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Voxel-Based Distribution of Metabolic Impairment in Corticobasal Degeneration

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Summary: This report emphasizes the precise topographic distribution of cerebral metabolic impairment in corticobasal degeneration (CBD) and the pathophysiological differences between CBD and progressive supranuclear palsy (PSP). Statistical parametric mapping (SPM96) analysis of ^{18}FDG positron emission tomography (PET) data was performed in 22 patients with CBD compared with 46 healthy subjects (HS) and 21 patients with PSP who were studied at rest. A statistical threshold of $p < 0.001$ was fixed, further corrected for multiple or independent comparisons ($p < 0.05$). In comparison with HS, the metabolic impairment in CBD was asymmetrically distributed in the putamen, thalamus, precentral (Brodmann's area, BA 4), lateral premotor (BA 6/44) and supplementary motor areas (SMA, BA 6), dorsolateral prefrontal (8/9/46) cortex, and the anterior part of the inferior parietal lobe (BA 40) including the intraparietal sulcus (BA 7/40). A similar hypometabolic pattern was observed for most individual analyses. When PSP was compared with CBD, metabolic impairment predominated in the midbrain, anterior cingulate (BA 24/32), and orbitofrontal regions (BA 10). The reverse contrast showed more posterior involvement in CBD (BA 6 and 5/7/40) including SMA. Our data suggest that multiple components of neural networks related to both movement execution and production of skilled movements are functionally disturbed in CBD compared with both HS and PSP. **Key Words:** Corticobasal degeneration—Progressive supranuclear palsy—PET.

Following the initial description by Rebeiz et al.,[1] corticobasal degeneration (CBD) was forgotten until the late 1980s. Since then, the disorder has received increasing recognition and research interest. Although this asymmetric motor disorder is still recognized as a pathologic entity, increasing evidence has demonstrated clinical,[2,3] metabolic,[4] and neuropathologic[3] heterogeneity.

Several functional imaging studies concur in showing a frontoparietal decrease in activity, but they diverge concerning the most affected areas.[5–10] We report positron emission tomography (PET) studies in a large sample of patients with a clinical diagnosis of CBD using the ^{18}fluorodeoxyglucose (^{18}FDG) method. In an attempt to precisely characterize the distribution of metabolic impairment in CBD, the data obtained from patients with CBD and healthy subjects (HS) were contrasted using a voxel-by-voxel approach with the Statistical Parametric Mapping (SPM96) software.[11] We also directly contrasted the metabolic patterns observed in CBD and progressive supranuclear palsy (PSP) populations both between groups and individuals to emphasize significant metabolic differences between these conditions.

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MATERIAL AND METHODS

Subjects

Twenty-two consecutive patients (15 women and 7 men; mean age ± standard deviation [SD], 63.9 ± 7.4 yrs; age range, 45–73 yrs) referred to the Cyclotron Research Centre (CRC) of Liège from January 1992 to December 1998 were clinically diagnosed as having CBD by neurologists experienced in movement disorders. Twelve patients with CBD were referred from the Regional University Hospital of Lille, France. None had their diagnosis proven by pathology. Mean duration of illness was 3.7 ± 2.5 years (range, 1–10 yrs) at the time of the PET scan. Inclusion in the study was never based on the presence of abnormalities on functional imaging that might

have supported the diagnosis of CBD.[5,6] The patient's right body side was markedly more affected in 13 cases and left body side in nine cases. Twenty patients fulfilled modified clinical criteria proposed by Lang et al.[12] The two remaining patients (case nos. 1826 and 2519) did not have myoclonus or limb dystonia; they were nevertheless included in the study on the basis of association between an asymmetric dopa-resistant akinetorigid syndrome and bilateral ideomotor apraxia. This has been reported to justify a high index of suspicion for the diagnosis of CBD.[13] Clinical signs are summarized in Table 1. Frontal symptoms were observed in all patients tested, but formal neuropsychologic testing was lacking in some cases. Five patients had dementia confirmed on a Mattis scale.[14] Four patients had imitation syncinesia characterized by automatic imitation of movements of one limb by the contralateral limb. Magnetic resonance imaging (MRI) or computed tomography (CT) scans were normal or showed mild atrophy with moderate frontoparietal predominance. MRIs were obtained on different machines and coregistration between metabolic and functional imaging could not be performed.

Metabolic data from the CBD population were compared with those obtained from 46 normal, unmedicated volunteers (18 women and 28 men; mean age ± SD, 42 ± 20.5 yrs; age range, 19–75 yrs) labeled healthy subjects (HS). They were recruited from a general population invited to participate in a study of normal aging. All had a normal neurologic examination and none had a history of neurologic or medical disorders.

Finally, we selected 21 consecutive patients referred to the CRC of Liège from January 1992 to December 1998 with a clinical diagnosis of probable PSP made by neurologists experienced in movement disorders.[15–18] None had pathology-proven diagnosis. This group included 10 women and 11 men (mean age ± SD, 68.8 ± 6.9 yrs; range, 54–83 yrs). Mean duration of illness at the time of PET scanning was 4.2 ± 2.6 years (range, 2–11 yrs). Main clinical signs are described in Table 2. Two patients with PSP were detailed as having apraxia. Praxic errors in PSP were described in previous reports.[19,20] In our study, apraxia in both patients with PSP was tested using a homemade apraxia scale based on the cognitive model of Rothi.[21] Errors made by both patients with PSP were mild and symmetric compared with those in patients with CBD, and they were never similar to those found in patients with CBD. Cerebral MRI or CT scan was normal or showed only mild dilatation of hemispheric subarachnoid spaces or brain stem atrophy.

The Ethics Committee of the University Hospital of Liège, Belgium, approved this study. All subjects or a legally responsible relative gave informed consent to take part in the study before the scans.

PET Scanning and Image Processing

Images of glucose uptake were obtained on a Siemens CTI 951 R 16/31 tomograph (CTI, Knoxville, TN, USA) in two-dimensional mode using the ^{18}fluorodeoxyglucose (^{18}FDG) technique as previously published.[22] The camera had a field of view of 10.8 cm in the axial direction and collimated septa were extended. Physical characteristics have been described elsewhere.[23] In brief, a 20-minute transmission scan was acquired for attenuation correction using three rotating sources of 68 G prior to the tracer injection. An 8 mCi intravenous bolus injection of ^{18}FDG was followed 35 minutes later by 20-minute acquisition of the emission data under standard conditions (eyes closed in dimmed ambient light and ears unplugged). This scan was then reconstructed using a Hanning filter at a cut-off frequency of 0.5 cycles per pixel, giving a transaxial resolution of 8.7 mm full width at half maximum (FWHM) for each of the 31 planes.

All calculations and image transformations were performed on a Sun Sparc 20 workstation (Sun Computers Europe Inc, Surrey, UK). For each of the 89 scans, the 31 transverse planes were interpolated to 44 planes to render the voxels cubic (2.347 × 2.347 × 2.347). Functional brain images obtained from patients with CBD with predominant left-sided clinical signs were first flipped so the most affected hemisphere appeared on the left in all CBD images (see below for procedure validation). Each scan was then normalized into a standard stereotaxic anatomic space[24] using statistical parametric mapping (SPM 96, Wellcome Department of Cognitive Neurology, London, UK)[11] implemented in Matlab 4.2b (Math Works, Natick, MA, USA) using a bilinear interpolation method to allow for intersubject averaging. Scans were smoothed using an isotropic Gaussian filter (12 mm FWHM) to increase signal-to-noise ratio and to account for differences in gyral anatomy in the dataset. All images were checked visually before and after normalization to ensure that no cerebral region was incorrectly normalized in the stereotaxic space of Talairach. Because of slightly different positions in the tomograph, brain volume of interest extended from 32 mm below the bicommissural plane (between the anterior and posterior commissures) to 70 mm above that reference plane.

Data Analysis

The effect of global metabolism was removed by using proportional scaling.[25] The statistical program generated a group-specific adjusted mean value of cerebral

TABLE 1. *Clinical and demographic data from patients with corticobasal degeneration (CBD)*

Patient no.	Sex	Age (yrs)	Duration (yrs)	Most affected side	Limb akin/ rigid	Axial rigid	Limb tremor	Limb myoclonus	Limb dystonia	Postural instability	SGP	PBS	Dysarthria	Amimia	Apraxia	Alien limb	Babinski sign	CSL	FLT	MRI (CT scan)
16	F	56	2	R	+	+	Re + A	+	+	0	0	0	+	0	+	+	0	+	+	Mild L > R parietal atrophy
46	F	66	6	R	+	0	Re	0	+	0	0	+	+	0	+	0	+	0	+	N
466	F	64	3	R	+	0	Re + A	+	+	+	0	0	0	0	+	0	0	+	N/A	(N)
588	M	64	5	R	+	0	0	+	+	0	0	+	+	0	+	0	+	+	+	L > R fronto-parietal atrophy
607	F	73	2	L	+	+	0	0	+	+	0	0	+	+	+	+	0	+	N/A	(R > L fronto-parietal atrophy)
721	M	63	4	L	+	0	0	+	0	0	0	+	+	+	+	0	0	+	N/A	N
1073	F	65	10	L	+	0	0	+	+	+	0	0	0	0	N/A	0	+	+	N/A	N
1306	F	68	5	R	+	0	0	0	+	+	+	0	+	+	+	+	+	+	+	N
1655	M	66	2	L	+	0	0	0	+	+	0	0	0	0	N/A	+	0	+	N/A	N
1826	F	57	1	R	+	0	0	0	0	0	0	0	+	0	+	0	0	0	N/A	Mild cortical atrophy
2231	F	48	1	L	+	+	A	+	+	+	+	+	+	+	+	0	+	0	+	N
2296	F	70	3	R	+	+	0	+	+	+	+	0	+	+	+	0	+	+	+	Mild diffuse cortical atrophy
2502	M	45	3	R	+	0	Re + A	+	+	+	0	0	+	+	+	0	0	0	+	Mild diffuse cortical atrophy
2504	F	68	2	R	+	0	0	0	+	0	sacc	0	+	0	+	sync	0	0	+	Mild left parietal cortical atrophy
2514	F	60	2	L	+	+	Re + A	0	+	+	sacc	+	+	+	+	0	+	0	+	N
2515	F	72	6	L	+	+	A	+	+	+	sacc	+	+	+	+	sync	0	+	+	Mild right cortical atrophy
2516	F	69	3	L	+	+	Re + A	0	+	0	+	0	+	0	+	0	+	0	+	N
2519	M	57	2	R	+	0	0	0	0	0	0	0	+	+	+	0	0	0	+	(N)
2525	M	71	3	L	+	+	A	0	+	+	sacc	0	0	0	+	sync	+	0	+	Diffuse subcortico-cortical atrophy
2570	F	67	6	R	+	+	0	0	+	+	+	+	+	+	+	0	+	0	+	N
2572	F	70	9	R	+	+	0	0	+	0	0	+	+	+	+	sync	+	0	+	Mild diffuse cortical atrophy
2665	M	67	1	R	+	0	0	0	+	0	0	0	0	0	+	0	0	0	+	N

Akin, akinesia; rigid, rigidity; posture, postural instability; SGP, supranuclear gaze palsy; PBS, pseudobulbar syndrome; CSL, cortical sensory loss; FLT, impairment in "frontal lobe" tests; MRI, magnetic resonance imaging; +, present; 0, absent; Re, rest; A, action; sacc, impaired saccades; sync, imitation syncinesia; N/A, not available; N, normal.

metabolic rate of glucose and an associated adjusted error variance for each voxel. Significant differences between groups were estimated on a voxel-by-voxel basis. SPM{t} maps were transformed to the unit normal distribution SPM{z} maps with a total search volume greater than 175,000 voxels in each statistical analysis. We used an SPM with a Z-score threshold >3.09 (corresponding to p <0.001) in the group comparisons. Decreases in metabolism were then characterized in terms of the probability that the metabolic variation in a given voxel could occur by chance over the entire volume analyzed (p <0.05 after non-independent correction for multiple comparisons). Strictly speaking, firm conclusions can only be drawn about areas in which differences in activity survive correction for multiple comparisons. However, we also tentatively reported certain results as significant at p <0.001 uncorrected, corresponding to a Z-score >3.09 in group comparisons when appropriate hypotheses required testing. Age was introduced as a confounding covariate in all analyses because the mean ages of each group (HS, CBD, and PSP) were significantly different. In other words, significant differences in metabolism between those groups were independent of differences in the mean ages. Mean duration of illness was not statistically different between patients with CBD and those with PSP using a *t* test.

We performed the following independent statistical analyses with the SPM96 software: (1) metabolic brain images obtained from the nine patients with CBD with left-predominant clinical signs were flipped (see above) and were then compared with those obtained from the 13 patients with CBD with right-predominant clinical signs (left-CBD vs right-CBD and right-CBD vs left-CBD) to ensure that there were no significant differences in the metabolic patterns between both groups; (2) the metabolic pattern of the whole CBD group (whose most affected hemisphere was then on the left) was compared with that obtained in the HS and PSP groups (CBD vs HS, CBD vs PSP, and PSP vs CBD); (3) looking for cortico-cortical and cortico-subcortical disconnections, Pearson's linear regression was used to search for group-specific differences in correlation between regional adjusted relative glucose consumption in representative voxels of interest and metabolism in the remaining brain sample studied; individual relative values of glucose consumption in a given voxel were introduced as a centered covariate of interest for each group. Group-specific correlations were then compared using SPM96; (4) finally, individual metabolic pattern for both patients with CBD and those with PSP was compared with that obtained in HS using SPM96; it should be noted that contrary to the group comparisons, the results of these indi-

TABLE 2. *Clinical and demographic data from patients with progressive supranuclear palsy (PSP)*

Patient no.	Sex	Age	Duration (yrs)	Limb akinesia/ rigidity	Axial rigidity/ dystonia	Limb tremor	Limb myoclonus	Limb dystonia	Postural instability	SGP	PBS	Dysarthria	Amimia	Apraxia	Alien limb	Babinski sign	CSL	FLT	MRI (CT scan)
106	F	68	3	+	+	0	0	0	+	+	+	+	+	N/N	0	+	0	N/A	N
156	M	68	4	+	+	0	0	0	+	+	+	+	+	N/N	0	+	0	N/A	Mild cortical atrophy
235	M	75	2	+	+	0	0	0	+	+	0	+	+	N/N	0	+	0	N/A	N
391	M	76	11	+	+	Re	0	0	+	+	+	+	+	N/N	0	0	0	N/A	Midbrain atrophy
984	F	66	3	+	+	0	0	0	+	+	+	+	+	N/N	0	+	0	+	Mild cortical atrophy
1034	M	74	2	+	+	0	0	0	+	+	+	+	+	N/N	0	+	0	N/A	Midbrain atrophy
1082	F	66	2	+	+	0	0	0	+	+	+	+	+	N/N	0	0	0	N/A	N
1313	F	71	3	+	+	0	0	0	+	+	+	+	+	N/N	0	+	0	+	Mild cortical atrophy
1461	F	60	3	+	+	0	0	0	+	+	+	+	+	N/N	0	+	0	N/A	N
1470	F	77	2	+	+	0	0	0	+	+	+	+	+	N/N	0	+	0	+	N
1638	M	78	3	+	+	Re + P	0	0	+	+	+	+	+	N/N	0	0	0	N/A	N
1640	F	70	5	+	+	0	0	+	+	+	0	+	+	N/N	0	0	0	+	N
1653	F	83	4	+	+	0	0	0	+	+	0	+	+	N/N	0	0	0	N/A	N
1752	M	62	6	+	+	0	0	0	+	+	+	+	+	N/N	0	0	0	N/A	Mild cortical atrophy
1759	M	62	6	+	+	0	0	0	+	+	+	+	+	N/N	0	+	0	+	N
1974	F	71	5	+	+	Re	0	+	+	+	+	+	+	N/N	0	+	0	N/A	(N)
2119	M	54	2	+	+	0	0	0	+	+	0	+	+	N/N	0	+	0	+	N
2193	F	69	10	+	+	0	0	+	+	+	+	+	+	N/N	0	0	0	N/A	Mild frontal atrophy
2194	M	65	7	+	+	0	0	0	+	+	+	+	+	N/N	0	0	0	N/A	N
2232	M	68	4	+	+	Re	0	+	+	+	+	+	+	+	0	+	0	+	Mild diffuse cortical atrophy
2382	M	61	2	+	+	Re	0	0	+	+	0	+	+	+	0	0	0	+	N

SGP, supranuclear gaze palsy; PBS, pseudobulbar syndrome; CSL, cortical sensory loss; FLT, impairment in "frontal lobe" tests; MRI, magnetic resonance imaging; +, present; 0, absent; Re, rest; P, postural; N/N, not noticeable; N/A, not available; N, normal.

vidual analyses were thresholded at $p < 0.05$ without correction for multiple comparisons to obtain individual results in all patients. Given the low "empiric" statistical threshold used in those individual analyses, we considered only hypometabolic brain regions predicted by the group comparisons. The aim of those last analyses was only to compare patients with CBD with patients with PSP on an individual level, and not to find discriminant individual metabolic patterns.

RESULTS

Group Comparisons: Subtraction Analyses

After flipping of the metabolic data from patients with left-predominant CBD (see above), no significant differences in the metabolic pattern were found between patients with CBD with left- or right-sided clinical predominance.

Main significant results obtained in CBD compared with healthy subjects (HS) and PSP are summarized in Table 3 and Figures 1 and 2. Compared with HS, patients with CBD showed mainly an asymmetric cortical involvement in *discrete* frontoparietal metabolic networks and also in striatum and thalamus. Patients with PSP had greater metabolic impairment in midbrain and anterior cingulate regions than patients with CBD. The reverse contrast demonstrated preferential involvement of primary sensorimotor cortices, supplementary motor area (SMA), and superior lateral and medial parietal regions in CBD.

Group Comparisons: Correlation Analyses

In CBD, the functional connectivity between left putamen or left medial dorsal thalamus and frontal and parietal regions was not statistically different from that observed in healthy subjects. At the cortical level, the rostral inferior parietal region (BA 40) and the intraparietal sulcus (BA 7/40) were not functionally disconnected from frontal regions when patients with CBD were compared with HS.

Individual Comparisons

The metabolic pattern from each of the 43 patients was compared with that obtained from the healthy subject group using SPM96. Visual inspection of the individual statistical parametric maps from patients with CBD revealed asymmetric hypometabolism predominant in the hemisphere contralateral to the clinically most affected side in 20 cases; surprisingly, the two remaining patients (case nos. 16 and 2514) showed predominant hypometabolism in the hemisphere ipsilateral to the most affected body side. Cortical impairment was always present, whereas basal ganglia hypometabolism was found in only half of patients with CBD; cortical hypometabolism was always statistically more severe than that of basal structures, as indicated by the individual Z-values. When present, basal hypometabolism was always unilateral.

Although the metabolic pattern was slightly different for all patients with CBD, two discrete perirolandic cortical regions located in the hemisphere contralateral to the most affected body side appeared to be frequently impaired at the statistical level used (Fig. 3). One was centered on the inferior part of the precentral region (BA 4/6) extending further to the inferior frontal gyrus (BA 44), whereas the other was centered on the superior part of the postcentral gyrus (BA 1/2/3) and rostral inferior parietal lobe (BA 40). At the statistical threshold used ($p < 0.05$), 82% of our patients with CBD ($n = 18$) had at least one hypometabolic voxel located in both regions of interest within the same cerebral hemisphere (contralateral to the most clinically affected body side). On the contrary, only 19% of patients with PSP ($n = 4$) had at least one hypometabolic voxel located in both regions of interest within the same hemisphere.

DISCUSSION

The aim of this study was to highlight the predominant metabolic involvement measured at rest in a large sample of patients with probable CBD in comparison to both healthy subjects and patients with PSP. In an attempt to resolve discrepancies between previous studies concerning the most affected brain regions, we performed a voxel-by-voxel analysis using the SPM96 software. Advantages and limitations of SPM for this kind of application have been discussed elsewhere.[26,27] Limitations of this study were similar to those recently described in a previous report by our group.[28] A main difficulty of this kind of study was the heterogeneity of the disorders studied, especially CBD. Because none of our patients was examined by autopsy, the use of stringent clinical criteria probably biased our results toward clinically typical cases of CBD and PSP. Therefore, results presented in this study probably characterized most but not all cases of CBD and PSP.

We did not observe any significant metabolic differences when the data from patients with CBD with right-sided clinical predominance were compared with those obtained from patients with CBD with left-sided clinical predominance. Scintigraphic images from the latter group were then switched so the most affected hemisphere was on the left in all cases to increase the statistical power of our results.

The data derived from patients with CBD clearly indicate significant metabolic impairment in frontal and

TABLE 3. *Cortical areas and basal structures with significant relative decreases in metabolism at rest*

	CBD vs. HS		PSP vs. HS		CBD vs. PSP		PSP vs. CBD	
	L	R	L	R	L	R	L	R
Cortical areas								
Primary sensorimotor area (BA 1/2/3/4/6)	Z = 7.07 (-58 2 42)	Z = 5.88 (28 -8 66)	—	—	Z = 6.40 (-38 -20 -52)	Z = 4.70 (46 -26 50)	—	—
Dorsolateral premotor area (BA 6)	Z = 6.69 (-26 -10 58)	Z = 4.39 (34 8 60)	Z = 4.88 (-28 12 60)	Z = 5.11 (34 10 60)	—	—	—	—
Ventrolateral pre-central/motor area (BA 6/44/45)	Z = 6.85 (-40 6 32)	—	Z = 5.55 (-42 6 36)	Z = 4.57 (48 4 32)	—	—	—	—
Medial premotor area (BA 6)	Z = 5.45 (-6 2 50)	—	—	—	Z = 4.89 (-4 -14 58)	—	—	—
Dorsolateral prefrontal area (BA 8/9/46)	Z = 5.22 (-52 32 30)	—	Z = 4.49 (-52 30 26)	Z = 4.31 (6 42 52)	—	—	—	—
Anterior cingulate area (BA 24/32)	—	—	Z = 4.46 (0 32 28)	Z = 4.50 (8 12 38)	—	—	—	Z = 4.07* (20 14 34)
Orbitofrontal area (BA 10/11)	—	—	—	—	—	—	Z = 3.39* (-8 60 -10)	Z = 3.09* (2 60 -6)
Superior parietal lobe (BA 7)	—	—	—	—	Z = 5.81 (-28 -48 60)	Z = 4.26 (32 -48 62)	—	—
Intraparietal sulcus (BA 7/40)	Z = 4.73 (-36 -46 46)	—	—	—	—	—	—	—
Inferior parietal area (BA 40)	Z = 5.50 (-56 -36 44)	—	—	—	—	—	—	—
Paracentral lobule (BA 5)	—	—	—	—	Z = 5.60 (-4 -38 62)	—	—	—
Basal structures								
Striatum	Z = 5.64 (-24 -2 6)	—	Z = 4.81 (-18 2 6)	Z = 4.29 (18 2 14)	—	—	—	—
Thalamus	Z = 3.92 (-10 -20 10)	—	Z = 4.15* (-8 -20 12)	Z = 4.05* (8 -18 8)	—	—	—	—
Mesencephalon	—		Z = 5.01 (-4 -22 -4)		—		Z = 6.09 (6 -20 -8)	

CBD, corticobasal degeneration; HS, healthy subjects; PSP, progressive supranuclear palsy; BA, Brodmann's area.

The Talairach coordinates (x y z, in mm) of one hypometabolic voxel representative of the corresponding Brodmann's area are indicated between brackets. Most results presented in this table are thresholded to a Z value >3.09 ($p < 0.001$) corrected for multiple comparisons ($p < 0.05$). We tentatively reported certain results (marked with *), thresholded to a Z value >3.09 uncorrected for multiple comparisons (see *Methods*).

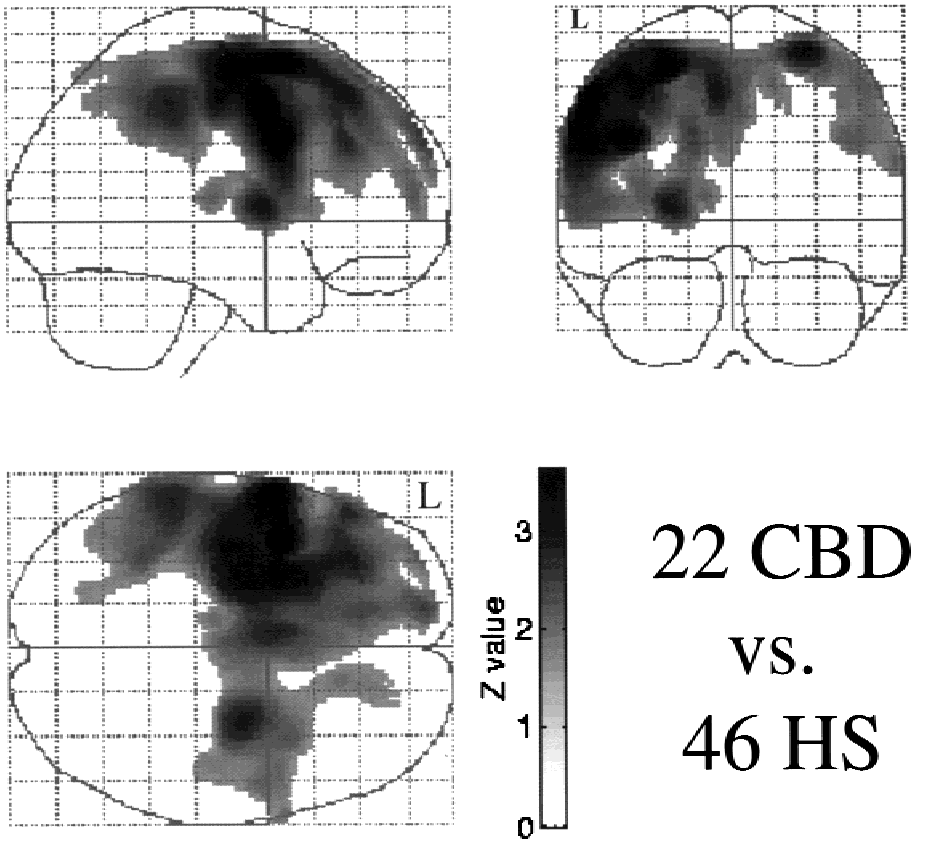

FIG. 1. Distribution of significant decreases in relative glucose uptake at rest when the metabolic pattern of the CBD group was compared with that of healthy subjects using SPM96. Results are displayed at a threshold of Z >3.09 by reference to the unit normal distribution and are further corrected for multiple comparisons ($p < 0.05$). Figures are displayed in sagittal, transverse, and coronal projections into the stereotaxic space of Talairach.[24] CBD, corticobasal degeneration; HS, healthy subjects; L, left.

parietal motor networks in which harmonious activation in healthy subjects leads to integrated movements (Table 3; Fig. 1). This widespread hypometabolism at rest is probably the consequence of both anatomic and functional changes. The neuropathologic changes in CBD predominate in parietal or frontoparietal cortical regions. The subcortical neuropathologic lesions are usually observed mainly in the substantia nigra, but are also seen to a lesser extent in the thalamus and striatum.[1,29,30] Even if a component of the metabolic pattern observed here is the result of structural changes, they cannot account for the full array of regional effects found in this study because all patients with CBD who had a normal MRI had regional hypometabolism on individual analysis (see below). Given the high significance of our results, mild radiographic changes in the other patients with CBD could not fully account for the regional decreases of glucose metabolism revealed by our SPMs. No significant differences in functional connectivity were found between the putamen and thalamus and the frontal and parietal regions when patients with CBD were compared with healthy subjects, suggesting that these basal structures and cortical areas are probably not functionally disconnected in CBD. Thus, the hypothesis of functional deactivation through cortico-subcortical connections is plausible in CBD.

The precise distribution of metabolic impairment described in Table 3 can be clearly related to the clinical motor disturbances that constitute frequent disorders of most patients with CBD, such as clumsiness of one hand, arm, or leg, and loss of manual dexterity for fine motor tasks. Effectively, involvement of pre- and postcentral regions, medial and lateral premotor areas, the parietal cortex, and the basal ganglia in the execution of movements has been extensively confirmed by activation studies using functional imaging.[31–35] More precisely, primary motor and medial and lateral premotor cortices have been shown to play a role in complex finger movements[36] and individualized finger movements,[37] which patients with CBD frequently fail to perform correctly early in the course of the disease.[38] The parietal rostral region (BA 40) and intraparietal sulcus (BA 7/40) were noted to be metabolically impaired in CBD; these areas are also activated during movement execution. On one hand, lesions in rostral BA 40, a supramodal integration area, have been preferentially related to impairment in the production of skilled movements, but not to comprehending or discriminating gesture.[39] On the other hand,

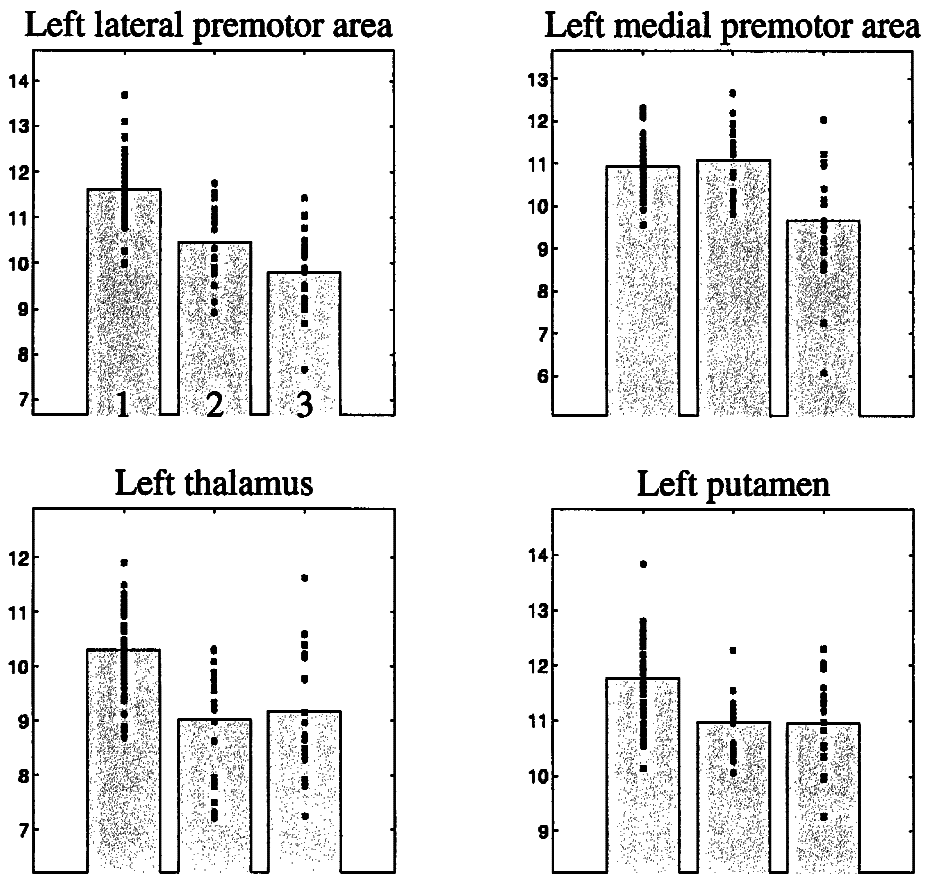

FIG. 2. Comparison of relative adjusted mean glucose metabolism in representative voxels of left lateral and medial premotor regions, putamen, and thalamus in healthy subjects,[1] patients with progressive supranuclear palsy,[2] and patients with corticobasal degeneration.[3]

the intraparietal sulcus is thought to serve as an associative area for sensorimotor integration and feedback, and has been recently suggested to play a major role in controlling sequences of finger movements and object grasping.[40–42] Our SPMs indicated relative sparing of the caudal part of the inferior parietal lobe in our CBD population. This is in keeping with testing of praxis in CBD which usually reveals an intact conceptual system but an impaired production system (following the concept of Roy and Square[43]), suggesting either parietofrontal disconnection between systems or specific system impairment.[44–47] Because of preserved functional connectivity between parietal and frontal regions, our metabolic data preferentially support the second hypothesis. However, studies of changes in effective connectivity[48] rather than analyses of functional connectivity would probably be more useful to characterize the reorganization of motor networks in CBD. Moreover, our data support the hypothesis that severe impairment of gesture execution in CBD depends on decreases of metabolism in networks thought to participate in the control of both low- and high-level motor organization. Further clinicometabolic studies are needed to more precisely elucidate cerebral dysfunction underlying motor impairment in CBD.

The precise nature of difficulty in realizing gestures in CBD and PSP is a matter of debate in the literature.[19,20,44,45] Our SPMs showed that lateral premotor regions have similar decreases in glucose consumption (Fig. 2) in both populations. However, we found a predominant involvement of perirolandic, medial premotor, and parietal regions in CBD. This would contrast with the more anterior metabolic pattern in PSP. Anterior cingulate and medial orbitofrontal cortices, found to be impaired when patients with PSP were compared with patients with CBD, have been shown to be important for selective attention, attention prior to action, and response selection.[49–51] In this group comparison, our SPMs also indicate greater metabolic impairment in the midbrain in patients with PSP than in patients with CBD. The precise identity of the structure(s) lying in this tegmental mesencephalic region remains difficult to determine given the relatively low spatial resolution of the PET technique and the small size and anatomic complexity of this region, but they could possibly participate in the axial motor and ocular disturbances frequently observed in

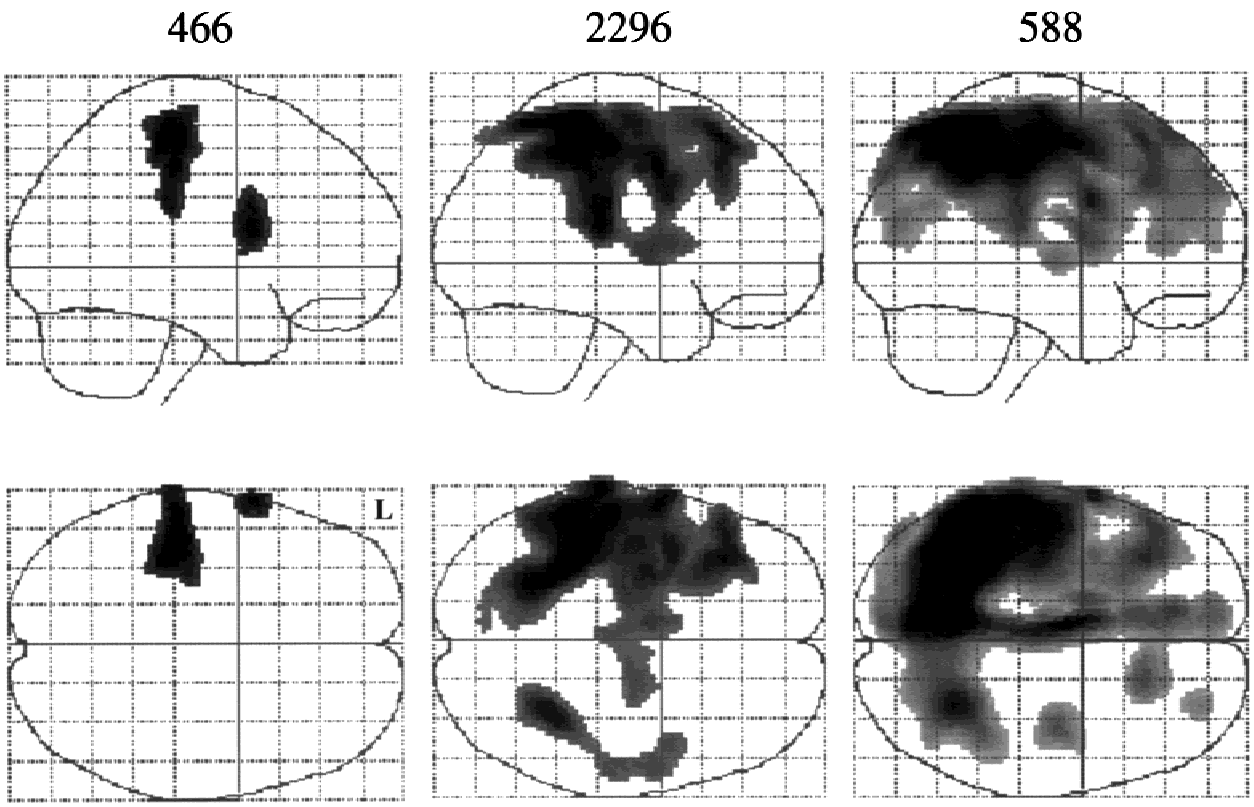

FIG. 3. Hypometabolic brain areas in three patients (case nos. 466, 2296, and 588) with probable corticobasal degeneration (CBD). Results are displayed at a threshold of $p < 0.05$ uncorrected for multiple comparisons. Figures are displayed in sagittal and transverse projections into the stereotaxic space of Talairach.[24] Case no. 466 best illustrates the spatial location of both perirolandic regions, which are frequently impaired as shown by case-by-case analyses of patients with CBD compared with healthy subjects (HS) using SPM96. L, left.

PSP.[52–54] As indicated in Table 3, no significant differences in resting glucose metabolism were seen in the dorsolateral prefrontal cortex, either in CBD compared with PSP or in PSP compared with CBD patients. This is in keeping with a report showing that the intensity of the dysexecutive syndrome in CBD is comparable to that observed in PSP.[45]

Individual Analyses

The metabolic pattern from each patient was compared with that obtained from the healthy subject group using SPM96. This method has recently received clinical validation.[27] Our results were displayed at a threshold of $p < 0.05$ uncorrected for multiple comparisons to obtain an individual map in all patients. Unfortunately, the use of a low statistical threshold increases the risk of false-positive results. Given that possible bias, we considered only hypometabolic brain regions strongly predicted by the group comparisons: our aim was only to compare patients with CBD with patients with PSP on an individual level, and not to define the most significantly affected areas. To date, there are only two voxel-by-voxel techniques for the assessment of individual patient scans: SPM and 3-Dimensional Stereotaxic Surface Projection (3D-SSP). Differential features between both techniques and limitations of SPM were reviewed recently.[27]

As expected, visual inspection of the individual statistical parametric maps from patients with CBD revealed asymmetric hypometabolism correlated with the laterality of the clinical features in 20 cases; the two remaining patients (case nos. 16 and 2514) showed predominant hypometabolism in the hemisphere ipsilateral to the clinically most affected body side. The interpretation of that surprising result involves a number of issues. First, both cases can have a pathologic diagnosis different from CBD. Secondly, both patients differed from others by the presence of severe and permanent unilateral dystonic movements of upper and lower limbs that could be related to the abnormal expression of certain motor metabolic networks in the contralateral hemisphere in a mechanism similar to that described in patients with idiopathic torsion dystonia.[55]

When referring to the spatial coordinates of the hypometabolic voxels in the Talairach space,[24] individual metabolic patterns were heterogeneous. Cortical impairment was always present, whereas basal ganglia hypometabolism was found in only half of patients with CBD; cortical hypometabolism was always statistically more severe than that of basal structures, as indicated by the individual Z-values. Contrary to cortical hypometabolism, basal ganglia hypometabolism was never observed in the hemisphere ipsilateral to the most clinically affected side. In agreement with a recent clinicopathologic report,[56] those findings could suggest that neurologic disturbances in patients with CBD depend more on cortical than basal structure functional impairment.

Although the individual map was slightly different for all patients with CBD on visual inspection, a portion of the hypometabolic voxels was clearly distributed in two distinct perirolandic regions within the same cerebral hemisphere. The first region was centered on the inferior part of the precentral gyrus (BA 4/6) extending further to the inferior frontal gyrus (BA 44), whereas the second was centered on the superior part of the postcentral gyrus (BA 1/2/3) and rostral inferior parietal lobe (BA 40) (Fig. 3). At the statistical threshold used, 82% of our patients with CBD had at least one hypometabolic voxel located in both cortical regions within the same cerebral hemisphere (contralateral to the clinically most affected body side). On the contrary, that individual pattern was only observed in four patients with PSP. Because our patients were categorized as clinical syndromes, it would not be surprising, for example, that the presence or the absence of inferior perirolandic and parietal involvement could be related to the presence or absence of certain clinical signs such as apraxia and cortical sensory loss. Further studies, including patients with pathology-proven diagnoses, are needed to evaluate the sensitivity and specificity of individual analysis of ^{18}FDG-PET data as a biologic marker of CBD.

CONCLUSIONS

Our study aimed to precisely characterize the distribution of metabolic impairment in CBD and the pathophysiological differences between CBD and PSP. Given the clinical heterogeneity of CBD, our results probably characterized most but not all patients with CBD. However, the metabolic impairment of sensorimotor, premotor, and parietal areas in CBD suggests that multiple components of neural networks related to both movement execution and production of skilled movements are functionally disturbed in the disease. In PSP, our SPM showed preferential involvement of more anterior cortical neural networks subserving motor response inhibition, movement, and response selection. Finally, it would appear that individual analyses using the SPM96 software is a useful technique to interpret ^{18}FDG-PET scans obtained at rest in patients with CBD.

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