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Anterior Cingulate and Motor Network Metabolic Impairment in Progressive Supranuclear Palsy

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Abstract: Progressive supranuclear palsy is the prototype of subcortical dementia. Using positron emission tomography and statistical parametric mapping, we compared the glucose metabolic pattern obtained in this subcortical dementia to that observed in elderly healthy controls and in Alzheimer's disease, the prototype of cortical dementia. Progressive supranuclear palsy was characterized by a relative decrease of metabolisminanterior cingulate, adjacent supplementary motor area, precentral cortex, middle prefrontal cortex, midbrain tegmentum, globus pallidus, and ven-trolateral and dorsomedial nuclei of thalamus. The data in progressive supranuclear palsy highlight predominant metabolic impairment in brain structures engaged in response selection, in attention for action, and in motor networks.

INTRODUCTION

The term ''subcortical dementia'' was introduced to describe a clinical syndrome observed in progressive supranuclear palsy (PSP) and characterized by forget-fulness, slowing of thought processes, emotional or personality changes, and impaired ability to manipulate acquired knowledge (Albert *et al.,* 1974). Other conditions such as Huntington's disease and Parkinson's disease have also been labeled subcortical dementia. In the absence of aphasia, apraxia, and agnosia, the subcortical dementing pattern was contrasted to that occurring in cortical dementia such as Alzheimer's disease (Albert *et al.,* 1974). However, the distinction between cortical and subcortical dementia is a matter of debate; both distinguishing as well as overlapping neuropsychological and neuropathological patterns are reported in the literature (Whitehouse, 1986; Pillon *et al.,* 1991; Hauw *et al.,* 1990; Gearing *et al.,* 1994). Characteristic patterns of cerebral blood flow and metabolism have been described in degenerative dementias using positron emission tomography (PET) or single-photon emission tomography, but the precise differences and similarities between cortical and subcortical dementias have rarely been specifically addressed (Habert *et al.,* 1991; Goto *et al.,* 1993).

The metabolic pattern observed in PSP using PET and regions of interest analysis is characterized by combined cortical (mainly frontal) and subcortical involvement (D'Antona *et al.,* 1985; Leenders *et al.,* 1988; Foster *et al.,* 1988; Goffinet *et al.,* 1989; Blin *et al.,* 1990). However, new image-processing technology allows analysis of all available metabolic information, without a priori hypotheses based on anatomic regions of interest (Friston *et al.,* 1995). Such analyses recently emphasized a predominance of metabolic impairment in posterior cingulate cortex among the associative posterior regions typically involved in Alzheimer's disease (Minoshima *et al.,* 1994; Reiman *et al.,* 1996).

Using statistical parametric mapping (Friston *et al.,* 1995), we contrasted the glucose metabolic patterns obtained with PET in progressive supranuclear palsy to that observed in healthy controls with similar age, and inAlzheimer's disease of the senile type (SAD) with mild dementia, to emphasize the specific brain areas functionally involved in the disease. We observed in PSP a predominance of metabolic impairment in subcor-ticofrontal motor and cognitive networks, the latter comprising anterior cingulate cortex which is a key structure in some executive functions (Devinsky *et al.,* 1995).

MATERIALS AND METHODS

Subjects

The metabolic pattern of glucose utilization was studied in 10 patients (mean age 67.8 6 5.9 years) with a clinical diagnosis of progressive supranuclear palsy (Steele *et al.,* 1964; Daniel *et al.,* 1995; Collins *et al.,* 1995), 12 patients (mean age 69.3 6 4.6 years) with probable Alzheimer's disease (McKhann *et al.,* 1984), and 8 elderly healthy volunteers (mean age 63.4 6 6.1 years). All patients with PSP had supranuclear down-gaze paresis, postural instability, bradykinesia, axial rigidity, nonblinking facies, dysarthria, and poor response to dopatherapy. None had dopaminergic treatment at PET time, and parkinsonian score ranged from 13 to 45 on the King's College Parkinson's disease scale (Parkes *et al.,* 1970; Table 1). All patients met NINDS– SPSP clinical research criteria for the diagnosis of probable PSP (Litvan *et al.,* 1996). All patients with AD fulfilled the DSM-III-R criteria for dementia (American Psychiatric Association, 1987) and most of them were of the SAD type (Table 2). The diagnosis, according to widely accepted criteria (McKhann *et al.,* 1984), was based on general

medical, neurological, and neuropsy-chological examination and normality of laboratory tests. PSP patients had questionable to mild dementia, so that SAD patients with mild dementia were selected (Hughes *et al.,* 1982); mean disease duration was shorter in SAD (1.6 year) than in PSP (3.9 years). CT scan showed, at most, mild atrophy. All subjects and a relative gave informed consent to take part in the study, which was approved by the University of Liège hospital ethics committee.

TABLE 1: Demographic and Clinical Data for Patients with Progressive Supranuclear Palsy

Patient	Age (years)	Duration (years)	P score (max 93)	CDR (max 3)
1	68	2	29	1
2	65	4	27	1
3	75	1	40	1
4	75	11	41	0.5
5	58	3	13	0.5
6	65	3	30	1
7	74	3	26	1
8	66	2	17	0.5
9	61	7	18	1
10	71	3	45	0.5

Note. P score, parkinsonian score, is calculated from Parkes *et al.* (1970). CRD, clinical dementia rating scale (Hughes *et al.,* 1982): 0.5 is questionable, 1 is mild.

PET Image Acquisition and Analysis

Scans were obtained during quiet wakefulness with eyes closed, on a Siemens 951/31R tomograph (CTI, Knoxville, TN) with collimated septa extended, using the [^{18}F]fluorodeoxyglucose technique (Phelps *et al.,* 1979). A transmission scan was acquired for attenuation correction using three rotating sources of 68 Ge. Emission scans were reconstructed using a Hanning filter at a cutoff frequency of 0.5 Hz, 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 31 planes, with a total field of view of 10.8 cm in the axial direction.

PET scans were analyzed by using statistical parametric mapping (SPM 95, Wellcome Department of Cognitive Neurology, London, UK; Friston *et al.,* 1995), in Matlab (Math Works, Natick, MA). For each scan the 31 transverse planes were interpolated to 43 planes to render the voxels approximately cubic. Images were subsequently normalized into a standard stereotactic anatomical space (Talairach and Tournoux, 1988) and were smoothed using a Gaussian filter (12-mm FWHM) to accommodate intersubject differences in gyral and functional anatomy and to increase the signal to noise ratio in the data set. Differences in global metabolism between subjects were removed by analysis of covari-ance (ANCOVA), on a pixel by pixel basis, using the global mean as covariate (Friston *et al.,* 1991). For each pixel in the stereotactic space, the ANCOVA generated an adjusted mean value of cerebral metabolic rate of glucose and an associated adjusted error variance. Significant differences between groups were estimated on a pixel by pixel basis using the *t* statistic and age as covariate. The resulting sets of *t* values constituted the statistical parametric map SPM(*t*) (Friston *et al.,* 1991). The SPM(*t*) was transformed to the unit normal distribution to give a SPM(*Z*). We used a SPM with a *Z* score threshold of 3.09 ($P < 0.001$, uncorrected for multiple comparisons). Decrease of metabolism was then characterized in terms of probability that a brain area of the observed number of pixels could have occurred by chance over the entire volume analyzed (P value < 0.05, corrected for multiple comparisons). The table displays the location of pixels with the maximal *Z* values comprised in these brain areas.

TABLE 2: Demographic and Clinical Data for Patients with Alzheimer's Disease

Patient	Age (years)	Duration (years)	MMSE (max 30)	CDR (max 3)
1	64	1	23	1
2	77	1	28	1
3	60	1	23	1
4	69	1	23	1
5	69	2	26	1
6	71	3	23	1
7	74	1	23	1
8	74	3	23	1
9	70	1	22	1
10	66	1	29	1
11	69	1	28	1
12	69	3	22	1

Note. MMSE, minimental score exam (Folstein *et al.,* 1975). CDR, clinical dementia rating scale (Hughes *et al.,* 1982): 1 is mild.

TABLE 3: Relative Decrease of Metabolism in PSP Patients Compared to Controls

	x (mm)	*y* (mm)	*z* (mm)	*Z* value
L. anterior cingulate (32)	-8	28	28	3.61
	-8	8	40	3.58
L. callosomarginal sulcus (32)	-26	8	44	4.21
L. middle frontal (6/8)	-18	20	44	3.56
L. middle frontal (6)	-34	2	40	4.00
L. precentral (6)	-36	2	32	4.06
Midbrain tegmentum	0	-26	-8	3.78
Globus pallidus (internal)	-14	4	8	3.90
R. dorsomedial thalamus	8	-12	8	3.90
L. dorsomedial thalamus	-8	-14	8	3.43

Note. Metabolic decrease in 10 patients with PSP compared to 8 healthy controls of similar age. Coordinates refer to the stereotactic space of Talairach and Tournoux (1988). Numbers in parentheses refer to Brodmann's areas. Areas reported are included in a SPM thres holded to $Z = 3.09$ ($P < 0.001$), further corrected for multiple comparisons. L, left; R, right.

RESULTS

Our first aim was to determine the precise location of brain metabolic impairment in PSP. When normalized images obtained from PSP patients were compared to those from elderly healthy controls (Table 3 and Fig. 1a, $P < 0.001$ and further correction for multiple comparisons), glucose metabolism was reduced in left anterior cingulate (Brodmann area BA32) and callosomarginal sulcus (BA 32), left middle frontal gyrus (BA 6 and 8), left rostrodorsal globus pallidus, dorsomedial nucleus of thalamus (lateral portion), and midbrain tegmen-tum. The left lateralization of cortical involvement corresponded to a bias of population selection, for clinical signs were strictly bilateral in three patients, but mildly predominated on the right body side in six, and on the left side in only one PSP patient. Effectively, SPM with a Z score threshold decreased to 2.58 (Fig. 1a, $P < 0.005$) demonstrated a more widespread and bilateral cortical involvement, extending to the left BA 46 (middle frontal gyrus) and to the right cingulate and callosomarginal regions.

Our second aim was to contrast the relative metabolic distribution in prototypes of cortical and subcorti-cal dementia. When PSP images were contrasted to those in SAD (Table 4 and Fig. 1b), relative metabolic

impairment in PSP was observed in anterior cingulate and along the horizontal portion of the callosomarginal sulcus, and also in adjacent supplementary motor area (SMA, BA 6); in precentral cortex (BA 4/6); in superior, middle, and inferior frontal cortex (BA 9, 8, and 44); in midbrain tegmentum; and in the ventrolateral nucleus of thalamus. The reverse contrast showed that preferential metabolic involvement in SAD patients (compared with PSP) was located in posterior cingulate gyrus (BA 31) and in left parietooccipital sulcus (Table 4 and Fig. 1c, $P < 0.001$ and further correction for multiple comparisons), and to a lesser degree in the middle temporal gyrus, the posterior part of the superior temporal gyrus, the inferior parietal gyrus, the superior occipital gyrus, and the left cuneus (Fig. 1c, $P < 0.005$).

TABLE 4: Contrasted Patterns of Relative Decrease in Metabolism

	x (mm)	*y* (mm)	*z* (mm)	*Z* value
PSP versus SAD				
L. anterior cingulate (32)	-10	2	44	4.51
L. callosomarginal sulcus (32)	-12	16	44	4.11
	-8	-14	44	3.48
	-10	-24	44	3.26
R. callosomarginal sulcus (32)	14	20	40	4.08
	14	30	32	3.82
R. supplementary motor area (6)	10	6	44	3.97
L. precentral (4/6)	-34	-12	40	4.84
	-36	-22	40	4.24
	-44	-14	32	3.87
R. precentral (4/6)	46	-6	32	4.03
L. inferior frontal (44)	-44	16	20	3.65
L. middle frontal (8)	-46	12	32	3.36
L. superior frontal (8/9)	-12	38	32	3.20
Midbrain tegmentum	0	-28	-12	4.65
L. ventrolateral thalamus	-16	-12	8	4.28
R. ventrolateral thalamus	14	-14	8	3.96
SAD versus PSP				
R. posterior cingulate (31)	16	-56	28	5.03
L. posterior cingulate (31)	-12	-48	28	3.25
L. parieto-occipital sulcus	-14	-70	20	4.26

Note. Reciprocal metabolic comparison between 12 SAD patients and 10 patients with PSP. Coordinates refer to the stereotactic space of Talairach and Tournoux (1988). Numbers in parentheses refer to Brodmann's areas. All areas reported for PSP are included in a SPM thresholded to $Z = 3.09$ ($P < 0.001$), further corrected for multiple comparisons. L, left; R, right.

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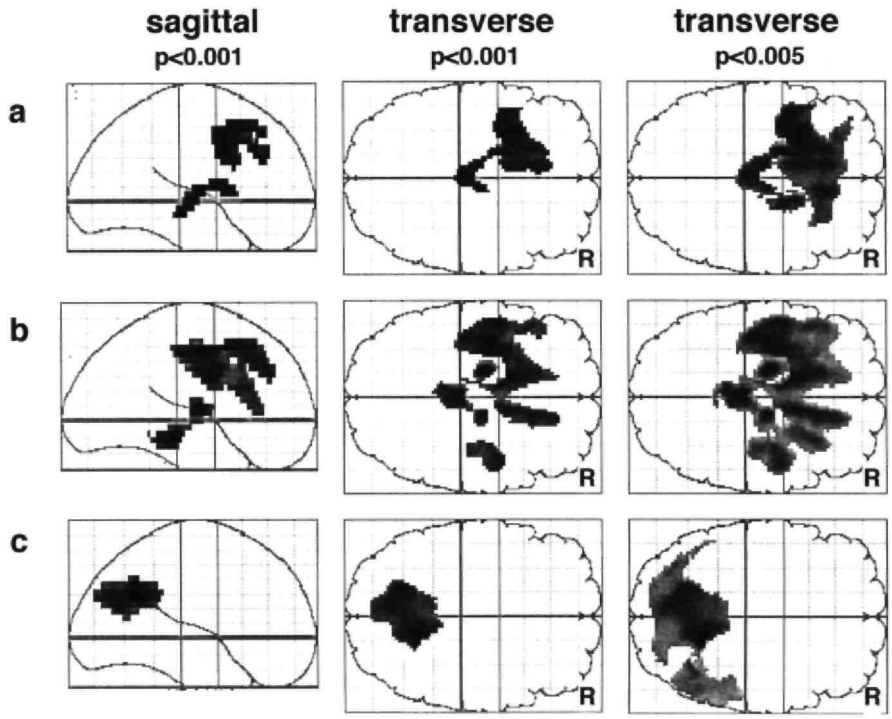

FIG. 1. Statistical parametric maps thresholded to $Z = 3.09$ ($P < 0.001$) and to $Z = 2.58$ ($P < 0.005$), showing the distribution of brain areas with significant metabolic differences between PSP and controls (a), between PSP and SAD (b), and (reverse contrast) between SAD and PSP (c). Figures are displayed in sagittal and transverse projections into a stereotactic space (Talairach and Tournoux, 1988).

DISCUSSION

Previous studies using PET and regions of interest analysis in patients suffering from PSP already showed hypometabolism in cortical (and mainly frontal) regions, striatum, thalamus, and brain stem (D'Antona *et al.,* 1985; Leenders *et al.,* 1988; Foster *et al.,* 1988; Goffinet *et al.,* 1989; Blin *et al.,* 1990). Frontal lobe metabolism correlates with performances on tests assessing frontal dysfunction (Blin *et al.,* 1990). Striatal accumulation of [^{18}F]fluorodopa is decreased in PSP (Brooks *et al.,* 1990), while D2 dopaminergic receptors are only mildly reduced (Brooks *et al.,* 1992). Those markers of dopaminergic transmission are not related to locomotor dysfunction, while caudate and thalamic metabolic values correlate with parkinsonian motor score (Blin *et al.,* 1990). Regions of interest analysis, however, did not allow concordant location of metabolic impairment within the frontal lobe: metabolic decrease involved ''medial and lateral'' frontal cortex (D'Antona *et al.,* 1985), superior and inferior parts of prefrontal regions (Blin *et al.,* 1990), superior anterior frontal (Foster *et al.,* 1988), or the motor/premotor division of the frontal lobe (Goffinet *et al.,* 1989). Moreover, frontal lobe hypometabolism is not specific for PSP, but metabolic differences between degenerative dementias have rarely been explored (Habert *et al.,* 1991; Goto *et al.,* 1993). We used statistical parametric mapping to better localize and characterize the pattern of metabolic impairment in PSP, by comparing brain metabolic images obtained in this prototype of subcortical dementia to those observed in healthy controls of similar age and in Alzheimer's disease with similar dementia severity (taken as prototype of cortical dementia). Standard clinical CT scan showed at most mild atrophy in all patients, but we could not obtain individual magnetic resonance images suitable for localizing more precisely hypometabolic areas or for quantifying focal atrophy (Masucci *et al.,* 1995).

Metabolic comparison between PSP and controls emphasized involvement of subcorticofrontal circuits comprising anterior cingulate, middle frontal cortex, and mediodorsal thalamic nucleus. There are anatomic connections between these different regions (Vogt *et al.,* 1979; Bates and Goldman-Rakic, 1993). They participate in response selection and attention for action, and they play an important role in the initiation, organization, and maintenance of goal-directed behaviors (Pos-ner and Petersen, 1990; Mesulam, 1990; Devinski *et al.,* 1995). Anterior cingulate and prefrontal cortex are activated during neuropsychological tasks such as Stroop paradigm (Pardo *et al.,* 1990) or verbal fluency (Frith *et al.,* 1991), which PSP patients frequently fail. A posterior middle frontal region (close to the precen-tral cortex) affected in PSP may also be part of the frontal eye field (Paus *et al.,* 1993). There is a left lateralization of frontal metabolic impairment in our PSP population, which probably reflects a selection bias, for we observed bilateral involvement of the above-mentioned regions when statistical threshold was lowered. It should be noted that a predominantly left metabolic involvement has already been reported in normal aging (Martin *et al.,* 1991) and inAlzheimer's disease (Lowenstein *et al.,* 1989).

The comparison of the metabolic pattern observed in PSP to that seen in SAD also demonstrated relative metabolic impairment in anterior cingulate, in calloso-marginal sulcus, and in adjacent SMA, which participate in motor networks (Alexander *et al.,* 1986; Dum and Strick, 1991; Luppino *et al.,* 1991; Paus *et al.,* 1993). In the motor networks, metabolism was also impaired in globus pallidus and midbrain tegmentum, which are consistent sites of neuropathological involvement in PSP, and in the precentral cortex (Brodmann area 4/6), known to be a preferential location of cortical tangles in the disease (Hauw *et al.,* 1990; Daniel *et al.,* 1995). Preferential metabolic impairment of motor/ premotor frontal cortices was already reported in PSP (Goffinet *et al.,* 1989). Finally, statistical analysis in a stereotactic space allowed us to demonstrate a significant reduction of metabolism in the ventral lateral nucleus of thalamus in PSP compared to SAD. Different parts of this nucleus receive inputs from central cerebel-lar nuclei (via the tegmentum) and pallidum and send projections to premotor and supplementary motor areas (Schell and Struck, 1984; Wiesendanger and Wiesen-danger, 1985; Hirai and Jones, 1989).

When SAD metabolic images were compared to those obtained in PSP, glucose metabolism was preferentially impaired in the posterior cingulate cortex of patients suffering from Alzheimer's disease (Minoshima *et al.,* 1994; Reiman *et al.,* 1996). Neuronal degeneration is observed histologically in posterior cingulate cortex of AD patients (Brun and Englund, 1981). Dysfunction of this region probably plays a role in the memory deficits seen in AD, based on its relay position between frontal and parietal associative cortices on the one hand and hippocampal and parahippocampal regions on the other hand (Vogt and Pandya, 1987; Pandya *et al.,* 1981; Goldman-Rakic *et al.,* 1984). In addition to posterior cingulate involvement, our data are consistent with the literature and confirm metabolic impairment in interconnected associative regions, including temporal, parietal, and occipital cortices. These areas subserve complex cognitive processes (which are impaired in AD) and participate in a posterior attentional network (Mesulam, 1990). As in many studies using functional imaging, hippocampal metabolic impairment is not demonstrated inAD (Minoshima *et al.,* 1994; Reiman *et al.,* 1996).

Although many workers in the field emphasize the overlapping between some metabolic, neuropsychologi-cal, or neuropathological characteristics of cortical and subcortical dementias, the present study aimed to differentiate the specific pattern of regional metabolic dysfunction observed in ''prototypes'' of both types of dementia. The precise location of metabolic impairment obtained with positron emission tomography is difficult to ascertain in subregions of structures such as globus pallidus or thalamic nuclei, but our results in PSP patients demonstrate involvement of the frontosub-cortical circuits described by Alexander and colleagues (1986). More precisely, the data show predominant functional impairment in brain areas participating in motor, anterior executive, and anterior attentional networks in PSP, and they justify viewing the clinical syndrome as a subcorticofrontal dysfunction. This is in contrast to the preferential involvement of posterior cingulate and multimodal associative cortices observed in Alzheimer's disease (Minoshima *et al.,* 1994; Mesu-lam, 1990; Herholz *et al.,* 1993; Reiman *et al.,* 1996).

The differential anterior and posterior metabolic impairment that we observed in PSP and AD could now be used to interpret the respective neuropsychological profiles in terms of variable dysfunction of cognitive networks.

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