Within-subject correlations for controls were lower owing to the smaller range, 0.74 (SD, 0.14; range, 0.37-0.96; Figure 2). Within-subject correlations for controls averaged 0.78 (SD, 0.08; range 0.64-0.88). Besides the similarity in image pattern between the measures, the magnitude of the deficits correlated highly. Within-subject correlations of the z scores relative to controls averaged 0.74 (SD, 0.14; range, 0.37-0.96; supplementary figure 1 at http://sitemaker.umich.edu/albinsupdata). Z-score correlations for controls averaged 0.54 (SD, 0.25; range, 0.05-0.82). The much broader range of z-score correlations is due to the nature of the z-score measure. Control and subjects with mild dementia or MCT who have image patterns similar to the normal mean pattern will have low correlations owing to the limited range of data values.

Across-subject correlations between FDG and DTBZ 

K1 varied considerably across the regions examined. Correlations across the 34 regions average 0.78 (SD, 0.14; range, 0.51-0.94) in subjects with mild dementia or MCI and 0.76 (SD, 0.13; range, 0.48-0.91) in controls. Correlations across the patient-subjects were uniformly high (r > 0.83) in cortical regions that show deficits in these patient groups (parietal, frontal cortex, and posterior cingulate), while correlations in regions not primarily involved in disease (subcortical structures) were typically much lower. Correlations for a highly affected region, the parietal cortex, are seen in Figure 3.

SSP ANALYSIS

Stereotaxic surface projection analysis was applied to FDG CMRglc and DTBZ K1 images for each subject as described above. The resulting z-score maps were compared for qualitative similarity. The FDG and DTBZ K1 z-score maps were similar for all patients, regardless of diagnosis (Figure 4). In general, DTBZ K1 z-score maps tended to identify a smaller number of abnormal surface map pixels. This is due primarily to the slightly higher noise at the pixel level of DTBZ K1 images than FDG images. For all surface pixels, the coefficient of variation of DTBZ K1 control subjects averaged 10.4%; that of FDG was 9.6%. In all cases, however, DTBZ K1 z-score maps were readily identifiable as abnormal and qualitatively identical to FDG-PET CMRglc z-score maps. The number of surface map pixels found to be abnormal (more than 2.5 SDs below the normal mean) in the most affected regions was higher for FDG than DTBZ K1 (Figure 5). The total surface map pixels in the most affected areas (posterior cingulate, lateral parietal, lateral temporal, and lateral and medial frontal areas) was 8920 (supplementary figure 2 at http://sitemaker.umich.edu/albinsupdata). In the most severe patients, more than half the surface pixels have z-score deficits of greater than 2.5. The regression line of DTBZ K1 on FDG shows a slope of less than unity (0.863), indicating fewer significant pixels for DTBZ. Many of the pixels found to be significant in FDG but not DTBZ K1 are located in the frontal cortex.

COMMENT

Our results indicate similar properties of FDG-PET assessment of CMRglc and DTBZ-PET K1 assessment of regional cerebral blood flow to identify regional cerebral metabolic deficits in subjects with MCI and early, mild dementia. Regional cerebral metabolic deficits are characteristic of dementias and specific patterns of deficits are associated with each major form of degenerative dementia.6-15,27-35 We did find that DTBZ K1 assessments tended to be somewhat less sensitive in SSP analysis because of higher variation in surface pixel values. This was most noticeable in frontal regions. This could reduce sen-
Differentiation of dementias, based on clinical criteria and using structural imaging and laboratory studies to exclude other causes of dementia, has relatively poor specificity. Fludeoxyglucose F18–PET is suggested to improve diagnosis of dementias and may be cost-effective in evaluating patients with early, mild dementia. Recent work demonstrates that FDG-PET with SSP analysis differentiates early dementia and controls in a clinically representative population of early dementia and MCI. The gold standard for diagnosis of dementias remains histopathologic evaluation. Small series with FDG-PET evaluations followed by histopathologic analysis indicate that FDG-PET evaluation significantly improves specificity without sacrificing sensitivity. These results are consistent with studies in which FDG-PET results were compared with systematic, longitudinal clinical evaluations. Differentiation of dementias at initial evaluation is particularly difficult. Jagust et al found that initial clinical evaluation of a series of mildly demented patients who were followed up to autopsy had relatively poor sensitivity (76%) and specificity (56%) for diagnosis of pathologically confirmed AD, and that diagnostic precision improved significantly with addition of FDG-PET imaging data. Diagnostic sensitivity and specificity of FDG-PET evaluation was comparable with clinical evaluation after several years of follow-up.

While characteristic metabolic deficits occur in many individuals with dementia, confounding features can reduce accuracy of FDG-PET. There is considerable overlap between AD and LBD. Not all individuals with LBD...
exhibit the typical visual cortex abnormalities; the sensitivity and specificity of FDG-PET for differentiating AD and LBD are not significantly better than application of clinical criteria.2,30 Pathologic studies indicate that a high percentage of individuals with focal cortical syndromes typical of FTDs exhibit AD pathology.72 These AD focal cortical syndromes are likely to be classified as FTDs by both clinical criteria and FDG-PET criteria.49,73 Positron emission tomography tracers aimed at characteristic pathologic features of dementias are likely to be useful in overcoming the limitations of FDG-PET. Positron emission tomography and single-photon emission tomography ligands identifying the characteristic nigrostriatal dopaminergic deficit of LBD improve differentiation of AD and LBD. Similarly, [11C]Pittsburgh Compound B is likely to be useful in identifying dementias characterized by substantial β amyloid deposition, such as AD and cases of LBD with substantial fibrillary amyloid burden.

Ligand-binding results and assessment of regional cerebral metabolic deficits may be complementary. [11C]Dihydrotetrabenazine–PET studies, for example, could identify nigrostriatal dopaminergic deficits in both LBD and some cases of FTDs.72 The pattern of regional cerebral metabolic deficits would be useful in differentiating these different syndromes. [11C]Dihydrotetrabenazine itself is not likely to become a clinically used ligand, but fluorinated DTBZ analogues or another tracer quantifying nigrostriatal terminal density may become available for clinical use. Obtaining both ligand binding and regional cerebral metabolic deficit data from a single PET study will be advantageous in terms of cost, safety, and patient convenience. Positron emission tomography ligands with high brain-to-blood extraction fractions yield K1 parametric image data comparable with those obtained with FDG-PET, and K1 parametric image data can be represented in SSP maps. Use of K1 parametric image data from PET ligands aimed at characteristic pathologic features of dementias is likely to enhance the clinical utility of PET methods for characterization of MCI and early, mild dementias.

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