^{11}C-DTBZ and ^{18}F-FDG PET Measures in Differentiating Dementias

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Accurate, early differentiation of dementias will become increasingly important as new therapies are introduced. Differential diagnosis by standard clinical criteria has limited accuracy. PET offers the potential to increase diagnostic accuracy. ^{18}F-FDG studies detect metabolic abnormalities in demented patients, but with limited specificity. PET also offers the ability to quantify other biochemical markers that can yield additional useful diagnostic information. We demonstrate that (+)-^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) studies, which provide an index of nigrostriatal terminal density (distribution volume; DV), also provide a measure of transport (K_1) that produces information comparable to the metabolic measure of ^{18}F-FDG. **Methods:** Fifty-two patients and 19 control subjects underwent both ^{11}C-DTBZ and ^{18}F-FDG PET scans. Seven had the clinical diagnosis of frontotemporal dementia (FTD), 25 had Alzheimer's disease (AD), and 20 had dementia with Lewy bodies (DLB). DTBZ scans provided maps of K_1 and DV, whereas ^{18}F-FDG scans provided maps of glucose metabolism. Correlation analyses were performed between the different PET measures both within and across subjects. Discriminant analysis using logistic regression compared the performance of ^{11}C-DTBZ K_1 and ^{18}F-FDG in differentiating subject groups. Three experienced PET researchers participated in an interrater reliability study using both ^{11}C-DTBZ K_1 and ^{18}F-FDG images. **Results:** Within-subject correspondence between ^{11}C-DTBZ K_1 and ^{18}F-FDG measures was high, with correlations averaging 0.92. Correlations between the ^{11}C-DTBZ DV and either K_1 or ^{18}F-FDG were far lower, averaging 0.37 and 0.31, respectively, indicating the much higher degree of similarity in information provided by K_1 and ^{18}F-FDG compared with the very different information provided by ^{11}C-DTBZ DV. Discriminant analysis demonstrated that ^{11}C-DTBZ K_1 and ^{18}F-FDG yielded similar levels of sensitivity and specificity for differentiating the subjects in this study. Including ^{11}C-DTBZ DV in addition to either K_1 or ^{18}F-FDG improved discrimination between groups. The raters classified PET scans nearly equivalently using K_1 and ^{18}F-FDG. **Conclusion:** Multiple PET measures, whether 2 parameters from a single PET study such as ^{11}C-DTBZ K_1 and DV, or 2 parameters from different studies such as ^{18}F-FDG and ^{11}C-DTBZ DV, offer complementary information useful for diagnosing dementias. K_1 and DV images generated from a single ^{11}C-DTBZ scan provide as much diagnostic information as 2-scan studies using both ^{11}C-DTBZ and ^{18}F-FDG.

Key Words: PET; dementia; nigrostriatal terminals; (+)-^{11}C-dihydrotetrabenazine; ^{18}F-FDG

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Dementia is a highly prevalent problem causing considerable disability and mortality and exacting great costs to individuals, their families, and society as a whole (1–3). The 4 most common forms of dementia are vascular dementia and 3 degenerative dementias: Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). AD is the most common form of dementia. Autopsy series suggest that DLB may be the second most common form of dementia though some epidemiologic studies suggest that DLB and vascular dementia have approximately the same prevalence (4–8). FTD accounts for a small but significant fraction of the dementias (9,10). Convergent clinical, pathologic, and genetic evidence indicates that the 3 degenerative dementias have different underlying etiologies and pathogenetic mechanisms. Treatment approaches probably will be different for each major form of degenerative dementia. Precise differentiation of dementias is possible presently only with postmortem brain examinations. When specific treatments become available, accurate diagnosis will be crucial to avoid ineffective or inappropriate treatments. Even now, accurate diagnoses have clinical utility; precise diagnosis is important for counseling patients and families about prognosis, cholinesterase inhibitor therapy may not be effective for FTD, and DLB patients are dangerously susceptible to neuroleptic agents.

Clinical criteria exist for premortem diagnosis; however, these are imprecise guides for differentiating degenerative dementias (11–14). Studies comparing clinical criteria for degenerative dementias against the gold standard of pathologic evaluation reveal varying degrees of sensitivity and specificity (11,14). Studies evaluating the capacity of clinical criteria to differentiate degenerative dementias reveal

the relatively imprecise nature of these criteria (15–18). Furthermore, many of these studies involve patients with moderate and even advanced disease. Precise differentiation in early, mild dementia is even more challenging (19–22).

PET offers a potentially powerful tool for differentiating the degenerative dementias. ^{18}F-FDG, the most commonly used PET radiotracer, provides measures of regional brain glucose metabolism. ^{18}F-FDG scans reveal regional patterns of hypometabolism that distinguish demented from normal individuals and may differentiate some degenerative dementias (23–29). In AD, there is a well-characterized pattern of temporoparietal, posterior cingulate, and, often, lateral frontal hypometabolism (23,26,28,29). In FTD, hypometabolism in the frontal and temporal cortices is characteristic (24–26). Differentiation of DLB from AD is more difficult; DLB has a pattern of cerebral metabolic deficits similar to that of AD, though often with additional hypometabolism in the occipital cortex (27–29). Discrimination of AD from DLB on the basis of occipital hypometabolism is only moderately effective (27–29).

PET tracers designed to target specific brain neurochemical processes offer many new possibilities for improving differentiation of dementias. PET and SPECT studies with ligands that bind to nigrostriatal terminals show good differentiation of clinically ascertained DLB from AD (30,31). Such methods, however, may be less helpful in identifying FTD. Many FTD subjects develop parkinsonism, suggesting nigrostriatal injury, and loss of nigrostriatal terminals has been shown in one PET study of FTD (32).

PET studies assessing both regional brain metabolism and nigrostriatal terminal integrity could prove more accurate than other methods in the early diagnosis of dementia. Performing 2 PET procedures, however, requires several hours, which is both taxing for patients and expensive. A single PET study that provided information about both regional brain metabolism and nigrostriatal terminal density would eliminate these drawbacks.

We have assessed previously nigrostriatal terminal density in AD and DLB subjects using the PET tracer (+)-^{11}C-dihydrotetrabenazine (^{11}C-DTBZ), demonstrating good discrimination of clinically diagnosed DLB and AD (31). DTBZ PET studies can yield 2 relevant parameters: a measure of ligand binding to the vesicular monoamine transporter type 2 (VMAT2) sites, distribution volume (DV); and a measure of the rate of ligand influx into the brain, K_1 (33). ^{11}C-DTBZ has a relatively high single-pass capillary extraction fraction of ~60% (33). Consequently, regional K_1 is highly correlated with regional cerebral blood flow. As blood flow is coupled tightly to metabolism, ^{11}C-DTBZ K_1 measurements may yield nominally the same diagnostic information as ^{18}F-FDG metabolic measurements. Our primary goal in this study was to determine the extent to which ^{11}C-DTBZ K_1 provides information equivalent to ^{18}F-FDG in the setting of degenerative dementia, with a secondary goal of showing the promise of ^{11}C-DTBZ, which provides 2 important biologic measures in a single PET study. We

assessed the concordance between ^{18}F-FDG measurements of regional cortical metabolism and ^{11}C-DTBZ K_1 measurements of regional cortical blood perfusion in a population of healthy control subjects and subjects with AD, DLB, and FTD. We performed discriminant analysis to investigate the capacity of each PET measure to differentiate the forms of dementia. In addition, we assessed interrater reliability of visual interpretation of ^{11}C-DTBZ K_1 or ^{18}F-FDG with ^{11}C-DTBZ DV images.

MATERIALS AND METHODS

Subject Selection

The Institutional Review Board of the University of Michigan Medical School approved the study, and informed consent was obtained from all participants or their caregivers. Seventy-one subjects were studied: 25 with AD (age, 69 ± 9 y [mean ± SD]; range, 52–85 y; 7 men, 18 women), 20 with DLB (age, 73 ± 7 y; range, 54–81 y; 15 men, 5 women), 7 with FTD (age, 68 ± 8 y; range, 54–78 y; 4 men, 3 women), and 19 healthy elderly control subjects (age, 69 ± 8 y; range, 55–86 y; 10 men, 9 women). These patients were recruited from the Cognitive Disorders and Movement Disorders Clinics of the Department of Neurology, University of Michigan. National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria were used for the diagnosis of AD (13), consensus criteria for the diagnosis of probable DLB (15), and work group criteria for the diagnosis of FTD (34). Diagnoses were established by the clinicians caring for the patients and verified by the investigators before study. No diagnoses were altered during the course of the study, and no patients who met criteria and volunteered for study were eliminated. AD and DLB subjects have been described in prior studies (29,31). AD and DLB subjects were matched well for dementia severity with similar Mini-Mental State Examination (MMSE) scores and symptom duration. FTD subjects, on average, had less advanced disease. MMSE scores averaged (mean ± SD) 15 ± 7 (range, 2–27) for AD, 17 ± 6 (range, 8–29) for DLB, and 23 ± 5 (range, 15–29) for FTD. Disease durations averaged (mean ± SD) 5 ± 3 y (range, 1–13) for AD, 5 ± 3 y (range, 2–13) for DLB, and 4 ± 2 y (range, 2–8) for FTD.

PET

All subjects underwent ^{11}C-DTBZ and ^{18}F-FDG PET either in the same imaging session or on consecutive days if they were not able to tolerate the 4-h procedure. Subjects were positioned supine and awake in a quiet dimly lit room with eyes open. For ^{11}C-DTBZ, 666 ± 66 MBq (18 ± 1.8 mCi) of ^{11}C-DTBZ were administered intravenously. An equilibrium protocol was used, infusing 55% of the dose over 30 s, followed by continuous infusion of the remaining 45% over 60 min (33). ^{18}F-FDG studies were performed as a single 20-min scan acquired 30 min after intravenous injection of 296 ± 29 MBq (8.0 ± 0.8 mCi) of ^{18}F-FDG.

All scans were performed in 3-dimensional (3D) mode. Measured attenuation correction was performed using a 6- to 8-min 2-dimensional (2D) transmission scan followed by segmentation and reprojection. Scatter correction was performed on all scans. After Fourier rebinning of the 3D projection sinograms into 2D datasets, images were reconstructed with smoothing parameters that provided in-plane and axial resolution of 8.5- to 9.0-mm full

width at half maximum. During the course of this project, we replaced our PET scanner. The first 25 subjects were scanned with a Siemens/CTI ECAT Exact-47 scanner (10 DLB, 9 AD, 6 normal controls [NCs]) and the final 46 subjects were scanned with a Siemens/CTI ECAT Exact HR+ scanner (10 DLB, 16 AD, 7 FTD, and 13 NCs). Greater smoothing was applied during reconstruction of HR+ scans due to their higher intrinsic resolution, resulting in images of the same spatial resolution. Statistical checks revealed that scanner effects were negligible and had no substantive impact on any results or conclusions.

Image Processing and Data Analysis

The single 20-min ^{18}F-FDG image acquired starting 30-min after injection provided an index of glucose metabolism. For the ^{11}C-DTBZ scan, the average of the first 4 min of uptake provided our index of ligand transport, K_1. An equilibrium estimate of DV with occipital cortex as the reference region (35) was selected as the index of VMAT2 binding-site density. PET images for all 3 measures for each subject were reoriented to a common coordinate system based on the stereotactic atlas of Talairach and Tournoux (36). After reorientation, all images underwent linear scaling and nonlinear warping (37). A single transformation based on the individual's summed ^{18}F-FDG and K_1 images was calculated for each subject and then applied to all 3 image sets.

All transaxial levels of the atlas have been digitized, and a set of standardized volumes of interest (VOIs) defined on the atlas images. VOIs include both cortical Brodmann areas (BA) and subcortical regions. A subset of 22 cortical VOIs was selected and applied automatically to all images (^{18}F-FDG, ^{11}C-DTBZ K_1, and ^{11}C-DTBZ DV) for each subject. Data were averaged over the corresponding areas of each hemisphere. This set of regions consisted of cortical areas hypothesized to provide the best differentiation between groups. We expected frontal regions, particularly medial, to be affected more in FTD (23) than AD or DLB and posterior parietal/posterior cingulate regions to be more affected in AD and DLB than FTD (27). We expected the occipital region to be more affected in DLB than AD or FTD and the region that best differentiates DLB from AD (27,28). Motor and premotor regions (BA4 and BA6) were included as cortical regions likely to be affected least in these dementias. ^{18}F-FDG and ^{11}C-DTBZ K_1 data were normalized to the mean VOI value obtained from the cerebellar vermis. The vermis was selected as the normalizing factor because it is a structure 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.

Discriminant Analysis

Logistic regression was used to determine linear combinations of the regional ^{18}F-FDG and ^{11}C-DTBZ variables that best differentiated control subjects and patient groups. For ease of interpretation, 3 binary comparisons were assessed: NC versus all dementias (FTD/AD/DLB), FTD versus AD/DLB, and AD versus DLB. For each binary comparison, forward stepwise variable selection was used to determine the regional PET measure(s) that best differentiated the 2 groups. Regional PET measures were transformed to a logarithmic scale. Attention was paid to the degree to which similar regions entered the analysis, whether the coefficients in the logistic regression were similar, and whether the power to discriminate was similar for ^{18}F-FDG and K_1.

Interrater Reliability Study

A subset of the 46 subjects scanned on the ECAT HR+ was selected randomly for rating. The test set comprised ^{11}C-DTBZ scans from 6 FTD, 8 AD, 8 DLB, and 5 NC subjects. For each subject, a composite of transaxial K_1 and DV images at 10 brain levels was created. A second composite was created for each subject by replacing the K_1 images with the corresponding ^{18}F-FDG slices. Three authors, including one nuclear medicine physician with full neurology residency training and 2 neurologists, both experienced PET researchers, first viewed all K_1+DV image sets in randomized order (the same for each rater). The raters were told that the order was random and that all subjects had a clinical diagnosis of FTD, AD, DLB, or NC but were not told the number of subjects in each group. The primary criteria for classifying patients as FTD was the presence of primary K_1 or ^{18}F-FDG deficits in frontal or temporal cortex, with frontal deficits being greater than posterior deficits. Classifying patients as either AD or DLB was based on the presence of primary K_1 or ^{18}F-FDG deficits in the posterior cingulate, superior parietal, and inferior temporparietal cortex, sometimes with frontal deficits, but with relative sparing of the sensorimotor cortex. The criterion for separating AD from DLB was the presence of ^{11}C-DTBZ DV deficits in the striatum of DLB patients. Each rater was asked to choose the single best diagnosis for each subject based on visual inspection of the images. Six weeks later, the raters again were assigned diagnoses based on review of ^{18}F-FDG+DV image sets in a different randomized order so they would be unlikely to recall their scoring in the first session.

RESULTS

^{11}C-DTBZ K_1–^{18}F-FDG Correlations

A high degree of similarity existed between K_1 and ^{18}F-FDG images in patients from all dementia groups and NC subjects (Fig. 1). Regional cortical deficits seen in one measure were seen distinctly in the other measure, consistent with the known coupling between flow and metabolism in both normal and diseased brains. We quantified the degree of similarity through several measures, including the magnitudes of cortical deficits in patient scans relative to NC subjects for K_1 and ^{18}F-FDG (Fig. 2); correlations between the 2 measures across both subjects and regions (Fig. 3; Tables 1 and 2); and the capacity of each PET measure to discriminate between groups (Table 3).

Figure 2 depicts the magnitudes of regional cortical deficits for each dementia group relative to NCs. Cortical areas are grouped by general brain region and, from left to right, are anterior cingulate and medial frontal (BA24, BA32, BA8, BA9, and BA10); lateral frontal (BA44, BA45, and BA46); temporal (BA38, BA20, BA21, and BA22); occipital (BA17, BA18, and BA19); posterior parietal and posterior cingulate (BA37, BA39, BA40, BA7, and BA31); and motor and premotor cortex (BA4 and BA6). The regional patterns of ligand transport (K_1) and glucose metabolism deficits are parallel in all 3 groups, with the least-affected regions decreased from normal on average by 5%–10% and the most-affected regions decreased by ~30%. Deficit patterns in AD and DLB appear similar, with a notable exception of the occipital regions, where deficits in both
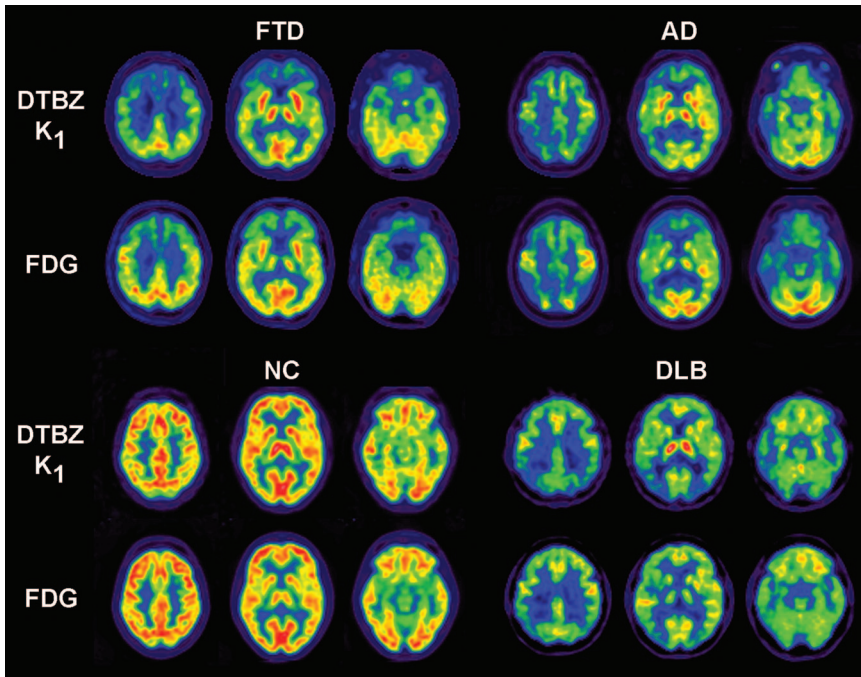
FIGURE 1. ^{11}C-DTBZ K_1 and ^{18}F-FDG images at 3 brain levels for one representative subject from each group. All images are normalized to cerebellar vermis.

PET measures are more pronounced in DLB. Deficit patterns in FTD and AD appear more similar than expected for both K_1 and ^{18}F-FDG. Though AD subjects do show relatively larger posterior than anterior deficits, both K_1 and ^{18}F-FDG measures revealed deficits of roughly equal magnitude in these regions in FTD, rather than the expected larger deficits in frontal cortex. Whereas some FTD subjects showed the expected FTD pattern (Fig. 1, upper left), several had images more typical of AD (Fig. 4, left). These findings suggest that some subjects with a clinical diagnosis of FTD in the current relatively early stage of the disease may prove to have AD on further clinical evaluation over time and, ultimately, by postmortem examination.

Within-subject correlations between ^{18}F-FDG and ^{11}C-DTBZ K_1 measures across cortical regions were very high (Table 1), averaging 0.924 ± 0.043, with individuals' r values ranging from 0.808 to 0.992. Figure 3 depicts this relationship in representative FTD, AD, DLB, and NC subjects. Displayed are data from the individuals whose correlation coefficients were closest to their group mean. Correlations in NC subjects tended to be slightly lower than in dementia subjects due to the lower dynamic range of values.

Though the within-subject ^{18}F-FDG–K_1 correlations averaged above 0.9, we addressed next the question of whether this correlation was specific to this parameter pair, reflecting a close functional relationship between K_1 and ^{18}F-FDG, or whether the correlation was more reflective of other factors such as anatomy. The within-subject correlations between the other estimated ^{11}C-DTBZ parameter, DV, and either ^{18}F-FDG or K_1, averaged <0.4 (Table 1). The much lower within-subject correlations with DV demonstrate that the high correspondence between ^{18}F-FDG and

^{11}C-DTBZ K_1 is not due primarily to the matched anatomic features.

Additional correlations were calculated between each PET measure (^{18}F-FDG, ^{11}C-DTBZ K_1, ^{11}C-DTBZ DV) from one individual with each PET measure from all other individuals (Table 2). The mean value of the correlation coefficient for ^{18}F-FDG and ^{11}C-DTBZ K_1 between subjects averaged 0.58 ± 0.22. Between-subject correlations were lower than within-subject correlations due to both anatomic differences and functional differences (flow/metabolism pattern) across individuals. Between-subject correlations were far more variable, ranging from correlations nearly as high as those observed within-subject (for subjects with similar anatomy and function) to correlations near zero (for subjects with very different anatomy or function). There was no significant difference in between-subjects correlation strength for same-parameter correlations versus between-parameter correlations, as the ^{18}F-FDG–K_1 correlations averaged nearly as high (0.58) as the ^{18}F-FDG–^{18}F-FDG and K_1–K_1 correlations (0.61 and 0.59, respectively). This indicates that differences attributable to pattern mismatches in ^{18}F-FDG versus K_1 are almost inconsequential relative to differences attributable to anatomic and functional variability between individuals. Results from correlations with ^{11}C-DTBZ DV were noticeably different (Table 2, bottom). ^{11}C-DTBZ DV values were more uniform across the cortex than were ^{18}F-FDG or ^{11}C-DTBZ K_1 values and, thus, same-parameter correlations were lower for DV (0.29) due to the more limited dynamic range of values than ^{18}F-FDG (0.61) or K_1 (0.59). When the comparisons included DV as one measure, there was a significant drop in correlation strength when moving from same-parameter to between-
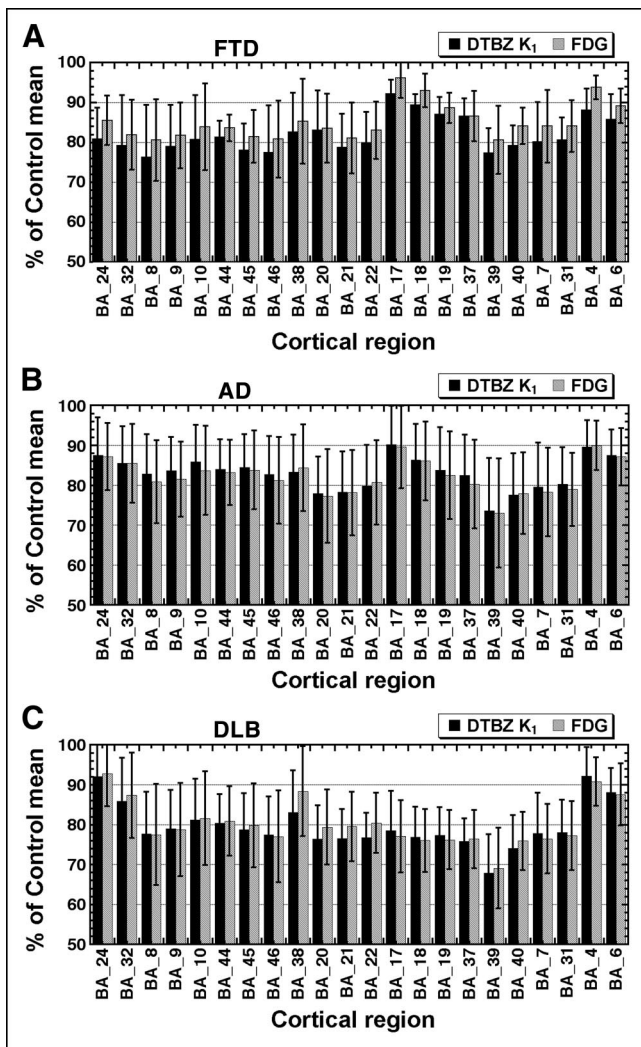
FIGURE 2. Group average deficits of ^{11}C-DTBZ K_1 (solid bars) and ^{18}F-FDG (hatched bars) relative to NC for 22 cortical regions. Shown are mean and SD for FTD (A; $n = 7$), AD (B; $n = 25$), and DLB (C; $n = 20$) expressed as a percentage of NC ($n = 19$) mean. All values are normalized to cerebellar vermis.

parameter correlations, as correlations involving cortical ^{11}C-DTBZ DV values and either ^{18}F-FDG or ^{11}C-DTBZ K_1 averaged nearly zero. This illustrates that it is not a general property of PET measures to be highly coupled, further suggesting that the high degree of correspondence between ^{18}F-FDG and DTBZ K_1 indicates that these measures provide nearly the same biologic information.

Logistic Regression Analysis for Subject Classification

Results from the logistic regression analysis are presented in Table 3. Three distinct 2-group classification tests were performed: (a) normal versus all dementias (FTD/AD/DLB); (b) FTD versus AD/DLB; and (c) AD versus DLB. Logistic regression models were fitted with the binary classification as outcome and predictor variables consisting of (i) regional ^{11}C-DTBZ K_1 measures alone, (ii) regional ^{18}F-FDG measures alone, (iii) regional ^{11}C-DTBZ K_1 measures in conjunction with the ^{11}C-DTBZ DV putamen measure, and (iv) regional ^{18}F-FDG measures in conjunction with DV in the putamen. In each of measures i–iv, forward selection was used to choose the best 1 or 2 regions that differentiated the groups. Additional variables did not yield significant additional predictive power. In support of our hypothesis that DTBZ K_1 and ^{18}F-FDG yield nearly identical information, forward selection picked the same regions as best discriminators (Table 3): BA40 for NC versus FTD/AD/DLB; BA24 and BA31 for FTD versus AD/DLB; and BA17 and BA24 for AD versus DLB. Furthermore, the coefficients of the log(PET) measures were similar whether ^{11}C-DTBZ K_1 or ^{18}F-FDG was used to discriminate. This resulted in similar odds ratios and P values for the regressions when using either measure alone or in conjunction with DV (Table 3).

When differentiating dementia from control, or FTD from AD/DLB, sensitivity and specificity using either ^{11}C-DTBZ K_1 or ^{18}F-FDG alone were similar to classification using ^{11}C-DTBZ DV and either K_1 or ^{18}F-FDG. However, when differentiating AD from DLB, which have similar K_1 or ^{18}F-FDG patterns but markedly different VMAT2 bind-
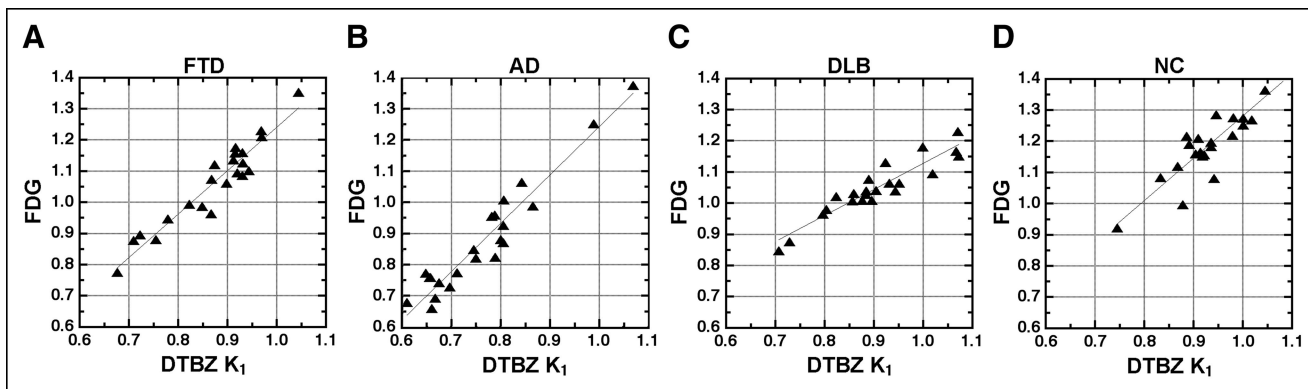
FIGURE 3. Correlations between ^{18}F-FDG and ^{11}C-DTBZ K_1 across 22 cortical regions for selected individuals from each diagnostic group. Both ^{18}F-FDG and K_1 values are normalized to cerebellar vermis. The subject selected from each group was the individual having a correlation coefficient closest to the group average (Table 1, column 2). Correlation coefficients are 0.953, 0.945, 0.919, and 0.887 for the selected FTD (A), AD (B), DLB (C), and NC (D) subjects, respectively.

TABLE 1
Within-Subject Correlations Across 22 Cortical Regions

Group	n	^{18}F-FDG vs. ^{11}C-DTBZ K_1	^{18}F-FDG vs. ^{11}C-DTBZ DV	^{11}C-DTBZ K_1 vs. ^{11}C-DTBZ DV
FTD	7	0.947 ± 0.024	0.08 ± 0.22	0.20 ± 0.24
AD	25	0.944 ± 0.038	0.28 ± 0.30	0.34 ± 0.29
DLB	20	0.922 ± 0.037	0.49 ± 0.22	0.51 ± 0.22
NC	19	0.893 ± 0.042	0.23 ± 0.28	0.34 ± 0.26
All	71	0.924 ± 0.043	0.31 ± 0.27	0.37 ± 0.26

Values are mean ± SD of Pearson correlation coefficients (*r*) for each group.

ing levels, not only did sensitivity and specificity improve significantly but also the certainty of classification increased dramatically.

Interrater Reliability

Interrater agreement on the diagnostic classification of subjects based on visual interpretation of PET images was high for image sets containing either ^{11}C-DTBZ K_1 or ^{18}F-FDG. When viewing ^{11}C-DTBZ K_1 and DV images, all 3 raters agreed on 23 of 27 cases yielding a mean unweighted Cohen's κ of 0.85 for the between-rater comparisons. In 5 cases, all 3 raters agreed on the classification, but one that was different from the clinical diagnosis. Four of these were clinical FTD subjects, which all raters classified as AD (Fig. 4, left). All raters classified one subject, a clinical AD patient, as DLB due to low ^{11}C-DTBZ DV in the putamen (Fig. 4, right).

Ratings using the ^{18}F-FDG plus ^{11}C-DTBZ DV image pairs exhibited slightly higher consistency. All 3 raters agreed on 25 of 27 cases, yielding a mean unweighted Cohen's κ of 0.92 for the between-rater comparisons. Since each individual rated the ^{18}F-FDG+DV image sets approximately 6 wk after the K_1+DV ratings, a learning effect may

TABLE 2
Between-Subject Correlations Across 22 Cortical Regions

Correlation	Correlation parameter	Mean ± SD
Same-parameter	^{18}F-FDG vs. ^{18}F-FDG	0.61 ± 0.22
Same-parameter	^{11}C-DTBZ K_1 vs. ^{11}C-DTBZ K_1	0.59 ± 0.23
Between-parameters	^{18}F-FDG vs. ^{11}C-DTBZ K_1	0.58 ± 0.22
Same-parameter	^{11}C-DTBZ DV vs. ^{11}C-DTBZ DV	0.29 ± 0.41
Between-parameters	^{11}C-DTBZ DV vs. ^{18}F-FDG	0.03 ± 0.32
Between-parameters	^{11}C-DTBZ DV vs. ^{11}C-DTBZ K_1	0.06 ± 0.32

Values are mean ± SD of Pearson correlation coefficients (*r*) for all possible between-subject combinations (71!/[69! × 2!] for same-parameter correlations; 71!/69! for between-parameter correlations).

have contributed to the small improvement in interrater reliability. The 5 cases that were classified by all raters differently than the clinical diagnosis when using ^{11}C-DTBZ K_1 were again classified differently when using ^{18}F-FDG.

Within-rater classification between K_1+DV and FDG+DV image sets was the same in 23, 24, and 25 of the 27 cases for the 3 raters, respectively (72 of 81 total ratings), yielding a mean unweighted Cohen's κ of 0.83. In comparison, rater and clinical diagnoses agreed 59 of 81 times for ^{11}C-DTBZ K_1+DV and 60 of 81 times for ^{18}F-FDG+[11]C-DTBZ DV. This level of agreement with clinical diagnosis was significantly lower than both across- and within-rater agreement, indicating that while K_1 and ^{18}F-FDG provide very similar information it is not always concordant with the clinical data.

DISCUSSION

Our results demonstrate excellent correlation between regional cortical K_1 values derived from ^{11}C-DTBZ imaging and regional cortical glucose utilization values measured with ^{18}F-FDG. Qualitative visual examination of individual ^{11}C-DTBZ K_1 and ^{18}F-FDG image sets confirm that K_1 images reproduce the regional metabolic alterations characteristic of the 3 major degenerative dementias. This was true both when PET results matched the working clinical diagnosis (Fig. 1) and in all cases in which the qualitative assessment by the raters disagreed with the working clinical diagnosis (Fig. 4). This is not surprising as regional cerebral perfusion is tightly coupled to regional cerebral metabolic demands. ^{11}C-DTBZ K_1 provides nearly equivalent data to ^{18}F-FDG not only with respect to regional cortical patterns but also in the magnitudes of the deficits in specific cortical regions (Fig. 2). The correlation between regional K_1-derived estimates of cortical perfusion and ^{18}F-FDG-derived estimates of cortical metabolism is even stronger in demented subjects than in control subjects, due mostly to the higher degree of variation (broader range of values) in cortical metabolism/perfusion in demented subjects. In 45 of the 52 patients, the correlation between the 2 PET measures exceeded 0.90.

The results of both the quantitative logistic regression analysis and the visual ratings indicated that ^{11}C-DTBZ K_1

TABLE 3
Classification by Logistic Regression

Classification	PET parameter	Discriminating variable*	Odds ratio†	P value‡	Sensitivity§ (%)	Specificity§ (%)
FTD/AD/DLB vs. NC	K_1	BA40 K_1	0.81	<0.0001	90.4	84.2
	^{18}F-FDG	BA40 ^{18}F-FDG	0.72	0.0005	92.3	78.9
	K_1+DV‖	BA40 K_1	0.81	0.0002	88.5	84.2
		DV	0.99	0.396		
	^{18}F-FDG+DV	BA40 ^{18}F-FDG	0.72	0.0012	90.4	78.9
		DV	1.00	0.881		
AD/DLB vs. FTD	K_1	BA24–BA31 K_1	1.13	0.0116	73.3	57.1
	^{18}F-FDG	BA24–BA31 ^{18}F-FDG	1.14	0.0087	77.8	71.4
	K_1+DV	BA24–BA31 K_1	1.14	0.0320	73.3	57.1
		DV	0.99	0.286		
	^{18}F-FDG+DV	BA24–BA31 ^{18}F-FDG	1.12	0.0282	68.9	57.1
		DV	0.99	0.345		
DLB vs. AD	K_1	BA24–BA17 K_1	1.12	0.0007	70.0	76.0
	^{18}F-FDG	BA24–BA17 ^{18}F-FDG	1.28	0.0020	85.0	84.0
	K_1+DV	BA24–BA17 K_1	1.15	0.311	90.0	96.0
		DV	0.84	0.178		
	^{18}F-FDG+DV	BA24–BA17 ^{18}F-FDG	1.04	0.737	90.0	96.0
		DV	0.83	0.159		

*BA(s) that provided best discrimination for each given test.

†An increase of 0.01 in the discriminating variable multiplies the odds of being in the first of the 2 comparison groups by this factor. A value of 1.0 corresponds to lack of discrimination. The magnitude of deviation from 1.0 is a measure of the ability of variable to discriminate the 2 groups.

‡P value for a test of null hypothesis that odds ratio of the discriminating variable is 1.0.

§Sensitivity and specificity are based on cross-validation—that is, when each case is classified, logistic regression is recomputed with that case excluded.

‖DV is bilateral average of ^{11}C-DTBZ VMAT2 binding measures in putamen.

data/images and ^{18}F-FDG data/images are nearly interchangeable when classifying a patient's dementia. ^{18}F-FDG imaging may be slightly superior to ^{11}C-DTBZ K_1 due to the inherently better noise properties of the images, but there were no cases in which a diagnosis appeared clear-cut with one measure and not the other. In contrast, the agreement between these methods and the working clinical diagnosis was much lower. This suggests that, without autopsy confirmation, the use of clinical diagnosis as a gold standard for assessing sensitivity and specificity of diagnosis by PET is problematic. Varma et al. demonstrated that clinical criteria do a poor job of distinguishing FTD from AD (17). Among the 7 clinically diagnosed FTD patients in this study, 4 had both qualitative appearance and quantitative measures more consistent with AD than FTD.

The key result from the logistic regression is that both K_1 and ^{18}F-FDG data were consistent in suggesting a diagnosis of AD or DLB. Discrimination between FTD and AD/DLB
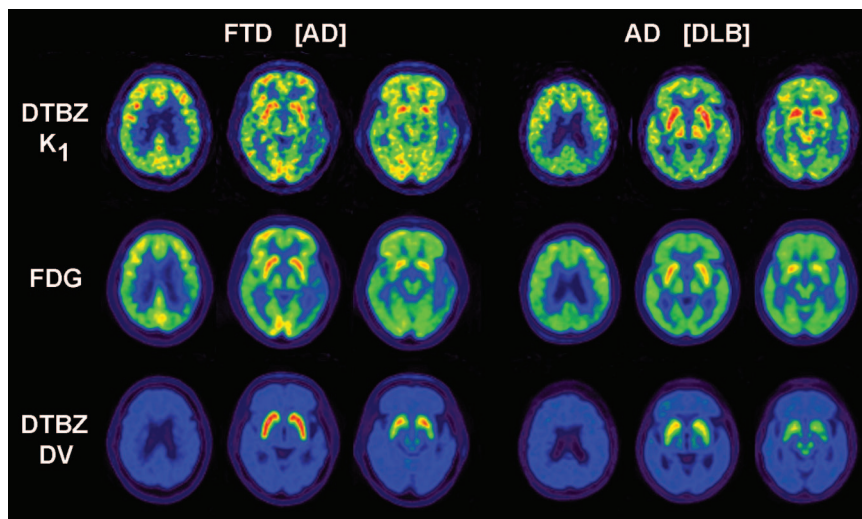
FIGURE 4. Discrepancies between clinical and PET diagnoses. Shown are ^{11}C-DTBZ K_1, ^{18}F-FDG, and ^{11}C-DTBZ DV images at 3 brain levels for 2 subjects whose clinical diagnosis at time of PET was different than classifications by both logistic regression and all physician ratings. Clinical diagnosis at time of scan is given first, followed by PET classification in brackets.

was limited for 2 reasons. First, the FTD group comprised only 7 of the 52 patients. Second, any clinical misdiagnoses in this group would alter the probability estimates and the probability threshold for classification.

^{18}F-FDG has been proposed as a method for the diagnosis and differentiation of dementia. Silverman et al. (26) presented data on a large number of demented subjects of mixed etiologies studied prospectively with ^{18}F-FDG. A substantial fraction of these subjects had autopsy confirmation of diagnosis. Their study, which included individuals with pathologically verified DLB and FTD, showed that ^{18}F-FDG was excellent at confirming the presence of AD and other degenerative dementias (sensitivity, >90%) but that discrimination of AD from other forms of degenerative dementia had a specificity of only ~70%. Results from the present study are in accord with those from their study, as our sensitivity for detecting the presence of dementia was ~90%, while our sensitivity and specificity for differentiating between dementias using either K_1 or ^{18}F-FDG alone was just over 70%. A major obstacle to the use of ^{18}F-FDG in differentiating dementias is overlap between DLB and AD. These disorders have similar patterns of cortical hypometabolism/perfusion, with the exception of the occipital cortex (Fig. 2, bottom), where DLB exhibits greater deficits. The presence or absence of occipital hypometabolism, however, is not a particularly sensitive discriminator of AD and DLB. Previous studies of pathologically confirmed DLB suggest that the sensitivity and specificity of ^{18}F-FDG imaging are equal to or slightly better than those based on clinical evaluation (27,28). As DLB is a major cause of dementia, imprecise discrimination of AD and DLB is a major obstacle to using ^{18}F-FDG to differentiate dementias.

Methods visualizing nigrostriatal terminals provide a more promising approach to differentiating DLB and AD. Postmortem studies indicate that nigrostriatal dopaminergic terminal density is essentially normal in AD and markedly reduced in DLB (38,39). PET and SPECT studies with ligands binding to nigrostriatal terminals provide good discrimination of clinically ascertained AD and DLB (30,31). The precision of this approach, however, is confounded by the fact that nigrostriatal pathology occurs in FTD, and a previous PET study indicates that some FTD subjects have marked reductions in nigrostriatal terminal density (32). FTD, however, has a distinctive pattern of frontotemporal cortical hypometabolism, often with greatest decreases in the medial frontal cortices. Distinguishing patterns of cortical hypometabolism is the most promising avenue for differentiating FTD from AD and DLB. Frontotemporal perfusion or metabolic deficits are included as "strong supporting evidence of FTD" in existing guidelines for clinical diagnosis of FTD (40). Perfusion or metabolic imaging methods have been used both clinically and in research to characterize FTD (40,41). Another potentially confounding, though rare, situation would be individuals with both Parkinson's disease and AD, which could mimic the pattern of DLB.

A PET method such as ^{11}C-DTBZ, providing accurate characterization of both regional cortical perfusion/metabolic deficits and nigrostriatal terminal density, offers the possibility of diagnosing and differentiating AD, FTD, and DLB. Our interrater reliability assessment demonstrated high reliability. In this exercise, images were presented transaxially and diagnostic classification was based only on qualitative impression of images. No effort was made to extract quantitative data from the images, which may further improve classification accuracy. Viewing of transaxial images alone is likely not optimal for the differential diagnosis of neurodegenerative dementias. Three-dimensional stereotactic surface projection analysis (42), for example, is an easily applied alternative for viewing and quantifying regional perfusion/metabolism deficits with demonstrated superiority in both diagnostic sensitivity and specificity (27). Fully automated quantitative methods such as discriminant analysis using logistic regression may prove useful, but will require further optimization of the formulas for calculating classification probabilities and thresholds. Use of ^{11}C-DTBZ PET or any other imaging method for differentiation of dementias will require validation in large prospective studies of representative patient populations. Evaluation of diagnostic precision in subjects with early, mild dementia will be particularly important.

Although we have focused on ^{11}C-DTBZ, the extraction of reliable regional cortical perfusion/metabolism data is not unique to this PET tracer. Any radiotracer that has a reasonably high extraction fraction can yield a K_1 measure proportional to cerebral blood flow and can be used to assess both regional perfusion/metabolism and disease-specific neurochemistry.

CONCLUSION

Multiple PET measures, whether 2 parameters from a single PET study—such as ^{11}C-DTBZ K_1 and DV—or 2 parameters from different studies—such as ^{18}F-FDG and ^{11}C-DTBZ DV—offer complementary information useful in categorizing dementias. Due to the near-equivalence of K_1 and ^{18}F-FDG, images from a single ^{11}C-DTBZ scan provide as much diagnostic information as a 2-scan study using both ^{11}C-DTBZ and ^{18}F-FDG, while requiring only half the time yet far more information than can be obtained for a single ^{18}F-FDG study alone.

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