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Comparison of Impaired Subcortico-Frontal Metabolic Networks in Normal Aging, Subcortico-Frontal Dementia, and Cortical Frontal Dementia[1]

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Normal aging, progressive supranuclear palsy (PSP), and frontotemporal dementia (FTD) are characterized by different degrees of decline in frontal lobe functions. We used ^{18}FDG-PET and statistical parametric mapping (SPM96) to compare relative subcorticofrontal metabolic impairment at rest in 21 healthy elderly subjects (HES), 20 PSP patients, and 6 FTD patients. When HES were compared to 22 healthy young subjects, widespread decrease in metabolism was observed in bilateral medial prefrontal areas including anterior cingulate cortices, in dorsolateral prefrontal areas, in left lateral premotor area, in Broca's area, and in left insula. In PSP compared to the 43 healthy subjects (HS), we observed subcorticofrontal metabolic impairment including both motor and cognitive neural networks. Impairment of functional connections between midbrain tegmentum and cerebellar, temporal and pallidal regions was demonstrated in PSP as compared to HS. When comparing FTD to HS, glucose uptake was primarily reduced in dorsolateral and ventrolateral prefrontal cortices and in frontopolar and anterior cingulate regions. There was also bilateral anterior temporal, right inferior parietal, and bilateral striatal hypometabolism. Finally, FTD showed more severe striatofrontal metabolic impairment than PSP, while mesencephalothalamic involvement was only observed in PSP. Our data suggest that subcorticofrontal metabolic impairment is distributed in distinct subcorticocortical networks in normal aging, PSP, and FTD. Subcorticofrontal dementia in PSP is related to hypometabolism in discrete frontal areas, which are probably disconnected from certain subcortical structures. The concept of subcortical dementia is reinforced by our data, which show disrupted functional connections between mesencephalon and cerebellar cortex, inferior and medial temporal regions, and pallidum.

Key Words: **normal aging; progressive supranuclear palsy; frontotemporal dementia; PET; ^{18}FDG.**

INTRODUCTION

The volume of the frontal lobes increases dramatically as one ascends the evolutionary ladder, to finally represent 25–30% of brain mass in humans. The frontal cortices are involved not only in a wide array of behavioral functions, including movement, language, visuospatial capacity, praxis, and executive abilities, but also in characteristics thought to distinguish humans from lower primates such as emotion, will, judgement, foresight, and abstraction abilities (Absher and Cummings, 1995). However, synaptic density seems to decline preferentially in the frontal lobes in humans with advancing age (Huttenlocher, 1979; Gibson, 1983; Masliah *et al.*, 1993). Accordingly, several authors have suggested that many age-related cognitive changes are consequences of the decline in frontal lobe functions (Mittenberg *et al.*, 1989; Daigneault and Braun, 1993). Positron emission tomography (PET) studies of age-related changes in the regional pattern of cerebral metabolism or cerebral blood flow have yielded conflicting results, but most highlight the relative involvement of frontal lobes (Kuhl *et al.*, 1982; de Leon *et al.*, 1987; Leenders *et al.*, 1990; Salmon *et al.*, 1991; Waldemar *et al.*, 1991; Moeller *et al.*, 1996; Blesa *et al.*, 1997; Petit-Taboué *et al.*, 1998), which is sometimes predominant on the left side (Gur *et al.*, 1987; Martin *et al.*, 1991). Discrepancies may be attributable to different selection criteria, technical and methodological differences which limit scan resolution, and the use of *a priori* hypotheses linked to regions of interest (ROI) templates.

Progressive frontal impairment with increasing age has not yet been functionally contrasted to that classically observed in two prototypes of degenerative frontal dementia: the subcortical and the primary cortical types. Steele–Richardson–Olszewski syndrome (progressive supranuclear palsy, PSP) (Steele *et al.*, 1964) is a prototype of degenerative subcorticofrontal dementia (Albert *et al.*, 1974) clinically characterized by early postural instability and falls, supranuclear gaze palsy, parkinsonism, pseudobulbar palsy, and frontal lobe

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signs such as impairment of executive functions, forgetfulness, and slowing of thought processes (Steele *et al.*, 1964; Dubois *et al.*, 1996; Litvan *et al.*, 1996a; Bak and Hodges, 1998). Regional cerebral blood flow (rCBF) studied at rest in cases of PSP has been extensively described with single-photon emission computed tomography (SPECT) using ^{99m}Tc-HMPAO (Neary *et al.*, 1987; Defebvre *et al.*, 1995) or ^{123}I-lofetamine (Johnson *et al.*, 1992), and PET using $^{15}O_2$ (Leenders *et al.*, 1988). Data converge with those found with PET using ^{18}fluorodeoxyglucose (^{18}FDG); these techniques show subcorticofrontal involvement compatible with the hypothesis of frontal lobes disconnection from subcortical input (Grafman *et al.*, 1990). The data, however, differ concerning the most affected subcortical and cortical structures (D'Antona *et al.*, 1985; Foster *et al.*, 1988; Goffinet *et al.*, 1989; Blin *et al.*, 1990; Karbe *et al.*, 1992; Salmon *et al.*, 1997). On the other hand, approximately 10–15% of patients with primary degenerative dementia manifest a primary cortical dementia termed frontotemporal dementia (FTD) (Gustafson, 1987; Neary *et al.*, 1988). Using pathological and clinical features, the Lund and the Manchester groups (1994) have recently divided frontotemporal dementia into three subgroups: the Pick-type, the frontal lobe degeneration type, and the motor neurone disease type. Clinical criteria include behavioral disorders such as change in personality, breakdown in social conduct, disinhibition, and impulsivity, affective symptoms such as depression and apathy, speech disorders, and physical signs such as resurgence of primitive reflexes or incontinence. PET and SPECT studies in FTD concur in showing major decreases of cortical frontotemporal activity, but diverge concerning the most affected areas and the extent of basal ganglia involvement (Chase *et al.*, 1987; Neary *et al.*, 1987; Kamo *et al.*, 1987; Salmon and Franck, 1989; Miller *et al.*, 1991; Friedland *et al.*, 1993; Starkstein *et al.*, 1994; Ishii *et al.*, 1998).

In an attempt to resolve the discrepancies between these previously reported functional neuroimaging techniques in normal aging, PSP, and FTD, we first assessed the most affected areas (principally subcorticofrontal metabolic networks) using recent technical and methodological tools, i.e., a voxel by voxel approach using Statistical Parametric Mapping (SPM96) software (Friston, 1997a). We further tried to highlight the differences and similarities of the various metabolic patterns. Finally, we discussed our results with regards to the literature concerning possible pathophysiology of subcorticofrontal metabolic defects.

MATERIAL AND METHODS

Subjects

Forty-three normal unmedicated volunteers (18 females and 25 males; mean age ± SD, 42 years ± 20.5 years, range 19–75 years, healthy subjects, HS) were divided into two groups (Table 1): 22 healthy young subjects (HYS) (12 females and 10 males; mean age ± SD, 22.6 years ± 2.2 years, range 19–28 years) and 21 healthy elderly subjects (HES) (6 females and 15 males; mean age ± SD, 62.5 years ± 8.04, range 47–75 years). Recruitment was from a general population invited to participate in a study concerning normal aging. All had a structured interview that confirmed lack of cognitive complaint and impairment. Volunteers had a normal neurological examination and none had a history of neurological, psychiatric, or medical disorder.

We also selected 20 patients with a clinical diagnosis of probable PSP made by neurologists experienced in movement disorders (Table 1). None had pathology-proven diagnosis. This group included 10 females and 10 males (mean age ± SD, 69.2 ± 6.9 years, range 54–83 years). Mean duration of illness at the time of PET scanning was 4.4 ± 2.6 years (range 2–11 years). Presenting features were primarily motor in 18 patients and included instability, gait disturbance, falls, akinesia-rigidity, and speech difficulty. Neurobehavioral changes, mainly cognitive impairment and depression, were the initial symptoms in the two remaining patients. Clinical diagnosis was based on the following symptoms (Steele *et al.*, 1964; Daniel *et al.*, 1995; Collins *et al.*, 1995; Litvan *et al.*, 1996a, 1996b): early postural instability, supranuclear gaze palsy, dopa-

TABLE 1

Demographic and Clinical Data from Healthy Subjects and Patients Suffering from Probable Progressive Supranuclear Palsy and Frontotemporal Dementia

	Number of subjects	Sex (F/M)	Mean age ± SD (years)	Mean duration of illness ± SD (years)	Mean CDR (maximum = 3)
Healthy young subjects (HYS)	22	12/10	22.6 ± 2.2	—	—
Healthy elderly subjects (HES)	21	6/15	62.5 ± 8.04	—	—
Healthy subjects (HS) (HYS + HES)	43	18/25	42 ± 20.5	—	—
Progressive supranuclear palsy (PSP)	20	10/10	69.2 ± 6.9	4.4 ± 2.6	0.5
Frontotemporal dementia (FTD)	6	3/3	59.7 ± 8.8	2.2 ± 1.2	1.5

Note. F, female; M, male; CDR, clinical dementia rating scale (Hughes *et al.*, 1982).

resistant akinetic-rigid syndrome, amimia, dysarthria, pseudobulbar palsy, axial rigidity, or dystonia and pyramidal signs. Associated signs were focal rest and/or action tremor, limb apraxia, and facial and/or axial and/or limb dystonia. None had exclusion criteria (Litvan *et al.*, 1996b), including unilateral limb dystonia, alien-limb syndrome, early cortical dementia, prominent cerebellar signs, dysautonomia, hallucinations, or focal lesions, on clinical and radiological examination. The mean clinical dementia rating (CDR) score (Hughes *et al.*, 1982; Morris, 1993) was 0.5. Response to levodopa treatment was poor or absent in all 20 patients. Cerebral MRI or CT scan was normal or showed only mild dilatation of hemispheric subarachnoid spaces or brainstem atrophy.

Finally, six patients (3 females and 3 males; mean age $\pm$SD, 59.7 $\pm$ 8.8 years, range 46–70 years) fulfilled the Lund and Manchester Groups clinical criteria for the diagnosis of frontotemporal dementia (The Lund and Manchester Groups, 1994). None had pathology-proven diagnosis. The mean duration of illness was 2.2 $\pm$ 1.2 years (range 1–4 years) at the time of the PET scan (Table 1), and all patients had at least two or more symptoms or signs from each of the three following categories: (a) behavioral disorders (insidious onset and slow progression, early loss of social or personal awareness; early signs of disinhibition, mental rigidity and inflexibility, hyperorality, stereotyped and perseverative behavior, and distractibility); (b) affective symptoms (depression, anxiety, emotional unconcern, amimia, inertia, aspontaneity); (c) speech disorders (progressive reduction of speech, stereotypy of speech, echolalia and perseveration, late mutism). None of them had diagnostic exclusion criteria listed in The Lund and Manchester Groups criteria. At the time of the PET scan, clinical examination always revealed frontal dysfunction but formal neuropsychological testing was not available. The mean CDR score (Hughes *et al.*, 1982; Morris, 1993) was 1.5. Five patients had limited frontal release phenomena on neurological exam, and one showed a motor neurone disease confirmed by electrophysiology. The electroencephalogram was normal in all cases. Frontal atrophy was observed in one patient on CT scan and another had bilateral frontal and temporal atrophy on MRI. Seven patients fulfilling the clinical criteria for FTD were not included in the study because of technical difficulties on drawback: significant head movements in two patients during the transmission scan prevented the use of attenuation correction (see below); in five patients, the frontotemporal hypometabolism was so severe that their scintigraphic image was clearly misnormalized into the stereotaxic space (Talairach and Tournoux, 1988) in SPM96 (see below). The functional abnormalities from those patients were visually more severe than those from the six patients included in the study. Results are thus probably biased to the earlier stages of FTD.

The Ethics Committee of the University Hospital of Liège (Belgium) approved this study. Informed consent was obtained from all controls and from relatives of patients prior to 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) in 2D mode, using the [^{18}F]fluorodeoxyglucose (^{18}FDG) technique as previously published (Salmon *et al.*, 1997). The camera has a field of view of 10.8 cm in the axial direction and collimated septa were extended. Physical characteristics have been described elsewhere (Degueldre and Quaglia, 1992). The subject's head was placed in the scanner and held in a polystyrene support, with line markings along the subject's orbitomeatal reference plane. Correct alignment of the head within the aperture was maintained by aligning these marks with two perpendicular laser beams located on the gantry of the camera; careful observation of the subject throughout of image acquisition ensured there was no significant head movement. Subjects were asked to close their eyes, and ear plugs were not used. A 20-min transmission scan was acquired for attenuation correction using three rotating sources of ^{68}G. An 8-mCi intravenous bolus injection of ^{18}FDG was followed 35 min later by 20-min acquisition of the emission data. 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) and an axial resolution of 5 mm 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 scan, the 31 transverse planes were interpolated to 44 planes to render the voxels cubic (2.347 $\times$ 2.347 $\times$ 2.347). Each scan was first normalized into a standard stereotaxic anatomical space (Talairach and Tournoux, 1988) using statistical parametric mapping (SPM 96, Wellcome Department of Cognitive Neurology, London, UK), implemented in Matlab 4.2b (Math Works, Natick, MA), and a bilinear interpolation method to allow for intersubject averaging (Friston, 1997a). Scans were then smoothed using an isotropic Gaussian kernel of 12 mm to increase signal-to-noise ratio and to account for differences in gyral anatomy between individuals. All images were checked visually before and after normalization to ensure that no cerebral region was incorrectly normalized in the stereotaxic space, especially in patients with FTD.

Data Analysis

The effect of global metabolism was removed by using proportional scaling. The statistical program generated a group-specific adjusted mean value of cerebral 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 unit normal distribution (SPM[z]) maps with a total search volume of 174 986 voxels or 219.1 resels. We used an SPM with a Z score threshold >3.09 (corresponding to $P < 0.001$). 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 analysed (P value <0.05 with Bonferroni correction for multiple comparisons). We also tentatively reported certain results as significant at $P < 0.001$ uncorrected, corresponding to $Z > 3.09$, although strong conclusions cannot be drawn about these regions in the absence of correction for multiple comparisons. Age was introduced as a confounding covariate in analysis including HS, PSP, and FTD because the mean ages of each group 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 PSP and FTD patients using a t test, although FTD were referred earlier than PSP patients (Table 1). Cognitive status as assessed by CDR was significantly more impaired in the FTD group than in the PSP group (t test, $P < 0.01$). Theoretically, that difference in the level of cognitive impairment between both dementia groups could affect the results mainly in the FTD group. However, the hypometabolism in FTD was so severe (see Results) that taking the level of cognitive impairment into account did not have a major impact on the results.

We performed the following independent statistical analyses: (a) processed metabolic brain images obtained from the HES group were first compared to those obtained from the group of HYS: HES vs HYS and HYS vs HES; (b) the same procedure was applied for the four following comparisons in a second analysis: PSP vs HS, FTD vs HS, PSP vs FTD, and FTD vs PSP. (c) In further analyses, we employed Pearson's linear regression to search for group-specific differences in correlation between regional adjusted relative glucose consumption in a representative voxel of interest and that in the 174985 remainders. Individual relative values of glucose consumption of this voxel were introduced as a centred covariate of interest for each group. Group-specific values were then compared using SPM96.

RESULTS

Subtractions Analysis

See Table 2 and Figs. 1 and 2.

Healthy Elderly Subjects vs Healthy Young Subjects

The metabolic pattern of the 21 healthy elderly subjects was first contrasted to that obtained in the 22 healthy young volunteers. Frontal glucose consumption was substantially reduced in the healthy elderly population in the following regions: bilateral dorsolateral prefrontal (Brodmann's area, BA 8/9/46) and medial prefrontal (BA 8/9) areas including anterior cingulate cortices (BA 24/32) and possibly presupplementary motor area (pre-SMA), left lateral premotor area (BA 6), Broca's area (BA 44/45), and left insula. There was a tendency to symmetrical involvement if Z values were not corrected for multiple comparisons. We also found significant metabolic impairment in the anterior part the right superior temporal gyrus (BA 22). The highest Z values were noted in regions corresponding to the left medial prefrontal and cingulate areas. There was no metabolic difference at the subcortical level at the statistical threshold used.

PSP vs Healthy Subjects

In the 20 PSP patients, the topography of relative metabolic decrease predominated in frontal cortical areas but also in subcortical structures, as compared to HS. Cortical metabolic impairment involved bilateral precentral (BA 4/6) and dorsolateral premotor (BA 6) areas, left ventrolateral premotor (BA 6/44/45), left dorsolateral prefrontal (BA 8/9/46), left frontopolar (BA 10), and left anterior cingulate (BA 24/32) areas. Statistical parametric maps also revealed significant decreases of glucose utilisation in bilateral dorsal putamen rostral to the anterior commissure, left medial dorsal nucleus of the thalamus, and in the midbrain tegmental region. In this comparison, the highest Z values were observed in left putamen and in the mesencephalic region. Finally, at a statistical threshold of $P < 0.001$ uncorrected for multiple comparisons, glucose uptake was also reduced in right medial dorsal nucleus of the thalamus and right anterior cingulate area.

PSP vs FTD

When the metabolic pattern of the PSP cohort was compared to that present in the FTD group, statistical maps indicated a highly significant hypometabolism in midbrain tegmentum and lateral thalamus bilaterally. The maps showed also posterior extension of the relative hypometabolism in PSP to left lingular gyrus (BA 19) and bilateral occipital cortices (BA 17/18). There was no significant difference in glucose consumption in the frontal cortex in this comparison.

FTD vs Healthy Subjects

The relative metabolic impairment in FTD patients as compared to healthy subjects was observed bilaterally in most parts of the frontal lobes except bilateral precentral, bilateral medial prefrontal, and medial premotor regions. In general, Z values approached 7, and the highest values were observed in bilateral

TABLE 2

Frontal Areas and Basal Structures with Significant Relative Decreases in Metabolism at Rest

	HES vs HYS		PSP vs HS		FTD vs HS		PSP vs FTD		FTD vs PSP	
	L	R	L	R	L	R	L	R	L	R
Frontal lobes										
Precentral area (BA 4/6)	—	—	$Z = 5.57$ (−42 6 36)	$Z = 4.52$ (48 4 32)	—	—	—	—	—	—
Dorsolateral premotor area (BA 6)	$Z = 5.05$ (−52 12 48)	—	$Z = 5.35$ (−30 14 60)	$Z = 4.79$ (32 8 60)	$Z = 7.00$ (−14 28 60)	$Z = 7.32$ (18 24 58)	—	—	—	—
Ventrolateral premotor area (BA 6/44/45)	$Z = 4.74$ (−50 12 4)	—	$Z = 4.77$ (−52 10 32)	—	$Z = 7.48$ (−58 20 18)	$Z = 7.43$ (58 24 16)	—	—	$Z = 5.01$ (−54 26 2)	$Z = 6.68$ (58 24 12)
Dorsolateral prefrontal area (BA 8/9/46)	$Z = 4.96$ (−24 56 28)	$Z = 4.42$ (12 54 36)	$Z = 5.35$ (−12 40 56)	—	$Z = 7.52$ (−16 54 34)	$Z = 7.54$ (16 54 34)	—	—	$Z = 5.77$ (−34 36 34)	$Z = 6.98$ (20 50 26)
Ventral prefrontal area (BA 11/47)	—	—	—	—	$Z = 6.07$ (−28 38 −10)	$Z = 7.29$ (52 34 −2)	—	—	$Z = 5.78$ (−26 38 −10)	$Z = 6.77$ (30 30 −10)
Fronto-polar area (BA 10)	—	—	$Z = 4.44$ (−36 52 24)	—	$Z = 7.62$ (−14 60 26)	$Z = 7.70$ (24 58 14)	—	—	$Z = 6.72$ (−14 56 24)	$Z = 7.24$ (22 56 14)
Anterior cingulate area (BA 24/32)	$Z = 4.74$ (−2 26 30)	$Z = 5.37$ (2 10 42)	$Z = 4.36$ (−6 8 40)	—	$Z = 7.54$ (−6 32 24)	$Z = 7.06$ (4 20 34)	—	—	$Z = 6.49$ (−8 36 20)	$Z = 6.29$ (4 44 −4)
Medial prefrontal areas and pre-SMA (BA 6/8/9)	$Z = 5.47$ (−2 40 44)	$Z = 4.99$ (2 18 62)	—	—	—	—	—	—	—	—
Basal structures										
Putamen	—	—	$Z = 6.03$ (−18 2 12)	$Z = 4.47$ (16 2 12)	$Z = 7.18$ (−18 6 6)	$Z = 5.88$ (16 10 8)	—	—	—	—
Caudate nucleus	—	—	—	—	—	—	—	—	$Z = 4.98$ (−10 18 −4)	$Z = 4.80$ (14 18 −4)
Pallidum	—	—	—	—	—	—	—	—	—	—
Thalamus	—	—	$Z = 4.85$ (−6 −20 8)	—	—	—	$Z = 5.20$ (−20 −16 −10)	$Z = 4.67$ (22 −20 8)	—	—
Mesencephalon	—		$Z = 5.64$ (−2 −26 −6)		—		$Z = 7.33$ (2 −30 −10)		— —	

Note. The Talairach coordinates (x y z, in mm) of one hypometabolic voxel representative of the corresponding Brodmann's area are indicated between brackets. All results presented in this table are thresholded to a Z value >3.09 ($P < 0.001$) corrected for multiple comparisons ($P < 0.05$). BA, Brodmann's area. Pre-SMA, presupplementary motor area. L, left. R, right. HS, healthy subjects. HES, healthy elderly subjects. HYS, healthy young subjects. PSP, progressive supranuclear palsy. FTD, frontotemporal dementia.

frontopolar areas. This widespread hypometabolism extended to the anterior part of both temporal lobes, including bilateral middle and inferior temporal gyri (BA 20/21) and left superior temporal gyrus (BA 38), with a more posterior cortical involvement in the right inferior parietal lobe (BA 40). Finally, decreased glucose consumption was also present in putamen bilaterally.

FTD vs PSP

As opposed to the contrast between FTD and HS, there was more localized bilateral frontal metabolic impairment limited to bilateral frontopolar, bilateral dorsolateral prefrontal, bilateral ventral prefrontal, bilateral ventral premotor, and bilateral anterior cingu-

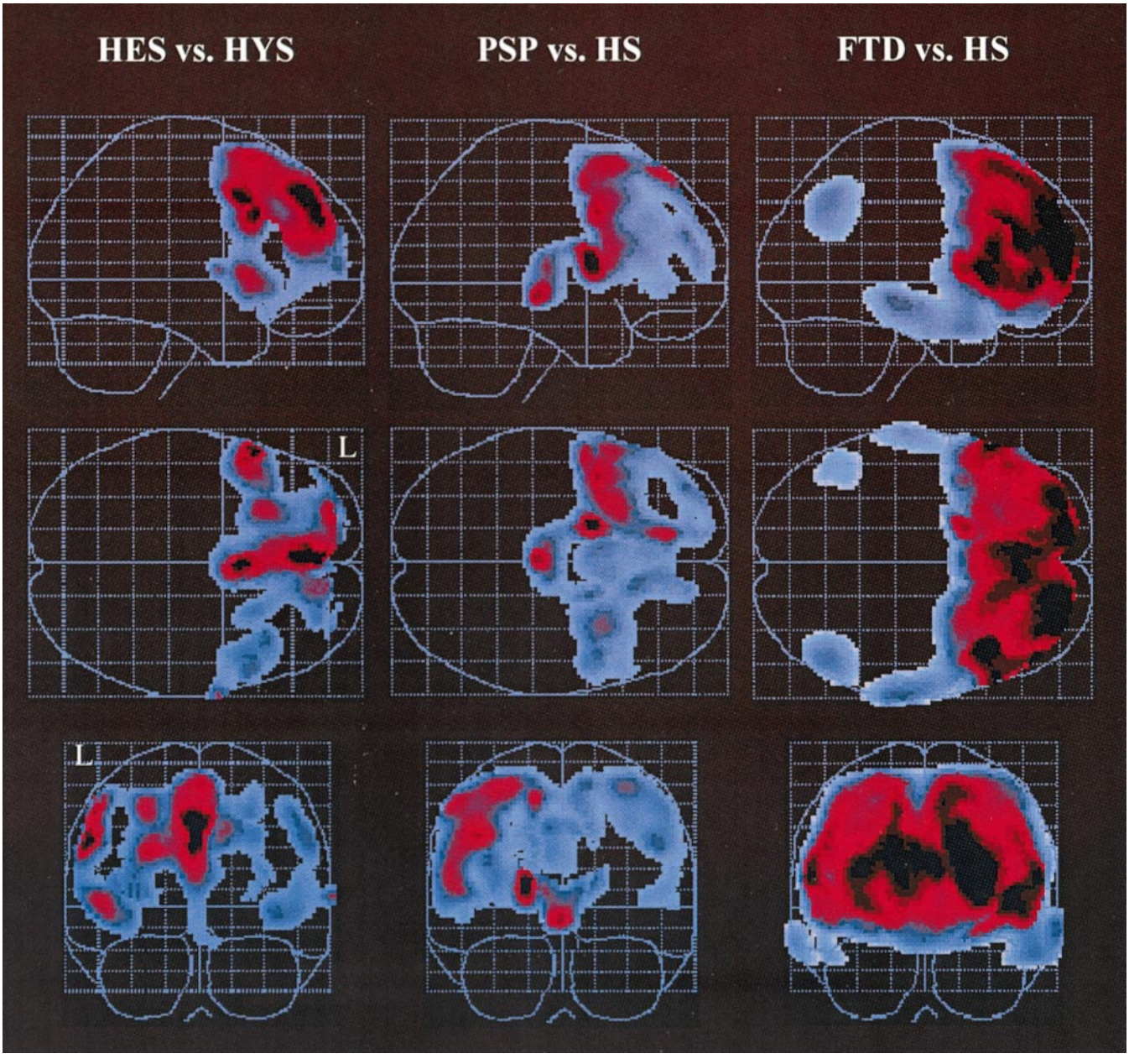

FIG. 1. Brain regions with significant decreases in relative glucose uptake at rest in the three patient group comparisons. Results are displayed at a threshold of $Z > 3.09$ ($P < 0.001$) by reference to the unit normal distribution and are corrected for multiple comparisons at a threshold of $P < 0.05$. Figures are displayed in sagittal, transverse, and coronal projections into the stereotaxic space of Talairach (1988). The pseudocolor scale illustrates increasing levels of statistical significance from light blue to dark red and black. HES, healthy elderly subjects. HYS, healthy young subjects. HS, healthy subjects. L, left.

late areas. Subcortical hypometabolism was only noted in the head of the caudate bilaterally.

Correlation Analysis

Correlation analysis was only performed in the PSP group and healthy controls, because the sample of FTD was too small. There were four areas where functional connectivity with the midbrain tegmentum region was statistically different from that observed in healthy subjects: the left inferior temporal region (BA 20), left parahippocampal gyrus (BA 28/36), left cerebellar cortex, and left pallidum (Table 3). A difference in correlation strength was also observed for the left hippocampus if results were not corrected for multiple comparisons. Similar analyses were also performed with voxels located in left and right putamen and left dorsal medial nucleus of the thalamus. No significant differences in functional connectivity were found between these voxels and the remaining brain regions.

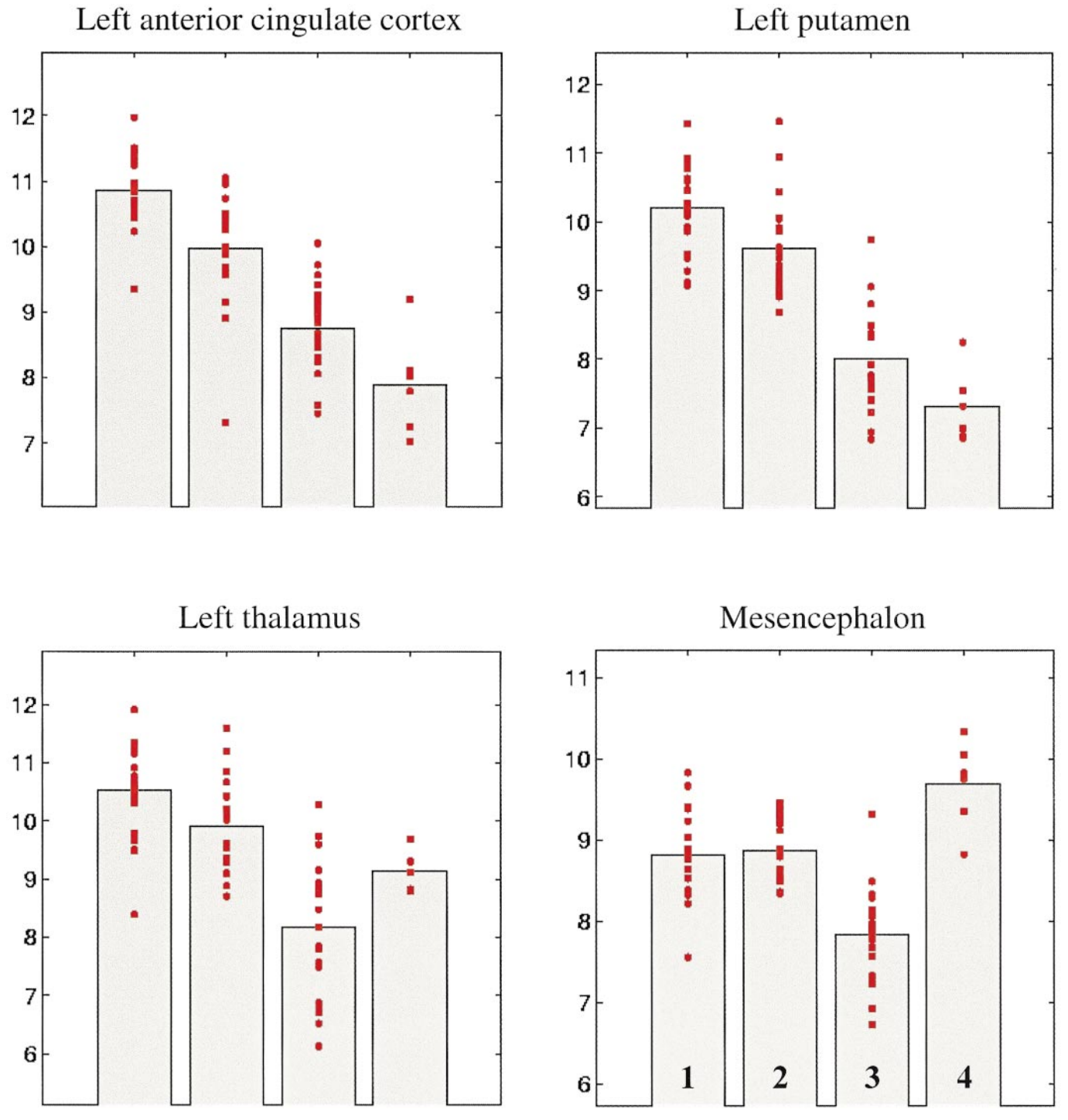

FIG. 2. Comparison of relative adjusted mean glucose metabolism in representative voxels of left cingulate cortex and subcortical structures in healthy young subjects (1), healthy elderly subjects (2), progressive supranuclear palsy (3), and frontotemporal dementia (4).

DISCUSSION

Methodological Considerations

The present PET study showed highly significant differences in the regional distributions of the most affected subcorticofrontal metabolic networks in healthy aging, subcorticofrontal dementia, and frontal cortical dementia (Table 2 and Figs. 1 and 2). Contrary to most previous reports on the subject, our results are based on powerful recruitment, technical and methodological tools.

In terms of the study groups, in the exception of pathology-confirmed diagnosis of normal aging, PSP or

TABLE 3

Brain Areas Functionally Disconnected from Midbrain Tegmentum in PSP Compared to Healthy Subjects

	x (mm)	y (mm)	z (mm)	*Z* value
Left inferior temporal gyrus (BA 20)	−40	−28	−30	4.59
Left hippocampal gyrus (BA 28/36)	−32	−22	−28	4.44
Left cerebellar hemisphere	−50	−44	−28	4.43
Left pallidum	−26	−20	−2	4.30
Left hippocampus	−32	−8	−14	3.23

Note. Coordinates are defined in the stereotaxic space of Talairach (1988). All results presented in this table are thresholded to $P < 0.001$, by reference to the unit normal distribution ($Z > 3.09$) corrected for multiple comparisons at $P < 0.05$ (except for left hippocampus).

FTD, until recently inclusion relied only on clinical criteria that varied considerably between studies, possibly introducing selection bias. Although there are no precise inclusion criteria to define the healthy state, PSP and FTD have now been the subject of internationally recognized and validated diagnostic criteria. These were used retrospectively in this study. Consequently, although the clinical and neuropathological heterogeneity of PSP and FTD are increasingly recognised (Collins *et al.*, 1995; Daniel *et al.*, 1995; Jackson and Lowe, 1996), the use of stringent clinical criteria probably biased our results toward clinically typical cases of PSP and FTD.

As for the technical aspect, the resolution of tomographs has evolved rapidly in the last decade, making it difficult to compare data between publications. Indeed, due to the limited spatial resolution of PET, the correct interpretation of metabolic data depends on physical limitations, mainly partial volume effects (Hoffman *et al.*, 1979) that underestimate the measured activity. Most previous similar PET studies used tomograph with a transaxial resolution ranging from 9 to 17 mm FWHM, and dead space between successive slices (Leenders *et al.*, 1988; Goffinet *et al.*, 1989; Blin *et al.*, 1990). The higher spatial resolution of more recent PET tomographs, such as ours (see Methods), partly avoids such biases. Moreover, when compared to many previous studies, our subjects were positioned in the tomograph so as to sample most brain volume (a total of 174,986 voxels were taken into account in the present study) without dead space between successive slices. Only the top of the brain and middle and inferior parts of the cerebellum and brain stem structures were excluded from the overall analysis.

Considering our methods, the number of subjects included in previous studies was usually too small to yield sufficient degrees of freedom for statistical analysis. Moreover, most of these used ROI templates that lack anatomic precision and suffer from *a priori* hypotheses, which combine to further errors in localizing most affected areas. The number, size, and shape of ROI varied between studies, and some used mean value of left and right activity, thus eliminating potential effects of lateralization in the functional pattern. On the contrary, we assessed metabolic differences in our three populations on a voxel by voxel basis. Few neuroimaging studies have reported the pattern of cerebral function at rest in normal aging or PSP analyzed on a voxel by voxel approach (Martin *et al.*, 1991; Salmon *et al.*, 1997; Petit-Taboué *et al.*, 1998). None have been reported for FTD. Advantages and limitations of SPM for this kind of application have been discussed elsewhere (Petit-Taboué *et al.*, 1998; Signorini *et al.*, 1999). Nevertheless, some limitations of our study should also be pointed out. First, we performed a cross-sectional and not a longitudinal study. Second, normal volunteers, PSP, and FTD patients had statistically different mean ages; thus, age had to be introduced as a confounding covariate in the statistical design. Third, neither PSP nor FTD patients had pathological confirmation of clinical diagnosis, and it is thus possible that false positive cases were included in our population despite using stringent internationally recognised selection criteria. We set high statistical thresholds to avoid, to the extent possible, false-positive results. Finally, 3D-magnetic resonance images (MRIs) were not available in our study and coregistration with the PET scans to more precisely localise hypometabolic areas, especially in deep brain structures and medial cortical regions, was not possible. Consequently, no attempt was made to correct for brain atrophy. It should be noted that there exists as yet no validated method for voxel by voxel PET data correction for cortical atrophy (Labbé *et al.*, 1996). Therefore, a component of the differences in metabolism recorded here were unavoidably the result of both functional and anatomical changes, as is the case in almost all comparable previously reported studies.

Finally, we examined group-specific differences in functional connectivity between brains regions of interest. The term functional connectivity is usually reserved for simple linear correlations of activity between brain areas, under rest condition in our study. A significant group difference in the correlation would then reflect significant group differences in functional connectivity in comparison to the reference population. Two types of conclusions could be drawn from this type of statistical analysis. First, differences in functional connectivity in patients in comparison to controls provide *in vivo* demonstration that such functional connections could exist in normal subjects. Second, in patient groups, this has proved to be a powerful method to help in understanding the pathophysiology of the disorders studied.

Normal Aging

In the contrast between healthy elderly subjects compared to healthy young subjects, our statistical maps indicated preferential cortical frontal hypometabolism distributed partially in neuronal networks distinct from those affected by PSP and FTD. As shown by *Z* values, the more intense regional effects were distributed, on the one hand, bilaterally in anterior cingulate, medial prefrontal (perhaps including pre-SMA), posterior part of dorsolateral prefrontal regions, and on the other hand in left superior and inferior lateral premotor areas, including Broca's area and extending to the anterior part of insular and/or superior temporal cortices. The medial aspect of the frontal lobes, operculum, and temporal areas have frequently been reported to be functionally impaired in previous studies. Results, however, were more discrepant concerning possible metabolic impairment of premotor and dorsolateral prefrontal regions. The only methodologically comparable report published to date is that of Petit-Taboué *et al.* (1998), who used what was essentially, a voxel-by-voxel approach with ^{18}FDG-PET metabolic images of 24 optimally healthy volunteers. In accordance with our study, but with less statistical power, age-related frontal metabolic declines were found to affect bilaterally medioventral frontal and anterior cingulate areas, and the posterior part of dorsolateral and ventrolateral prefrontal cortices extending to insular cortex. In two recent studies, significant functional impairment was related to increasing age in medial and inferior lateral frontal areas (Martin *et al.*, 1991; Blesa *et al.*, 1997). Finally, despite major differences in the statistical models used, our results most closely replicated those of Moeller *et al.* (1996), who identified topographic profiles of normal aging characterized by relatively decreased activity of the medial and lateral frontal, paracentral, and opercular regions.

This notion of preferential metabolic changes in anterior brain regions with advancing age is also supported by neuropsychological and anatomical studies. From a neuropsychological viewpoint, frontal regions that are metabolically impaired in healthy elderly subjects (particularly dorsolateral and medial prefrontal and anterior cingulate areas) participate in neuronal networks subserving various cognitive functions that are themselves relatively impaired with aging (Craik *et al.*, 1995). For example, prefrontal activation has been observed in tasks requiring central executive functions (D'Esposito *et al.*, 1995; Salmon *et al.*, 1996), deep encoding and free recall from long-term memory (Shallice *et al.*, 1994; Petrides *et al.*, 1995) or verbal fluency. Broca's area also showed metabolic impairment in the healthy elderly volunteers. This region has been involved in phonological loop (Paulesu *et al.*, 1993; Salmon *et al.*, 1996) and slight decreases of digit and word span have been observed with aging (Parkinson, 1982; Wingfield *et al.*, 1988). Anatomical studies have demonstrated that, contrary to the classical view of absolute loss of neuronal population with increasing age, there is a shrinkage of large neuronal population to a smaller size class associated with a decrease in synaptic density in the frontal neocortex (Huttenlocher, 1979; Gibson, 1983; Masliah *et al.*, 1993). Since baseline synaptic activity probably represents up to 75% of the resting glucose utilisation of the brain, it is tempting to relate results obtained with ^{18}FDG-PET in normal aging to a reflection of decrease in synaptic density. The extent of the functional changes we found suggests functional deafferentation between the affected frontal cortical areas and other brain regions, but the matter is not clear. In particular, discrepant results concerning subcortical metabolism with advancing age have been reported (Martin *et al.*, 1991; Moeller *et al.*, 1996; Blesa *et al.*, 1997; Petit-Taboué *et al.*, 1998). Whatever the direction of these changes, they could possibly affect cortical metabolism through cortico-subcortico-cortical loops. Further studies are needed to elucidate this finding by analysing changes in effective connectivity (Friston *et al.*, 1997b), an analysis that was not possible in a study such ours.

Progressive Supranuclear Palsy

As in normal aging, functional imaging studies in PSP have been imprecise and discrepant concerning the most affected subcorticofrontal networks. At the cortical level, there is little doubt concerning medial and lateral prefrontal involvement, but very few reports have detailed which area is maximally affected. Medial and lateral frontal cortical hypometabolism was first reported in six patients suffering from probable PSP when compared to eight healthy age-matched controls (D'Antona *et al.*, 1985). In two other studies, preferential decline in cortical cerebral blood flow was observed in the superior part of both frontal lobes in 4 and 11 PSP patients, respectively (Leenders *et al.*, 1988; Johnson *et al.*, 1992). Similar metabolic data were obtained from 14 probable PSP patients (Foster *et al.*, 1988). Studying metabolic changes in 25 probable and 16 possible PSP patients, Blin *et al.* (1990) demonstrated significant correlations between disease duration, intellectual deterioration, and frontal neuropsychological scores with relative frontal metabolism. Contrary to the studies described above, Goffinet *et al.* (1989) suggested preferential hypometabolism in motor and premotor areas with relative sparing of prefrontal cortex in nine probable PSP patients. We have previously demonstrated motor, premotor, and also left middle frontal and left anterior cingulate metabolic impairment in eight patients diagnosed as probable PSP according to NINDS-SPSP criteria using a voxel-by-voxel approach for the first time (Salmon *et al.*, 1997). Using similar selection criteria, scanning procedure,

and methodology on a larger sample of probable PSP patients compared to healthy subjects, the current report reproduces these previous results. Indeed, our SPM indicated fields of hypometabolism distributed in bilateral precentral (BA 4/6) and lateral premotor (BA 6), left ventral premotor (BA 6/44/45), including Broca's area, left anterior cingulate (BA 24/32), and left dorsolateral prefrontal cortices (BA 8/9/46), extending forward to the left frontopolar (BA 10) region. Normal aging and PSP shared elements of metabolic impairment in frontal cortical areas, but aging alone cannot explain regional effects in PSP because age was used as a confounding covariate in the statistical design. A left lateralization of the decrease of prefrontal cortical activity has already been reported in two independent studies (Foster *et al.*, 1988; Defebvre *et al.*, 1995). There is no clear explanation for this left prefrontal lateralization, although it is consistent with neuropsychological impairment, such as the decrease in verbal fluency or poor verbal free recall (Petrides *et al.*, 1995) frequently observed in PSP (Bak and Hodges, 1998).

The mechanism of reduced metabolism in these discrete frontal areas in PSP patients is still debated; despite the well recognized specific cortical pathology in PSP, predominating in posterior frontal cortex (Verny *et al.*, 1996), widespread frontal hypometabolism would be difficult to explain without partial functional deactivation. This could be due to anatomical and/or functional impairment of subcortical structures. In previous imaging studies, striatum (Leenders *et al.*, 1988; Foster *et al.*, 1988; Blin *et al.*, 1990; Karbe *et al.*, 1992; Johnson *et al.*, 1992; Salmon *et al.*, 1997), and thalamus (Goffinet *et al.*, 1989; Blin *et al.*, 1990; Salmon *et al.*, 1997) have frequently been described as functionally impaired in PSP. In our study, metabolic comparison between PSP and controls emphasized the highly significant metabolic involvement not only of bilateral putamen and left medial dorsal nucleus of the thalamus, but also of the midbrain tegmentum. Although putamen and thalamus are usually relatively spared on neuropathological examination of PSP patients, midbrain tegmentum is severely affected (Steele *et al.*, 1964; Daniel *et al.*, 1995; Verny *et al.*, 1996). Striatal and thalamic hypometabolism were most likely a consequence of functional changes in the basal neural circuitry. On the contrary, midbrain tegmentum hypometabolism could preferentially reflect the severe neuronal loss reported at that level. We further investigated the respective functional influences of each hypometabolic basal structure on the activity of other regions through correlation analysis. First, in keeping with the model of deactivation of discrete regions of the frontal lobes together with certain subcortical structures through multiple subcorticofrontal loops (Alexander *et al.*, 1986), it is conceivable that the significant hypometabolism in bilateral putamen described above was related to the bilateral precentral and premotor metabolic impairment, while left medial dorsal thalamic nuclear hypometabolism was possibly related to the left anterior cingulate, left dorsolateral prefrontal, and left frontopolar decreases in glucose consumption (Litvan, 1998). No differences in correlation were found between relative striatal and thalamic glucose metabolism and that of cortical areas when the PSP group was compared with healthy subjects. Such a correlation is in keeping with the hypothesis that these structures remain functionally connected with cortical areas, and that hypometabolism in striatum, thalamus, and cortex might result from lesions in pallidum and others subcortical structures. Second, our SPM also highlighted the importance of mesencephalic involvement, as shown by the corresponding high *Z* value in this region (Table 2). Upper midbrain metabolic impairment has already been reported by Karbe *et al.* (1992). More recently, we also emphasized the significant involvement of a region located in midbrain tegmentum in the metabolic pattern of height PSP patients compared to height age-matched controls (Salmon *et al.*, 1997). The coordinates of this region in the Talairach and Tournoux (1988) space were highly reproducible between both our studies. 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 anatomical complexity of this region. The oculomotor complex, superior colliculus, midbrain dopaminergic nuclei, red nucleus, and mesencephalic reticular formation (MRF) could all correspond anatomically to the co-ordinates of the voxel mentioned above. There is no doubt that all are frequently severely damaged on necropsy examination of PSP patients. Albert *et al.* (1974) argued for a role of the MRF in causing, at least in part, the subcortical dementia. More recently certain areas of the MRF have been related to the axial motor and ocular disturbances in PSP (Fukushima-Kudo *et al.*, 1987; Rottach *et al.*, 1996; Scarnati and Florio, 1997). It would more likely appear that multiple structures correspond to the hypometabolic region located in midbrain tegmentum. Furthermore, in PSP patients, in contrast to the situation in bilateral putamen and left medial dorsal thalamus, changes in functional connectivity from this region were highly significant with left pallidum, left cerebellar hemisphere, left inferior (BA 20) and medial temporal regions including hippocampal gyrus (BA 28/36), and possibly the hippocampus itself when compared to healthy subjects (Table 3). Neuropathological involvement of medial temporal lobe structures has been reported in PSP (Higuchi *et al.*, 1995; Wakabayashi *et al.*, 1997). Because the pallidum itself plays an important role in basal and frontal cortex circuitry, one can easily imagine that functional mesencephalopallidal disruption is an important find-

ing in the deactivation of certain cortical frontal areas. Taken together, these results help to enlarge the concept of subcortical frontal dementia in PSP (Albert *et al.*, 1974; Grafman *et al.*, 1990) to include disrupted functional connections between mesencephalon and pallidum, cerebellar cortex, and inferior and medial temporal regions.

Frontotemporal Dementia

In contrast to normal aging and progressive supranuclear palsy, most studies published to date are relatively concordant concerning the large anterior distribution of functional impairment in FTD, although none have used a voxel-by-voxel approach. This is likely due to the intense metabolic deficits, combined with their wide distribution. These are therefore easily visualised on functional images obtained from low-resolution tomographs. Nevertheless, the data vary concerning the most affected areas and the distribution of subcortical involvement. Dorsolateral prefrontal, frontal orbital and anterior temporal functional impairment have frequently been reported. On the one hand, very few large studies of glucose metabolism are available on FTD (Ishii *et al.*, 1998). Bilateral metabolic deficits were first observed in the fronto-temporal regions (Kamo *et al.*, 1987; Salmon and Franck, 1989; Kumar *et al.*, 1990). Recently, Ishii *et al.* (1998) found significant hypometabolism not only in frontal and anterior temporal lobes but also in parietal areas and subcortical structures in 21 FTD patients. On the other hand, rCBF studies have also shown consistent findings in anterior brain functional deficits (Neary *et al.*, 1987; Risberg, 1987; Miller *et al.*, 1991; Starkstein *et al.*, 1994). Starkstein *et al.* (1994) observed highly significantly decreased regional blood flow in frontal dorsolateral, frontal orbital, temporal anterior, temporal dorsal, and striatal areas in eight disinhibited FTD patients compared to eight age-matched controls. In this study, we compared the metabolic pattern in FTD to that obtained in healthy subjects and patients with PSP. In comparison with healthy subjects, the decline in glucose uptake extended symmetrically to both frontal lobes except precentral, medial prefrontal and medial premotor cortices. This probably reflects sensitivity of PET in detecting brain dysfunction, because only two patients had cortical atrophy on CTscan or MRI. The most impaired areas were located in frontopolar cortex. To a lesser degree, glucose uptake was also reduced in anterior temporal regions and bilateral striatum. The striato-fronto-temporal glucose uptake deficit was probably related to the topography and intensity of cortical neuropathological changes that are usually present in FTD (Mann *et al.*, 1993). We suggest, moreover, that striatal hypometabolism might partly be also the consequence of frontostriatal deafferentation in FTD, in a manner similar to that occurring after frontal cortex ablation in monkeys (Deuel and Collins, 1984; Dauth *et al.*, 1985).

The distribution and the severity of metabolic impairment in subcortico-frontal networks were different in PSP and FTD when compared to healthy subjects. Although cognitive impairment was greater in FTD than in PSP, this variable should not affect the results due to the severity of the hypometabolism in FTD as shown by the high *Z* values in FTD. In comparison to PSP, bilateral frontopolar prefrontal and striatal metabolic impairments were prominent in FTD. As expected, the reverse contrast obtained in PSP compared to FTD mainly showed highly significant mesencephalic and bilateral thalamic hypometabolism without significant frontal impairment. In addition to differences in the distribution of the metabolic impairment, both disorders could also be distinguished by the severity of the hypometabolism. Indeed, all hypometabolic frontal regions that were impaired in both PSP and FTD as compared to HS were significantly more affected in FTD. Nevertheless, the question of possibly comparable differences in cognitive decline is very complex and, as yet, poorly resolved.

Conclusions

Our study used new technical and methodological tools to demonstrate that normal aging, PSP, and FTD were associated with specific patterns of subcorticofrontal regional hypometabolism suggesting different pathophysiological mechanisms of subcorticofrontal and frontal dysfunction. Normal aging was associated with significant frontal lobe hypometabolism predominant in medial and posterior part of left lateral regions. Compared to the entire control group, PSP showed preferential metabolic impairment in bilateral precentral and lateral premotor regions extending to left prefrontal cortex. We have also shown preserved striatofrontal and thalamofrontal functional connections but disrupted mesencephalocerebellar, mesencephalotemporal, and mesencephalopallidal functional connections in patients with PSP. This distribution of metabolic impairment clearly distinguished PSP population from normal aging (Salmon *et al.*, 1997). Finally, we showed dramatic decrease of glucose uptake in most parts of the frontal lobes of FTD patients possibly responsible for striatal deafferentation. The natural history of these metabolic deficits remains, however, to be established through longitudinal studies. It is also necessary to study possible changes in effective connectivity rather than in functional connectivity in order to characterize the exact role of subcortical structures in frontal lobe metabolic impairment. Finally, clinicometabolic correlation might give additional clues to understanding normal aging and degenerative disorders.

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