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Activation of Cerebral Blood Flow During a Visuoperceptual Task in Patients With Alzheimer-Type Dementia

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Positron emission tomography Brain Alzheimer's disease Cognition Face perception Extrastriate cortex

THE cognitive impairments of dementia of the Alzheimer type (DAT) include memory dysfunction, language difficulties, impaired visuoconstruction, and deficits in attention (27,28,35,36,41,46,53). The perceptual abilities of these patients, specifically visual processing, have received somewhat less attention. Patients with DAT show impairments of contrast sensitivity, particularly at low spatial frequencies (8,49,52), voluntary saccades (18), visual tracking (42), and stereopsis (8). Symptoms of Balint's syndrome, which is characterized by ocular apraxia and deficits in visually-guided reaching, occur in some patients (38,39,49), as do deficits in the visual perception of objects, distinct from naming deficits (37,48). Color identification is not affected markedly in DAT (48), although errors in the blue range have been reported (6,8,17). Face perception, although impaired, is less affected than visuoconstructive abilities, such as drawing or block design (35).

The resting cerebral metabolic patterns in DAT obtained with positron emission tomography (PET) are well known, with defects seen primarily in association cortical regions and relative sparing of metabolism in primary sensorimotor cortex and subcortical areas (3,14,22,40,45). Parietal and temporal metabolic abnormalities are most common (14,20,23), although roughly half the patients have frontal lobe metabolic defects either in addition to the parietotemporal changes or as a predominant finding (5,30,36). Metabolism is reduced in occipital association areas as well, although primary visual regions are among those areas that are relatively spared (30,31).

Although the majority of PET studies in DAT have been done under resting conditions, it also is important to look at patients during the performance of neuropsychological tasks to examine the functional integrity of specific brain regions, particularly those that are hypometabolic at rest. However, ex-

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amination of metabolism or blood flow during a behavioral activation paradigm has not been widely pursued with DAT patients. Duara and colleagues have used two visual tasks, a picture preference test and a reading memory task, during measurement of cerebral glucose use with PET in DAT patients (13,15). They found the same degree of activation during both tasks in primary and association occipital regions as was found in controls, which was a 5–7% increase in normalized glucose metabolic values in both occipital regions. Deutsch et al. (12) used a visual rotation task with ^{133}Xenon inhalation to measure regional cerebral blood flow (rCBF) and found significant bilateral activation in patients with DAT, whereas controls had only significant right hemisphere activation. Kessler et al. (44) studied glucose metabolism in patients during a visual continuous recognition task of verbal and nonverbal stimuli, and found that only the controls showed a global increase in response to the task, but the regional patterns of activation were the same in patients and controls. Based on these results, patients with DAT appear to have the capacity to increase local cerebral blood flow or metabolism during cognitive processing, although the pattern or magnitude of activity may vary from that of controls. However, these studies were limited in that little is known about the neural circuits involved in these tasks.

The purpose of the present study was to examine an aspect of complex visual function, the visual processing of objects, for which the neural pathways involved have been studied extensively, and compare the pattern of rCBF increases that accompany this processing in DAT patients and controls. Research in nonhuman primates has shown the existence of two visual systems in extrastriate cortex- an occipitotemporal stream for identifying objects and an occipitoparietal stream for perceiving the spatial relations among objects (2,11,59). Reports of the differential effects of occipitotemporal versus occipitoparietal brain lesions in humans (9,43,51,60), support the idea of ventral and dorsal visual systems in man. We have examined the object vision pathway in healthy young and old subjects with PET and $H_2^{15}O$, using a face-matching task as a probe to stimulate the ventral visual stream, and found activation of rCBF in ventral occipital and occipitotemporal cortex (29,34). In extending our exploration of the object vision pathway to patients with DAT, we have examined both the location and magnitude of rCBF increases associated with face matching. Changes in the magnitude of rCBF increases in the same extrastriate locations that are activated in controls would indicate alterations in the capacity to use these regions for visual processing. Changes in the locations of rCBF activation would suggest a reorganization of function, and activation of other regions in addition to extrastriate visual cortex might represent compensation for failing cognitive ability. An abstract of this work has been published (26).

METHOD

Subjects

Seven male patients (mean age ± SD, 64 ± 7 years) with a clinical diagnosis of probable or possible Alzheimer's disease (AD) (47), and eight age-matched healthy male controls (mean age ± SD, 65 ± 9 years) were studied. Two patients were classified as possible AD: one was so classified due to nonprogression of the dementia, and the other had cognitive decline limited to one area of function (memory), although this patient had a family history of autopsy-proven AD. All patients and controls were screened to rule out any health problem (other than dementia in the patients) that might compromise cerebral blood flow, such as cardiovascular disease, hypertension, head trauma, or drug abuse (14). The patients were mildly to moderately demented, with a mean Mini Mental State Examination score (19) of 22 ± 4 (range 14–28). The experiment was approved by the research committee of the National Institute on Aging, and informed consent was obtained from each subject (and a family member in the case of the DAT patients).

Procedure

A face-matching task and a sensorimotor control task were administered to all subjects. Sample items from the two tasks are shown in Fig. 1. Pictures of faces were taken from a high school yearbook, with the clothes and hair blacked out. The faces were arranged in a triangular array (one on top and two on the bottom); the top face and one of the bottom faces were the same picture. In the face matching task the subject was asked to indicate which bottom square contained the face that was identical to the one shown in the top square. The response consisted of pressing a button with either the right or left thumb depending on whether the correct stimulus match was on the right or left side. The sensorimotor control task was designed to control for motor responses and the simple visual aspects of the face matching task. It consisted of three empty squares in the same configuration as for the face matching task, and the subject was required to alternate right and left button presses in response to the presentation of the stimulus. The tasks were subject-paced to maximize the proportion of time spent processing for both patients and controls. There was an interval of 1.5 s between the subject's response and the onset of the next stimulus. All subjects were administered each task twice before the PET scan to ensure adequate learning of the tasks prior to rCBF measurement. All patients performed above chance level (50%) on the face matching task during the pre-testing and during the scanning session. Performance of all subjects was monitored during the task conditions by an Apple IIe computer that was used to control the presentation of the stimuli as well as record reaction times and accuracy.

The scans were performed using a Scanditronix PC1024-7B tomograph which has a reconstructed transverse resolution of 6.5 mm and an axial resolution of 10–12 mm. A transmission scan was obtained with a ^{68}Ge/^{68}Ga rotating pin source and was used to correct subsequent emission scans for attenuation. Seven planes were obtained parallel to the inferior orbitomeatal (IOM) line, beginning at 15 mm above the IOM line, with a separation between planes of 14 mm (center to center). Three emission scans, two during the control task and one during the face matching task, were obtained on each subject after a bolus injection of 30 mCi (1110 mBq) of $H_2^{15}O$ for each scan. The control tasks were at the beginning and end of the procedure; the control subjects and two of the patients also performed other tasks as well as the face matching task during the scan session. Each task was begun 1 min prior to isotope injection and continued throughout the scanning period. Scanning began when the radioactive count rate in the brain exceeded a threshold value and was continued for 4 min thereafter. Arterial blood sampling was initiated at the time of injection and continued throughout the scanning period using an automatic blood counter to measure blood radioactivity. Sixteen scans were obtained during the scanning period: twelve 10-s scans followed by four 30-s scans. The data from the 16 scans and the arterial time-activity curve were used with a weighted integration algorithm (1) to reconstruct one seven-slice set of rCBF images for each task condition. Head movement during the scans was minimized by using a thermoplastic mask that

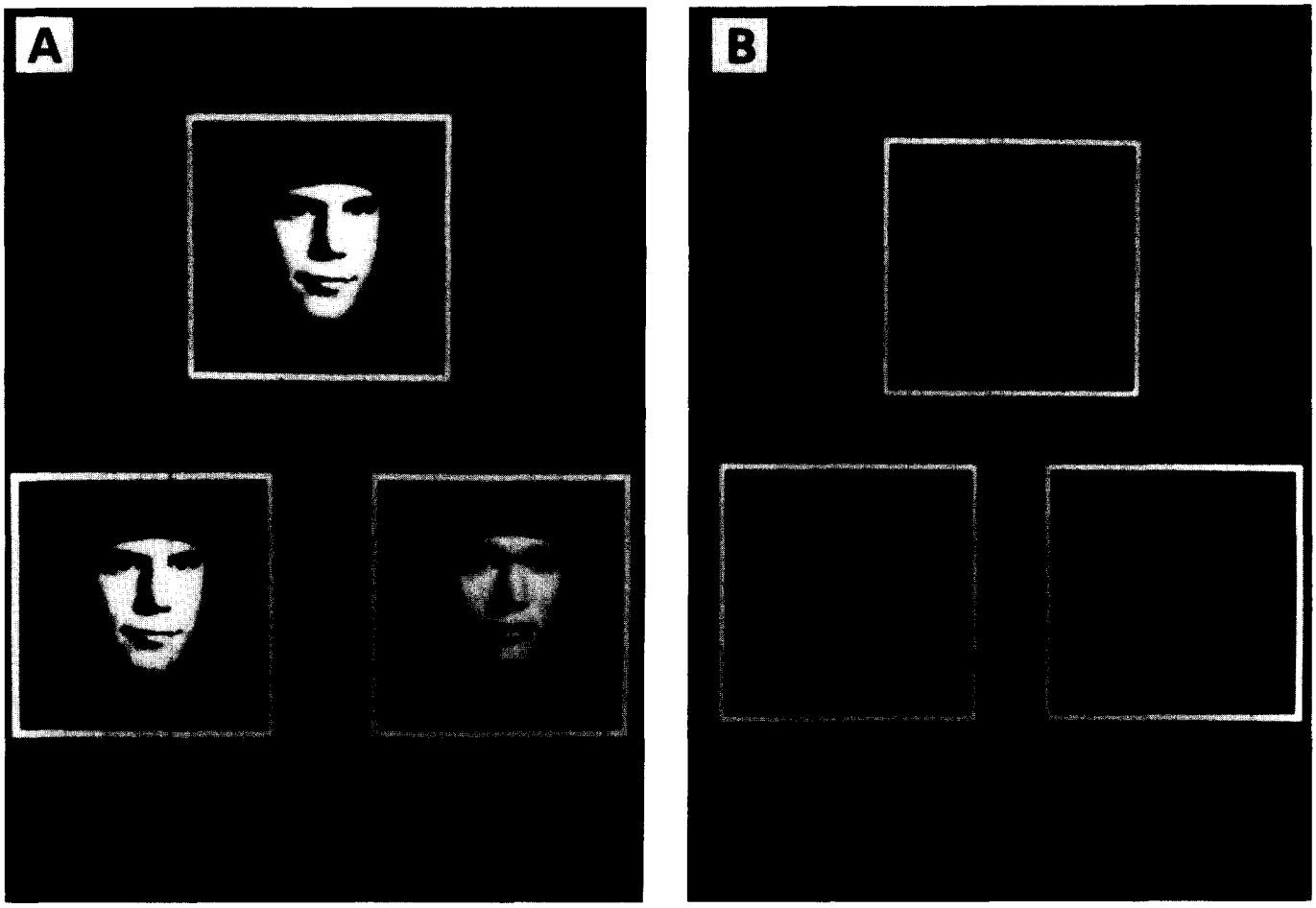

FIG. 1. Sample items from the face matching (A) and control tasks (B). Responses during face matching were with the right or left thumb depending on which of the two choice items seen below (either right or left) was a correct match to the top face. Right and left button presses were alternated during the control task.

was molded to each subject's head and attached to the scanner bed. Prior to data analysis, each subject's scans were examined visually, and no movement between scans was detected in those subjects included in this report.

Data Analysis

The image data were analyzed in two ways. The first analysis was to determine the location and extent of rCBF activations. The locations of rCBF activation were identified from difference images (face matching minus control task) and these locations were mapped to a schematic of the brain for each group separately. The extent of the activation was obtained from the total number of pixels in specified areas. Second, a region of interest (ROI) analysis was carried out on the images to determine statistical between-group differences in rCBF increases during task performance and to provide an estimate of the magnitude of activation. All of these analyses were carried out after normalizing regional flow values to a mean of 100% by dividing by whole brain flow (average of all brain pixel values). Although the patients had significantly lower whole brain CBF during the control task than did the control subjects (mean ± SE, DAT: 33.1 ± 3.0; control: 45.4 ± 3.0 ml/100g/min, after correction for arterial pCO_2 (54); $t = -2.9$, $p < 0.02$), neither group had a significant increase in whole brain CBF during face matching. Each analysis is described in detail below.

The two image-sets for the control task condition were averaged to obtain one seven-slice set of control images, and rCBF values were normalized to whole brain CBF for both control and face matching conditions. To identify the locations of rCBF activations in each subject, pixel-by-pixel difference images were obtained by subtracting the mean control task images from the images obtained during the face matching task. The difference images were smoothed using a Gaussian filter, with a resulting image resolution of 9 mm. Areas of rCBF increase or activation on each difference image were defined as those where at least 12 contiguous pixels (i.e., 48 mm^2) showed a difference of 30 percentage points or more above the control task (30% being approximately twice the SD of the statistical noise in the image) (34). These areas of activation were mapped using the following procedure. The anterior and posterior extents of these activated areas were determined relative to the anterior and posterior edges of the brain in the image and then were mapped by means of a linear transformation onto schematics of each hemisphere derived from a standard atlas (16). Lateral activations were mapped onto a lateral schematic and medial activations were mapped onto a medial schematic.

The lateral or medial position of each area of activation was determined by comparison of its location to the medial and lateral cortex visible in the control task images. The axial position of each activated area was determined by assigning each image a level above the IOM line based on visual comparison of the control task images to the atlas slices. The patients and control subjects were mapped separately, with activated areas in all slices for all subjects mapped onto the same schematic so that overlap of regions activated in more than one subject could be determined.

To compare the extent of the areas of activation in ventral extrastriate cortex between DAT patients and control subjects, the total number of pixels that met the above criteria was computed for each subject in the activated regions of occipitotemporal cortex. This included all activated regions in posterior lateral cortex (excluding the occipital pole) in the single image that was closest to 30 mm above the IOM line (range 25–35 mm above IOM). The pixel totals were then converted to mm^2 by multiplying the totals by 4 (pixels are 2 mm × 2 mm).

To obtain an estimate of the magnitude of rCBF activation in various brain regions and to determine statistical between-group differences, an ROI analysis was done. For this purpose we used a template of seven standard slices of circular ROIs (12 pixels, 48 mm^2) that was adapted from one developed for routine analysis of fluorodeoxyglucose images (45). The template was derived from the images of a young subject who participated in a pilot study for a previous experiment (29). The ROIs were placed throughout the cortex in an attempt to sample each anatomical area and were placed on the averaged control task images to avoid any bias of activated regions. The ROIs for each slice of the template were placed on the matching slices for each subject, and the ROIs were moved interactively to fit the individual brain (i.e., to cover the same areas of brain as in the template brain). The ROIs were located throughout lateral cortex and in some medial areas of cortex (occipital, parietal, anterior cingulate, orbitofrontal). The rCBF images were smoothed using the same Gaussian filter described above, and the ROIs for each subject were applied automatically to the images obtained during both control-task conditions and the face matching condition. Values of rCBF for larger brain regions [identified by comparison to two atlases (10,16), and shown schematically in Fig. 3] were obtained by averaging over two to four of the circular ROIs, resulting in 22 regions in lateral cortex, 7 regions containing both lateral and medial cortex, and 3 regions in medial cortex (primary occipital and two regions in anterior cingulate cortex). These regional flow values then were averaged over the two runs for the control task condition, and all regional flow values were normalized to whole brain CBF.

Statistical Analysis

Group comparisons of mean accuracy rates and reaction time on the face-matching task and pixel totals of activated regions were made using *t* tests. Regional rCBF values from the ROI analysis were compared using three-way analyses of variance (ANOVAs), with group as the independent factor and task and hemisphere as repeated measures. Some subjects did not have all 7 of the template slices due to individual differences in brain position relative to the skull landmarks used to identify the IOM line. The number of subjects for each ANOVA is given in the legend to Fig. 3. Correlations between rCBF activation and performance or MMS score were calculated using Spearman nonparametric correlation coefficients.

RESULTS

The performance measures for the DAT patients and control subjects are shown in Table 1 (due to technical problems, one control did not have any performance measures, one DAT patient did not have an accuracy measure, and one DAT patient did not have reaction time measures). There was no significant difference between groups in mean accuracy or reaction time, although the variance of the reaction time measure was greater in the patient group.

The lateral and medial cortical areas that showed increases in normalized rCBF of 30% or more above the control task during face matching, obtained from the pixel-by-pixel subtraction method, are shown in Fig. 2 for the right and left hemispheres. Both patients and controls showed areas of activation in lateral and medial occipital and occipitotemporal cortex bilaterally during face matching, although the occipitotemporal activation appeared to extend more anteriorly in the control subjects. In these areas as many as 7 controls and 6 patients showed activation in the same regions (areas of greatest overlap). In addition, some activation was seen in more dorsal occipital cortex, superior parietal cortex, and in lateral frontal cortex. These activations were smaller in area and showed overlap between only two or three subjects, except for a region in right frontal cortex in the DAT patients that was activated in 5 of the 7 patients. The total area of activation in occipitotemporal cortex was not different between groups (mean ± SE, 305.7 ± 81.4 mm^3 in DAT patients; 369.5 ± 106.7 mm^2 in controls).

The results of the ROI analysis are shown in Fig. 3. The results were essentially the same for both hemispheres, so only the right hemisphere is shown Fig. 3 (only one region showed a significant task × hemisphere interaction and is discussed below). There were three regions, inferior parietal and two temporal regions (regions 9, 15, and 23 in Fig. 3), in which the DAT patients showed lower normalized rCBF values than did the controls in both task conditions (significant group effect); neither group showed activation during face matching in these regions (Table 2 A), or in any of the medial cortical regions shown in Fig. 3. As was seen in the maps, significant activation of rCBF was found in most occipital and occipitotemporal regions in both groups during face matching, with no significant group effects or task × group interactions (Table 2 B). Significant activation also was seen in both groups in superior parietal cortex. Two regions showed significant task × group interactions—an occipital region near the occipital pole [region 13, $F(1, 13) = 6.2, p < 0.05$] and a frontal region [region 24, $F(1, 12) = 6.1, p < 0.05$]. In both of these regions, there was greater activation in the DAT patients (Table 2 B). In addition, the frontal region also showed a significant task × hemisphere interaction, $F(1, 12) = 9.2, p < 0.01$, indicating

TABLE 1
PERFORMANCE MEASURES

	Control (n = 7)	DAT (n = 6)
Accuracy (% correct)	92 ± 5 (84–97)	85 ± 8 (70–92)
Reaction time (msec)*	2069 ± 538 (1458–2773)	3323 ± 1484‡ (1383–4938)

Mean ± SD. Range in parentheses. *Median reaction time averaged across subjects. ‡Variance significantly greater than in controls (by F test), $p < 0.05$.

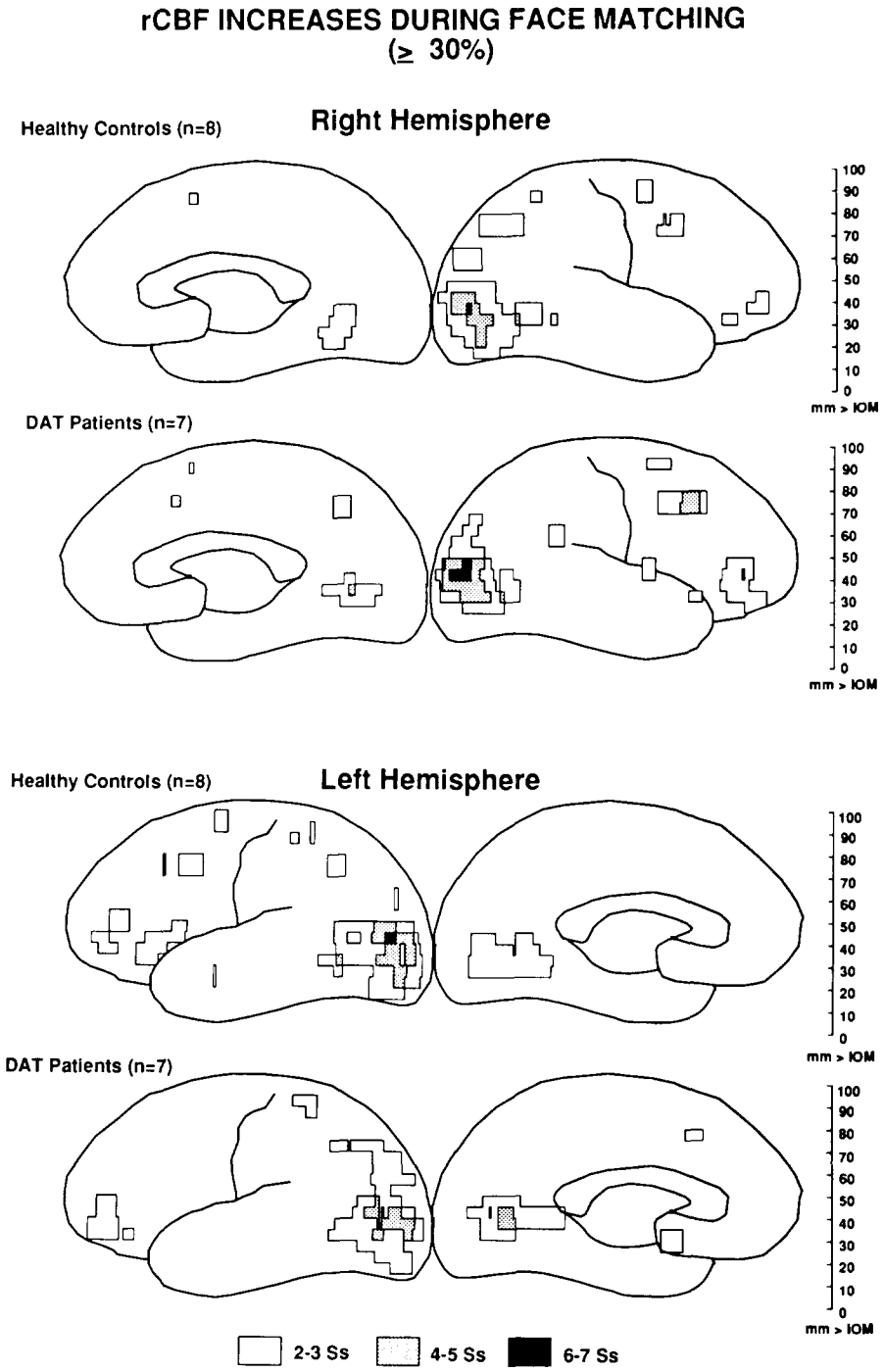

FIG. 2. Lateral and medial areas of activation during face matching (greater than 30% increase in normalized rCBF) in the right and left hemispheres for DAT patients and controls (lateral and medial areas are mapped separately). Shading of activated areas indicates the number of subjects with overlapping areas of activation in that region of cortex. Although not all subjects had activation in the same regions of cortex, all subjects had an activated area in occipitotemporal cortex in at least one hemisphere. In addition, four patients and four controls showed activated areas in superior parietal cortex. Five patients had an overlapping area of activation in right frontal cortex. Scale at right shows mm above the IOM line.

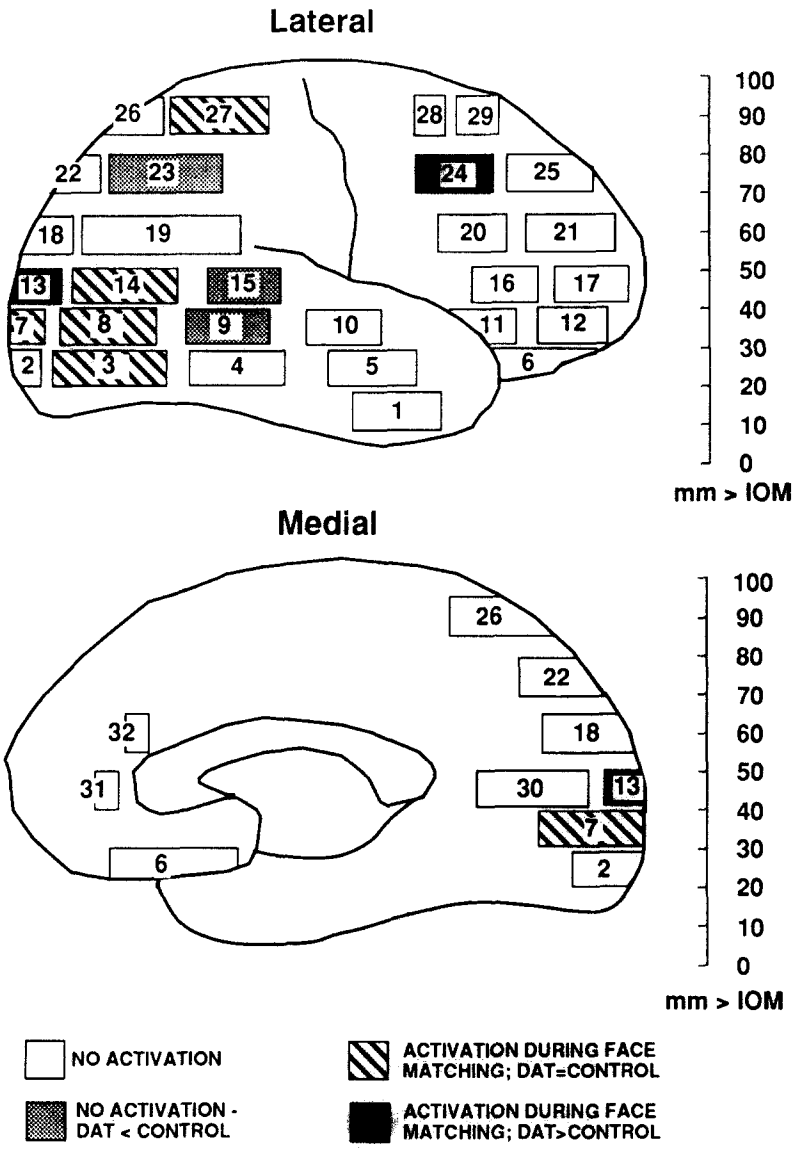

FIG. 3. Results of the ROI analysis of normalized rCBF shown for the right hemisphere (results for the left hemisphere were essentially the same). Regions are shown schematically on the lateral and medial surfaces of the brain. White regions showed no activation during face matching; lightly shaded regions showed no activation, but flow was reduced in these regions in the DAT patients; hatched regions had significant increases of rCBF during face matching (with no significant interactions); and black regions had significant main effects of task and task × group interactions, with greater activation in the patients. Only region 24 showed a significant task × hemisphere interaction (see text). Scale at right shows mm above the IOM line. Regions are identified as follows: 1: inferior temporal; 2, 7, 13: occipital polar; 18: occipitoparietal; 3, 8, 14: occipitotemporal; 4, 5, 9: middle temporal; 10, 15: superior temporal; 19: temporo-parieto-occipital; 23: inferior parietal; 27: superior parietal; 22, 26: medial parietal; 6: orbitofrontal; 11, 16, 20, 24, 28: premotor; 12, 17, 21, 25, 29: prefrontal; 30: primary occipital; 31, 32: anterior cingulate. Number of subjects in the ROI analysis for the regions at each scan level (starting at the base of the brain at the level of the inferior temporal): 1) 4 DAT, 4 controls; 2) 3 DAT, 5 controls; 3) 6 DAT, 7 controls; 4) 7 DAT, 8 controls; 5) 6 DAT, 6 controls; 6) 6 DAT, 8 controls; 7) 7 DAT, 8 controls.

greater activation in the right hemisphere compared to the left. The three-way interaction of task, group and hemisphere was not significant.

The significant increases in normalized rCBF were between 10% and 20% for both DAT patients and controls (Table 2 B), although activations of 5% also were statistically significant. To determine the relation between the magnitude of occipitotemporal activation and task performance, Spearman correlations

TABLE 2

NORMALZIED rCBF VALUES IN CONTROL AND FACE MATCHING TASK CONDITIONS

Region (Region No.)	Control Subjects	DAT Patients
A. Regions with significant reductions in DAT patients (tasks combined)		
Middle temporal (9)†	1.15 ± 0.03	1.02 ± 0.05
Superior temporal (15)†	1.31 ± 0.03	1.12 ± 0.05
Inferior parietal (23)†	1.20 ± 0.03	1.01 ± 0.07

Region (Region No.)	Control Subjects			DAT Patients		
	Control Task	Face Matching	Change[a]	Control Task	Face Matching	Change[a]
B. Regions with significant increases during face matching						
Occipitotemporal (3)**	1.12 ± 0.04	1.29 ± 0.05	17.1 ± 3.0	1.13 ± 0.07	1.29 ± 0.13	15.7 ± 5.8
Occipitotemporal (8)**	1.09 ± 0.02	1.25 ± 0.03	15.4 ± 2.1	1.07 ± 0.06	1.24 ± 0.09	17.5 ± 4.1
Occipitotemporal (14)*	1.15 ± 0.01	1.20 ± 0.03	5.2 ± 2.9	1.07 ± 0.05	1.13 ± 0.07	5.9 ± 2.8
Occipital (7)*	1.37 ± 0.04	1.41 ± 0.04	4.7 ± 2.7	1.40 ± 0.04	1.50 ± 0.03	10.2 ± 3.7
Occipital (13)§	1.23 ± 0.02	1.25 ± 0.04	2.6 ± 2.8	1.32 ± 0.04	1.42 ± 0.05	10.6 ± 1.2
Superior parietal (27)**	1.12 ± 0.04	1.17 ± 0.04	4.6 ± 1.6	1.08 ± 0.05	1.12 ± 0.06	4.7 ± 1.2
Premotor (24): right@	1.31 ± 0.04	1.35 ± 0.03	3.4 ± 2.6	1.34 ± 0.03	1.45 ± 0.03	11.4 ± 1.2
left	1.34 ± 0.03	1.31 ± 0.02	−2.3 ± 3.0	1.23 ± 0.05	1.24 ± 0.05	0.8 ± 1.5

All values are mean ± SE; Region Nos. from Fig. 3; [a]In percentage points [(Face rCBF—Control Task rCBF) × 100]
†Significant main effect of group, DAT < Controls: $p < 0.05$.
Significant main effect of task, face matching > control task: *$p < 0.05$, **$p < 0.005$.
§Significant effect of task and task × group interaction: $p < 0.05$.
@Significant effect of task, task × group, and task × hemisphere: $p < 0.05$.

were computed between accuracy, reaction time and rCBF increase in occipitotemporal region 8 [the region for which the greatest number of subjects had data available (Fig. 3), right and left hemispheres combined]. The correlation between accuracy and rCBF increase was 0.15 in the DAT patients and 0.49 in the controls. The correlation between reaction time and rCBF increase was −0.31 in the DAT patients and 0.09 in the controls. None of these correlations was statistically significant. The correlation between accuracy and rCBF increase in right frontal cortex was 0.97 ($p = 0.05$) in the DAT patients and 0.68 in the controls, and between reaction time and frontal rCBF increase was 0.03 in the DAT patients and −0.43 in the controls. Correlations also were computed between MMS score and activation in occipitotemporal (rho = −0.06) and right frontal cortex (rho = 0.44) in the patient group but neither of these was significant.

The DAT patients as a group did not show reduced normalized flow in the occipitotemporal regions that were activated during the face-matching task. However, the pattern of cerebral metabolic deficit can vary from patient to patient and not all patients have abnormalities in occipital association cortex (30). Therefore, we were interested in examining occipitotemporal rCBF during the control task in each patient individually. To do this, we calculated a Z score for each patient (based on the control subjects' mean and SD) of the rCBF in the occipitotemporal ROI for which the greatest number of subjects had data available (region 8, right and left hemispheres combined). Significant reductions in flow ($p < 0.05$) were found in two of the six patients with rCBF available for this region. In spite of this reduction in flow, the rCBF activation in region 8 (hemispheres combined) was 12.5% in one patient and 10.3% in the other. These increases were well within the range of increases seen in the control subjects for this occipitotemporal region (7.9%–25.2%). However, these two patients with reduced occipitotemporal flow during the control task also had two of the slowest reaction times during the face matching task (4938 and 4849 msec).

DISCUSSION

These results show that the pattern of rCBF activation found in normal older subjects during a face-matching task is maintained in a group of mildly to moderately demented DAT patients. Both patients and controls showed increased rCBF in occipitotemporal cortex, with lesser activation of parietal cortex. We have found activation in these areas of occipitotemporal cortex during a similar face matching task in young subjects (32,34), and in a different group of older subjects (29). We also have reported a similar parietal activation in this other group of older subjects during face matching (29). Thus, the areas of activation that we report here replicate our earlier results, in spite of the fact that the number of subjects in this study was relatively small, the number of regions analyzed relatively large, and the ROI analysis employed relatively gross in terms of anatomical precision. In addition, the magnitude of the rCBF increase in posterior extrastriate cortex was not significantly different between patients and controls, nor was the size of the activated area of cortex significantly less in the patients. These results are similar to those of Duara et al. (13,15) who reported increases in normalized glucose utilization in occipital areas during a variety of tasks in DAT patients that were not different from controls in magnitude. Kessler et al. (44), reported a similar pattern of regionally increased glucose use in DAT patients compared to control subjects during a visual recognition task, but the magnitude of the increases was less in the patients. Their subjects were somewhat more demented than ours (mean MMS score of 17) which might account for the reduced activation. However, there are several differences between our study and that of Kessler et al. that make comparison difficult: the patients in that study made many more errors (false positives) than did the controls, indicating that the two groups were performing the task quite differently; the patients were given versions of the memory tests that were easier and contained stimuli that were qualitatively different from those given to the controls; the baseline condi-

tion was a resting state, rather than a control task; and the baseline and task scans were done on different days, rather than within a single scanning session. Despite these differences, the conclusion to date would be that DAT patients can activate appropriate areas of cortex during a variety of visual tasks.

There were two brain regions which showed significantly more activation in the patients than in controls, a region at the occipital pole and one in frontal cortex. This occipital region showed increased rCBF during a more difficult face matching task in young and old healthy subjects (29). The lack of activation in the control subjects in this study may indicate that a less complex visual task results in less extensive occipital activation. It would follow from this interpretation that activation of this region in the DAT patients indicates that they found the face-matching task more difficult or required more processing to carry out the task. This explanation may also explain the increased frontal cortex activation in the patients. With the localization techniques employed here, it is not possible to know exactly what part of frontal cortex is involved. However, we have recently estimated the location of this area in terms of the stereotaxic space of Talairach and Tournoux (58), and have determined that the area of increased activation in the patients is probably just anterior to the precentral gyrus, corresponding to the frontal eye fields (56). This frontal activation in the patients could be an attentional effect, because frontal cortex, including the eye fields, and parietal cortex are considered part of a visual attention system that involves spatially selective attention, sustained attention, and voluntary eye movements (4,24,25,50,55). It is possible that the patients' reduced cognitive capacity makes this test of face matching more difficult for them to perform, resulting in an increased attentional load or perhaps reliance on a different strategy that is accompanied by an increased involvement of frontal cortex. An alternative explanation of this frontal activation in the DAT patients is that it is the result of frontal eye field activity due to increased eye movements, as bilateral activation of the frontal eye fields has been reported in PET studies of voluntary saccades (7,21). Eye movements were not monitored during the experiment, so it is unknown whether the patients made more eye movements than did the controls. Because the relation between rCBF increase and task difficulty is not known, either in DAT patients or healthy subjects, our understanding of greater rCBF increases in DAT patients in these cortical regions, as well as the precise location of these areas, must await further experiments.

Although the mean reaction time in the patient group was not significantly slower than that in the controls, the variance of this measure was increased, and with additional subjects the mean reaction time would likely be significantly reduced. There was not a significant correlation between performance and the magnitude of rCBF activation in occipitotemporal cortex in either the patients or controls, a result that we have reported previously in young subjects performing visuoperceptual tasks (33). Kessler et al. (44) also failed to find a correlation between increases of glucose metabolism and continuous recognition performance in DAT patients. However, they did report a tendency toward an association of metabolism in the middle frontal gyrus during stimulation and performance in control subjects, similar to the positive correlations found here between rCBF increase in right frontal cortex and performance in both patients and controls. These findings suggest that the magnitude of rCBF increase in extrastriate visual cortex does not reflect individual differences in performance, even in patients with impaired performance, but that if additional areas are activated, such as frontal cortex, the degree to which these areas aid performance may correspond to the magnitude of rCBF increase. However, the number of subjects examined so far has been small, and further comparisons with more subjects clearly are warranted.

We found a similar pattern of rCBF activation in posterior cortex of both patients and controls, despite the fact that the patients had lower whole brain flow, but it is doubtful that this global reduction influenced the activation patterns because there was no global increase in either group during face matching. The patients also had reduced normalized flow in regions of cortex that are known to be hypometabolic in DAT patients, namely parietal and temporal cortex. Flow in these regions also remained lower than in control subjects during the face matching task. Some DAT patients have reduced metabolism in occipital association cortex (30), but only two of the patients in this study had reduced normalized rCBF during the control task in occipitotemporal cortex. Nevertheless, these two patients showed an increase in rCBF in this region during face matching that was within the range of normal. Duara et al. (15) have suggested that preserved activation in regions with reduced baseline metabolism or flow would indicate that these regions are still viable. It is tempting to speculate that areas of cortex with reduced baseline rCBF have sustained some damage from the disease, but that the neural circuits mediating the visual perception of objects are intact to the extent that rCBF can be increased during task performance. However, the fact that these two patients had reaction times that were almost twice as slow as the slowest control subject, suggests that normal levels of activation alone do not always indicate that performance will be normal. The relation between rCBF activation, reductions in baseline measures of rCBF and performance is undoubtedly a complex one, and although the current finding is intriguing, until it is replicated in other patients and using tasks to probe the other cortical regions affected in DAT (e.g. parietal cortex), we cannot know how general a finding it is.

In summary, we have shown that mildly to moderately demented patients with DAT have a similar capacity to increase rCBF during a face matching task in occipitotemporal extrastriate cortex as do healthy controls. The patients also show greater activation in some occipital and frontal areas. The pattern of rCBF activation presented here may not be due to the perception of faces per se but may reflect the visual processing of objects in general. Other PET studies suggest that perception of faces, compared to nonface objects more complex than the squares used in the control task of this study, may be mediated by areas of occipitotemporal cortex more ventral than those reported here (32,57). Regardless of whether the activation patterns mediate a specific processing of faces, or a more general processing of objects, our results show that in the early stages of DAT, frontal cortex, as well as posterior cortex, is used by the patients for performance of this visual task, which may reflect an increased interaction among these brain regions to compensate for reduced ability to process visual stimuli.

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