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OBSESSIVE-COMPULSIVE AND OTHER BEHAVIOURAL CHANGES WITH BILATERAL BASAL GANGLIA LESIONS

A NEUROPSYCHOLOGICAL, MAGNETIC RESONANCE IMAGING AND POSITRON TOMOGRAPHY STUDY

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SUMMARY

Eight patients are reported who shared the combination of bilateral basal ganglia lesions and a frontal lobe-like syndrome. The main features were inertia and loss of drive, with preservation of intellectual function. Some patients showed stereotyped activities with compulsive and obsessive behaviour which were sometimes highly elaborate in pattern. Extrapyramidal clinical signs were absent or mild. Brain damage, related to anoxic or toxic encephalopathy, was demonstrated by CT scans and MRI. The lesions appeared to be confined to the lentiform nuclei, particularly affecting the pallidum, although there was generalized brain atrophy in 2 cases. Positron emission tomography (PET) in 7 patients revealed hypometabolism of the prefrontal cortex relative to other parts of the brain. The PET studies suggest dysfunction of the prefrontal cortex as a result of damage to the lentiform nuclei. These clinical, anatomical and functional observations emphasize the role of the circuits linking the prefrontal associative cortex and some specific areas of the neostriatum, including the pallidum. The existence of distinct nonoverlapping circuits in the motor field or in the associative field can explain the fact that basal ganglia lesions may give rise to a clinical picture that is either purely motor, purely behavioural (as in some of our patients), or both. Similarities existed between some symptoms found in our patients and certain features of major psychiatric illnesses such as severe depression, catatonic schizophrenia, and obsessive-compulsive disorder. This raises the hypothesis that some aspects of these psychiatric disorders could be related to structural and physiological disturbances in the systems linking the frontal associative cortex and the basal ganglia.

INTRODUCTION

The symptoms reported in cases of damage to the lentiform nucleus generally consist of motor disturbances (Marsden, 1982). We have previously reported

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instances where patients with bilateral lesions of the lentiform nuclei without or with very mild extrapyramidal symptoms, presented unusual behavioural abnormalities (Laplane *et al.*, 1981, 1982, 1984). The symptoms, which were summarized as a 'loss of drive', included a marked decrease in spontaneous activity, a loss of affect, and a notable reduction of spontaneous thought content. Also remarkable was the observation that their inertia was apparently reversible by external stimulation, such as the incitement by a relative. Moreover, on neuropsychological testing, intellectual capacities were largely preserved, except for a memory defect in 1 of the 3 cases.

The attributability of these disturbances to lesions of the lentiform nuclei was strongly suggested by the CT scan findings, but doubt remained as to the possibility of diffuse or multifocal brain damage, in spite of the normality of EEG recordings and the absence of other visible lesions on the scan images. In addition, the question was raised as to how these limited subcortical lesions could induce such behavioural changes. The hypothesis of a functional impairment of the prefrontal cortex was made on the basis of strong clinical resemblances between our patients' symptoms and a frontal lobe syndrome. This similarity, and the absence of motor disturbance, led to the suggestion that the lesions might have affected the 'association' circuits linking some compartments of the basal ganglia and the prefrontal cortex. Finally, the additional presence, in 2 of these 3 patients, of obsessive-compulsive behaviour was noteworthy, representing a likely example, if confirmed by further cases, of psychiatric symptoms being produced by focal brain impairment.

Since then, 2 other cases have been reported by Ali-Cherif *et al.* (1984) and we have now been able to examine 5 new similar cases. It was possible to perform magnetic resonance imaging (MRI) and positron emission tomography (PET) in 7 of our 8 cases, and in the light of this additional material, some progress can be made towards the understanding of the clinical features.

MATERIAL AND METHODS

All 8 patients were selected on the basis of symptoms of inertia, reversible under stimulation and the presence of lesions of the lentiform nuclei on CT scans.

Neuropsychological testing

Intellectual function and memory. The following tests were selected: the Wechsler Verbal Scale, the Raven's 1938 Progressive Matrices (PM 38) and the Wechsler Memory Scale. Patients were allowed unlimited time to perform these tests.

Frontal lobe function. The simplified version of the Wisconsin Card Sorting test (Nelson, 1976), tests of verbal fluency (names of animals in 1 min, words beginning with the letter M in 1 min) (Benton, 1968), and a graphic series (Luria, 1966) were chosen because they were known to be sensitive to frontal lobe dysfunction. Behavioural abnormalities (prehension, imitation and utilization), observed in patients with frontal lobe lesions (Lhermitte, 1983; Lhermitte *et al.*, 1986) were also evaluated.

Linguistic, gestural and drawing tests. These included the naming of objects, writing a sentence on dictation, calculation, execution of symbolic gestures, and the copying of a cube or the Rey-Osterrieth complex figure.

The 15 objects test (B. Pillon *et al.*, unpublished). This visual discrimination task, consisting of 15 superimposed images of objects, was chosen in order to evaluate cognitive slowing.

Objective personality tests. The Minnesota Multiphasic Personality Inventory (MMPI) or a self-rating depression scale (Pichot *et al.*, 1984) was used.

Magnetic resonance imaging

In 7 patients (Cases 2-8), MRI was performed on a superconducting MR imager operating at a field strength of 1.5 T. Coronal and horizontal (Virschow's plane) 5 mm slices were taken every 7.5 mm. T1 and T2 weighted sequences were used. Real-size printed photographs were obtained from the films and were compared with atlases (Salamon and Huang, 1980, for CT, and Roberts *et al.*, 1987, for MRI) in order to delineate the lesions.

Positron emission tomography

In 7 patients (Cases 2-8) regional cerebral glucose utilization (rCMRglu) was measured using the ^{18}F-fluorodeoxyglucose (^{18}FDG) technique as applied to PET using methods as described elsewhere (Phelps *et al.*, 1979; Baron *et al.*, 1982). Six PET studies were performed on the multiring LETI. TTV01 time-of-flight tomograph. Seven planes parallel to the orbitomeatal (OM) line and located respectively at 10, 25, 40, 55, 70, 85 and 100 mm above this line were obtained simultaneously. The axial and lateral resolutions were equal to 13 mm FWHM with an undetected interslice of about 5 mm. One study (Case 4) was performed on the single slice ECATII tomograph (lateral resolution was about 16 mm and slice thickness about 19 mm) and only 3 planes were studied (OM line +18, 38 and 58 mm, respectively). All images were corrected for attenuation using 68Ge-68Ga transmission scans. The PET scans were acquired from 40-56 min after the injection of about 7 mCi of ^{18}FDG. The time course of the changes in plasma ^{18}FDG concentration was obtained by means of serial arterial blood samples collected via a radial arterial catheter. The study was performed on subjects at rest with their eyes closed but ears unplugged, without significant external stimulation. Quantitative CMRglu images, in mg/100 g.min were obtained from the raw ^{18}FDG images using the in vivo 'autoradiographic' method developed by Phelps *et al.* (1979). This was accomplished using the operational equation which contained the 4 FDG rate constants (including the dephosphorylation constant rate k_4^*) measured in 13 young healthy volunteers, the 'lumped constant' estimated at 0.42, the pixel ^{18}FDG concentration at time of study (decay-corrected), the time course of arterial plasma ^{18}FDG concentration from injection time to acquisition time, and the plasma glucose content (mean of 5 determinations during the study).

PET data analysis. In order to compensate for the intersubject variability in head shape among patients and controls, 5 typical brain planes out of the 7 original PET cuts were selected from each study according to the atlas of the human brain of Matsui and Hirano (1978); these 5 typical planes, on which the 'region of interest' (ROI) positioning procedure was applied (*see* below), were the 'cerebellar cut', the 'frontobasal cut', the 'basal ganglia cut', the 'low centrum semiovale cut' and the 'high centrum semiovale cut' (labelled planes I, II, III, IV and V, respectively). In the present report, only the analysis for planes II-V will be given (fig. 1). The rCMRglu of the cerebral cortex was assessed by means of 3 cm^2 circular ROIs positioned over the cortical rim for each of the 4 selected planes using a standardized method detailed elsewhere (Samson *et al.*, 1986). The set of ROIs, defined first for the right cerebral hemisphere, was then automatically mirror copied over the left side with respect to the anteroposterior sagittal axis; in addition, one ROI was positioned in the medial frontal cortex of each plane. This method of ROI positioning is widely used as an objective procedure because the ROIs are positioned along the cortical rim, tangentially to one another (starting lateral to the medial frontal ROI) (fig. 1). The original ROIs were subsequently grouped within each one of the PET slices according to anatomical regions (Matsui and Hirano, 1978) as explained in the legend of fig. 1. After averaging the ROI CMRglu values of each anatomical region, this procedure yielded 13 cortical regions on each side, and 4 medial frontal regions, for a

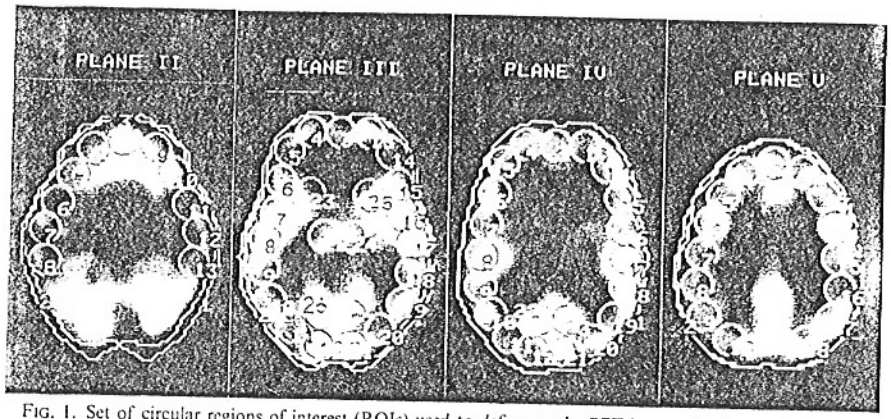

FIG. 1. Set of circular regions of interest (ROIs) used to define on the PET images the 'anatomical' regions over the cortical and subcortical structures on planes II ('frontobasal cut'), III ('basal ganglia cut'), IV ('low centrum semiovale cut') and V ('high centrum semiovale cut'). The cortical ROIs were positioned over the cerebral cortex tangentially to one another as well as to the computer-defined outer 30% isocontour (ROI 1). On plane II: the mediofrontal area (3) and on the left hand side (the right hemisphere): the laterofrontal (4, 5) and the temporal (7, 8) areas (ROI 6 was not used); on plane III: the mediofrontal (3) and on the left hand side the laterofrontal (4, 5, 6), the temporal (7, 8), the temporo-occipital (9, 10, 11), the occipital (12-26), the thalamic (22) and the striatal (23) areas; on plane IV: the mediofrontal (3), and on the left: the laterofrontal (4, 5, 6), the temporal (7, 8), the temporo-occipital (9, 10, 11) and the occipital (12-22) areas; on plane V: the mediofrontal (3), the laterofrontal (4, 5, 6), the parietal (7, 8) and the parieto-occipital (9, 10) areas. Symmetric ROIs were copied automatically on the left hemisphere with respect to an anteroposterior sagittal axis defined visually in such a way that the mirror 30% isocontour (ROI 2) was roughly superimposed over the original 30% isocontour (ROI 1).

total of 30 regions. For the ECATII data (Case 4), only 2 cuts across the cerebral hemispheres were available (OM + 38 mm and OM + 58 mm), providing a set of 12 regional CMRglu results.

The data analysis was carried out not only on the absolute rCMRglu values, but also on 'metabolic ratios' (or indices) which were calculated as rCMRglu divided by the average ipsilateral cortical CMRglu (the mean of all ipsilateral cortical ROIs of the same plane excluding the medial frontal ROI); for the medial frontal ROI, the metabolic index was calculated using the whole cortex mean CMRglu.

In addition to the cortical ROIs, one ROI was positioned over the area including the striatum and another over the thalamic area of the right hemisphere, and copied on the left side; these ROIs were positioned on plane III (plane OM + 58 mm of ECATII data, Case 4), because these anatomical structures are readily identifiable only on this plane (Kuhl *et al.*, 1982).

Statistical analysis

The patient data were compared with control values obtained in normal subjects using the same methods for PET scan and data analysis (n = 13 and n = 6 for the LETI and ECATII cameras, respectively) of similar age (40.5 ± 15.9 and 50.2 ± 10.0 yrs for the LETI and ECATII data, respectively, compared with 38 ± 17.8 yrs for the LETI patients, and 50 yrs for Case 4). The analysis first focused on individual data, by comparing each patient's values with the 95% confidence limits (CL) defined for each brain region from the control data, using the equation $CL = m \pm (t \times SD)$, where m is the mean control regional value, SD the standard deviation and t the student t value (two-tailed test, n − 1 degree of freedom). Thus the calculation of the CL incorporates the small number of control values. This method enabled us to determine whether significant deviations from

normality occurred for any brain region in each individual patient. Following this initial analysis, we also performed a comparison of mean regional data between patients and controls (exclusively on the LETI camera derived data, as only 1 patient was studied with the ECATII camera), using an analysis of variance.

CASE DESCRIPTIONS

Case 1 (see Laplane et al., 1984, Case 1)

V. was examined in our unit in 1980 when he was aged 53 yrs. Twelve years previously he had been stung by a wasp. This was followed by convulsions and then coma, which lasted several days. Before this he had been well, with no evidence of psychiatric symptoms. While recovering he had developed choreiform movements which had partially resolved, leaving some tic-like movements of the face and fingers. Gait was affected by a mixture of choreiform and parkinsonian-like disturbances. He had been considered to be demented, and would spend the day in a state of impassive inactivity, describing his own mental state as an 'empty mind'. His affect seemed normal when questioned about personal events, and there were no features of depression, but he reverted to his habitual state of indifference once left alone. Under stimulation he was able to perform complex tasks correctly (to play bridge, for example) and this was reflected by his performance on testing. Two years after the encephalopathy he began to develop stereotyped activities. The most frequent of these involved counting, often paced by finger movements. He would also spend long periods of time switching a light on and off. The fact that he would need to reach a certain multiple in his activities added to their compulsive character ('C'est plus fort que moi', he would say. When interrupted he would become angry but not apparently anxious as such. On one occasion, when kicking a stone along a street, he experienced difficulty as a result of his gait disorder and, apparently unaware of the inappropriateness of his behaviour, went down on his knees and began to push the stone along with his hands, again in multiples.

Standard and sleep EEGs were normal. CT scans were performed in the orbitomeatal plane and slices were taken every 3 mm in the region of the basal ganglia. The lesions consisted of low density areas situated bilaterally in the internal part of the lentiform nucleus (fig. 2). The rostral part of the nucleus seemed to be more affected than its caudal part. Some other small low density areas could be seen rostrally within the right putamen and in the head of the right and the left caudate nuclei. Mild ventricular enlargement was present. The patient later died from the inhalation of food.

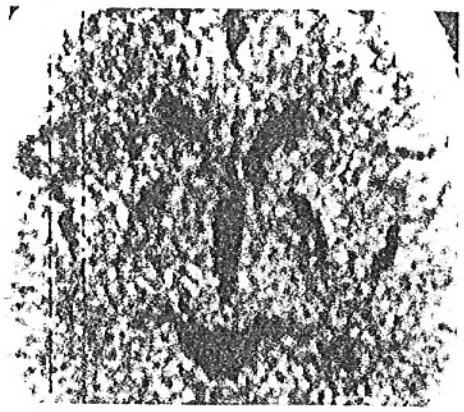

FIG. 2. *Case 1.* CT scan at basal ganglia level, in OM plane, showing small lesions in caudate and putamen and large bilateral lesions in the internal part of lenticular nuclei. (Left hemisphere is presented on the right side of the picture.)

Case 2 (see Laplane et al., 1984, Case 2)

D. was aged 23 yrs when he suffered from accidental carbon monoxide poisoning in 1979. There had been no evidence of previous psychiatric disorder. He was initially severely affected intellectually, but improved over the following months. Two years later there were no neurological signs. Intellectual performance was normal (Table 1), except for memory and verbal fluency. As with Case 1, however, there was an apparent lack of spontaneous activity, although he could be stimulated into action by his relatives. He also described his mental state as an "empty mind" but showed no features of depression. His relatives were unaware of his stereotyped activities, which were purely mental. When alone, he would count to himself, but he was able to stop easily, without seeming to become anxious. There were no compulsive features in his personality. The EEG was normal. A CT scan (orbitomeatal plane, slice thickness 10 mm) showed 2 low density areas almost symmetrically placed in the internal part of the lentiform nuclei. There were no other abnormalities. The patient was lost to follow-up until 1987, when a neuropsychological assessment showed similar results. MRI revealed symmetric clearly defined abnormal signals in the globus pallidus bilaterally in their rostral halves, probably involving parts of both medial and lateral segments (fig. 3).

PET scan performed 8 yrs after the onset revealed regional CMRglu values within normal ranges. There was a significant decrease of 3 regional metabolic indices: mediofrontal on planes III and IV ($P < 0.02$ and $P < 0.05$, respectively) and left laterofrontal on plane IV ($P < 0.02$). There was also a significant increase in the lateral occipital metabolic index of plane III ($P < 0.05$).

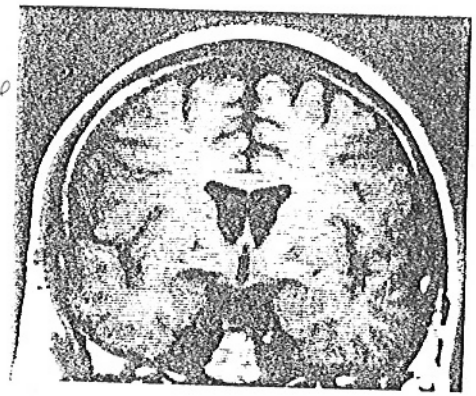

FIG. 3. *Case 2.* Bilateral pallidal damage on a coronal MRI slice (T1 weighted sequence).

Case 3 (see Laplane et al., 1984, Case 3)

P. was aged 59 yrs when, in 1970, he was accidentally poisoned by carbon monoxide. Other than his having lived alone with his mother and having never married, information concerning his past history was lacking. Following a brief period of coma, he suffered several days of headache and confusion. After recovering he tried to recommence his job as a messenger, but was dismissed because of slowness. Akinesia, extrapyramidal rigidity and reduction of verbal fluency were noted at that time, but there was improvement during the following years. Intellectual processes seemed slowed and there was an impression of mental deterioration, although he could perform complex tasks on request. The most striking feature was his passivity and lack of initiative, although his motor and mental capacities were largely preserved (Table 1). The interpretation of the apparent language disorder must be tempered by the fact that he was of Russian origin. He was institutionalized, spending most of his day inactive; he never attempted to leave hospital. His lack of initiative was not total, however, since he did from time to time help other patients to eat or shave, watch television, read a newspaper and so on. He was able to paint pictures, but for years he painted the same landscape. His affect was poor. The EEG was normal.

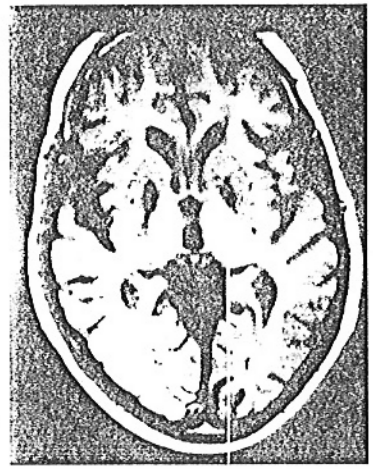

FIG. 4. *Case 3.* Bilateral calcified pallidal lesions on a horizontal MRI slice (T1 weighted sequence). Some degree of brain atrophy is present.

CT and MRI scans showed almost symmetric calcified lesions in the basal ganglia, occupying most of the region of the globus pallidus bilaterally (fig. 4). The dorsal parts of both pallidal segments seemed more affected, as seen on coronal sections, than the ventral segments. Cortical atrophy and ventricular enlargement were present.

The PET scan performed 14 yrs after the accident showed regional CMRglu values within the normal range. There was a significant decrease of the mediofrontal metabolic index on planes II, III, IV, V ($P < 0.02$, < 0.05, < 0.001, < 0.01, respectively), the right and left laterofrontal regions on plane II ($P < 0.01$ and < 0.02, respectively), the left laterofrontal region on plane IV ($P < 0.05$) and the right striatal region ($P < 0.01$). There were also significant increases of the metabolic indices in the right temporo-parieto-occipital area of plane III ($P < 0.001$) and in the left occipital area of plane III ($P < 0.01$).

Case 4

D., aged 52 yrs, was a former alcoholic who had been previously treated with disulfiram. Medical attention had been drawn to him because of his inactivity and lack of volition. He would lie in bed all day, and talked to no-one. If questioned, however, he would answer appropriately. He was not apparently bored with his lot, nor did he feel sad. His past history did not reveal any depressive or compulsive features. Neurological examination and EEG were normal.

CT scans (October 1984) showed bilateral low density areas visible on one slice (of 9 mm thickness) only. These lesions projected onto the pallidal areas. Unexpectedly, MRI abnormalities (5 months later, in March 1985) were less marked, with apparently a right-sided lesion only, involving parts of the putamen, of the lateral pallidal segment and of the head of the caudate nucleus (fig. 5). These lesions were attributed to intoxication by disulfiram which may have occurred several years previously.

The PET scan showed elevated rCMRglu values in all structures, but this increase reached statistical significance only in the lateral occipital cortex of both sides on plane III ($P < 0.02$). The left laterofrontal metabolic index on plane III was significantly decreased ($P < 0.05$).

Case 5

A. had at the age of 27 yrs suffered cerebral anoxia during general anaesthesia for appendicectomy. Before the accident she had been otherwise well. On recovery there was a pyramidal syndrome,

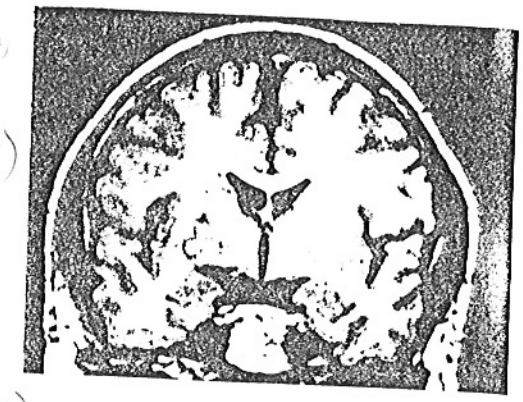

FIG. 5. *Case 4.* Right-sided lesion, probably due to disulfiram intoxication, involving parts of the putamen, of the lateral pallidal segment and probably of the caudate. This MRI section (coronal plane, T1 weighted sequence) showed less marked lesions than did the CT scan, where bilateral lucencies were present in the pallidal areas. CT scan was performed, however, six months earlier than MRI.

tremor, rigidity, and severe mental disturbance. Six years later, in contrast to her motor function, which had greatly improved, she was extremely inert. Housework was performed very slowly, and she would spend many hours doing nothing, sometimes in front of the television, in contrast to her premorbid behaviour. She felt sad, and was pessimistic about her future. In addition, she was subject to obsessive-compulsive behaviour. She was unable to restrain herself from timing her activities, and would schedule her tasks in detail. Some actions shared the features of a lack of inhibition of motor programs and those of compulsive behaviour. For instance, once when stirring soup, she was unable to stop spontaneously, and had to ask someone to immobilize her arm. The same phenomenon would occur if she began to scratch a part of her body.

The EEG was normal. CT scan and MRI showed small bilateral lesions within the lentiform nuclei. Although very narrow in the mediolateral dimension, they extended rostrocaudally along almost the whole of the globus pallidus, involving both the inner and outer segments (fig. 6). Frontal MRI slices were not obtained.

The PET scan performed 6 yrs after the onset showed no abnormality of the cortical CMRglu

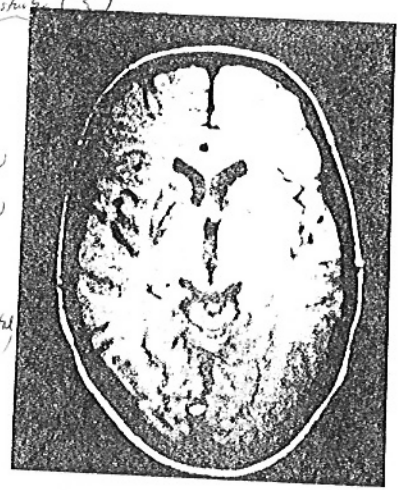

FIG. 6. *Case 5.* Horizontal MRI section (T1 weighted) showing abnormal signals in both pallidal areas.

values, but the striatal rCMRglu was significantly decreased on the right ($P < 0.02$). The metabolic indices were significantly decreased in the left laterofrontal area of plane IV ($P < 0.02$) as well as in both striatal regions ($P < 0.001$ and < 0.05 on the right and left sides, respectively).

Case 6

F. was examined by us in December 1985. Three years previously he had suffered an electric shock that had induced ventricular fibrillation followed by hypoxia and coma. He had been meticulous in his job as a clerk, but there had been no evidence of physical or psychological disturbance before the accident. Four months later, on return home from hospital, he was noted by his relatives to remain in bed until asked to rise, and would otherwise stay there. He seemed to make no initiative though he would perform tasks at the insistance of others. He showed a polymorphic compulsive behaviour. For instance, in walking down a corridor, he would feel obliged to turn on or off each light switch he encountered. He would walk on the pavement 'avoiding the lines'. He rechecked his behaviour constantly. In counting, he would avoid the number 13 and would often recite the alphabet. He did not seem to be disturbed by this behaviour and made no attempt to desist. He used to say that he was doing it 'pour rire'. If he was prevented from performing these acts, he would become angry, but not apparently fearful. Finally he had major memory difficulties which interfered with his daily life. Neurological examination and the EEG were normal. The neuropsychological examination is summarized in Table 1.

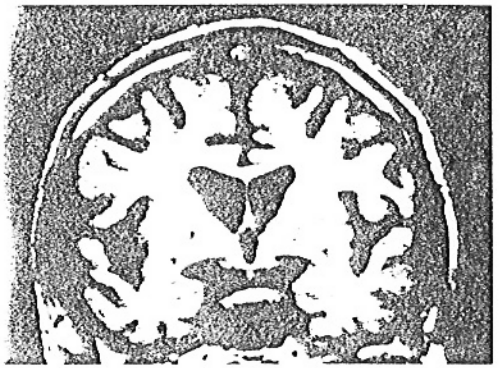

FIG. 7. *Case 6.* Frontal MRI section showing bilateral lesions which occupy predominantly the pallidum (dorsal part of medial segment) and the ventral part of the putamen (T1 weighted sections). Some degree of brain atrophy is present.

MRI showed almost symmetric bilateral lesions occupying the dorsal part of the globus pallidus, affecting mainly the lateral but also the medial segment (fig. 7). These lesions extended ventrally and laterally onto the two parts of the lentiform nucleus, pallidum and putamen, situated just above the lateral part of the anterior commissure. Some degree of cortical atrophy and ventricular enlargement was present.

The PET scan performed 2 yrs after the onset showed that the right striatal CMRglu value was significantly decreased ($P < 0.05$). No significant alteration of the metabolic indices was observed, although there was an increased mediofrontal CMRglu of planes III and IV which fell short of statistical significance.

Case 7

M., aged 31 yrs, was admitted because of unusual neuropsychiatric sequelae of self-induced carbon monoxide poisoning. Her past history had included, since the age of 15 yrs, depressive periods with suicide attempts, drug abuse, and alcoholism. Her marriage had failed and she had continued her life as a homosexual. Her personality had been considered to be psychopathic and

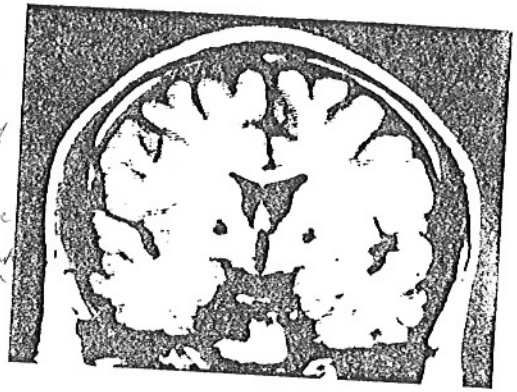

FIG. 8. *Case 7.* Frontal MRI section (T1 weighted sequence) showing symmetric clear-cut abnormal signals which project upon the rostral and dorsal parts of the globus pallidus.

impulsive by psychiatrists at the time. In 1983, following accidental carbon monoxide intoxication, she began to exhibit new compulsive activities. Three types of behaviour were noteworthy. She would repeatedly look at her watch and repeat the time to herself. She would count in her mind the number of words spoken by another person, and if the total was not a multiple of three, she would add words. This habit usually induced a delay before she was ready to answer any question posed. The third type of compulsion consisted of the repetition of a mandatory sentence, according to the action in progress ('Je n'ai pas fait cela pour rien' when finishing a cigarette, or 'Ceci appartient au passé' before drinking. In spite of the fact that she was well aware of the absurdity of these actions, she could not restrain herself from performing them. When she attempted to fight against them, she would at once experience anxiety and a compulsion to execute the action. A general slowing was noted, partly explained by the time demanded by some of her compulsions. Neurological examination was otherwise normal.

CT and MRI scans showed bilateral, well-delineated lesions of the lentiform nuclei (fig. 8). These lesions involved the anterior part of the globus pallidus, from the anterior commissure rostrally, as far as the anterior thalamic nuclei caudally, leaving unaffected the posterior and ventral parts of the nucleus. Lesions were primarily located in the lateral pallidal segment, although a part of the medial segment was also probably involved. This lesion, as evaluated from the MRI data, occupied approximately one-quarter of the volume of the globus pallidus. Lesions were roughly symmetric, although slightly more rostral on the left. A slight encroachment on the anterior limb of internal capsule could not be excluded.

The PET scan performed 3 yrs after the event showed no significant abnormality of rCMRglu values. With respect to the metabolic indices, they significantly decreased in the mediofrontal area of plane IV ($P < 0.05$), the right laterofrontal area on plane V ($P < 0.05$), the left laterofrontal area of plane II ($P < 0.05$) and the right striatal area ($P < 0.05$). In addition, the metabolic index of the left latero-occipital area of plane III was significantly increased ($P < 0.01$).

Case 8

K., a 22-yr-old, previously well, north African woman, was admitted to the intensive care unit at the Hôpital Beaujon unresponsive and stuporose following accidental carbon monoxide intoxication. The initial CT scan performed 2 days later showed bilaterally symmetric lucencies in the region of the internal segment of the globus pallidus. After progressive return of normal consciousness, marked psychomotor inertia remained. Whereas her family noted no intellectual deterioration, a formal neuropsychological assessment was not possible because of language difficulties. Her condition remained apparently unchanged for the next 2 months, when MRI and PET scans were performed. No obsessive or compulsive features were noted.

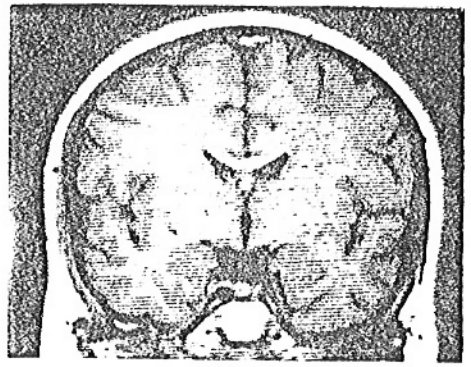

FIG. 9. *Case 8.* Frontal MRI shows symmetrically abnormal signals in the internal segment of the globus pallidus bilaterally (increased signal on T1 sequence).

The MRI scan showed symmetric punctate abnormal signals in internal globus pallidus segments bilaterally (hypersignals on both T1 and T2 sequences). No lesions were seen elsewhere, and no significant cortical or subcortical atrophy was noted (fig. 9). In spite of the lack of full neuropsychological assessment, this patient is included in the present series because it was possible to obtain a PET scan.

The PET scan, performed 2 months after the accident, showed that the rCMRglu (plane IV was unavailable) values were low throughout but this decrease reached statistical significance only in both striatal areas ($P < 0.01$ and 0.05 on the right and left, respectively). The metabolic indices of the right and left laterofrontal areas of plane III were significantly decreased ($P < 0.01$ and 0.05, respectively) as well as of the right striatal area ($P < 0.02$). There were significant increases of the metabolic indices in the right laterotemporal area of plane III ($P < 0.02$) as well as in both latero-occipital areas of plane III ($P < 0.02$ on the right and 0.001 on the left).

RESULTS

Neuropsychological assessment

The main results of neuropsychological testing are given for each patient (except Case 8 who was not testable) in Table 1. In spite of some degree of interpatient variability, several common features were present. (1) Intellectual function remained within normal limits in most of the patients, although performance might have been affected by variability of attention. Learning was disturbed in Cases 2 and 6. (2) Linguistic and gestural specific activities, calculation and drawing were intact. (3) Orientation in space and time was preserved. (4) Recall of early-acquired general knowledge and of old or recent personal memories was correct, except in Cases 2 and 6, providing appropriate questions were asked of the patients. (5) Spontaneous activity was very restricted, but it improved greatly with stimulation by the examiner. (6) Cognitive slowing, although it consistently affected daily living, varied during examination from one patient to another, and sometimes from one test to another in the same patient. (7) Reduced digit span, forwards and backwards, and unexpected exhaustion or variability of performances in some tests, revealed attention disorders. (8) Mental control subtests using patterned

TABLE 1. NEUROPSYCHOLOGICAL RESULTS*

	1	2	3	4	5	6	7	8
Age (yrs)	52	26	70	50	33	36	31	88
Education (yrs)	15	12	10	8	12	10	8	99
WAIS verbal IQ (114-119)	103	116	80	93	108	79	88	
Raven's PM 38 (IQ normal for age)	114	99	100	111	108	85	99	
Wechsler Memory Scale								
MQ = prorated Sum								
Mental control	91	70	97	100	108	57	98	
Working memory: Digits forward 3-9, Imp < 4	9	9	4	7	8	4	8	
Digits backward 2-8, Imp < 3	5	6	3	6	6	2	7	
Logical memory A	9	3	2	4	4	2	3	
Logical memory B	7	2	10	11	22	1	18	
Wisconsin Card Sorting test		2	7	9	14		4	
Categories		5						
Perseverations		9	0	2	6	1	2	
Verbal fluency (60 s)		4	10	1	0	10	0	
Animals 2 (10 Abnormal)		8						
Words beginning with M	12	12	4	20	14	14	9	
Perturbation in motor series		2	1	1	14	1	3	
Rey Complex Figure	+	+	+	+	+	+	–	
Copy		Details ✓	Rectangle	Rectangle	Rectangle	Rectangle	Details	Rectangle
Memory reproduction		Details ✓	Rectangle	Details	Details	Details	Details	Rectangle
Fifteen objects tests (time)					150 s	22 s		30 s
Specific difficulties		Writing disorders	Micrographia	Micrographia	Micrographia	Writing disorders	Attention disorders	Variability
Depression and anxiety						+	+	+
Psychiatric illness								
OCD								
Lesion		+	+	+	+	+	+	+
		+	+	—	—	—	—	—
		Bilat GP	Bilat GP	Bilat GP	Bilat GP	Bilat GP	d GP;	Bilat. GPi;
		R > L	R > L	D > V	B. put → GP, caud.	Entire	V Putamen	ant. GP
						Tremor, rigidity	L > R	Case 8
Neurol.		Chorea, Tics	—	Akinesia, Rigidity	—	—	—	Akinesia
PET (↓ only)	N/A	↓ med. Frontal, ↓ inf. Frontal	↓ M/L Frontal, ↓ Striatum	↓ Inf. Frontal	↓ Inf. Frontal, ↓ Striatum	↓ Inf. Frontal, ↓ Striatum, R/L Striatum	↓ Med. Frontal, ↓ Striatum, ↓ Inf. Frontal, L/R Striatum	↓ L/R Inf. Frontal, L/R Striatum

* Case 8 was not testable.

learned material were relatively well performed. (9) Verbal fluency for words of the same semantic category (animals) was normal for most of the patients. (10) The listing of words beginning with M (which required more innovation and thought), was poor. (11) Some patients had problems extracting a structure from the Rey-Osterrieth complex figure. (12) Tests of reproduction of the same figure from memory indicated that attention was directed either towards the large central rectangle or towards the details, but that the overall synthesis was never performed. (13) The elaboration of a new strategy, the shifting of attitude in order to adapt to a changing situation, and the sequential programming of activity were also disturbed, as shown by the Wisconsin Card Sorting test, Luria's arithmetic problems or graphic and motor series. (14) No abnormal imitation, prehension, or utilization behaviour was observed during testing, but for Case 6 the family reported compulsive utilization behaviour at home. (15) Refusal behaviour was never observed by investigators, but motivation decreased quickly in the face of difficulty or lack of success. (16) Personality, as evaluated by the MMPI, was preserved, but affect was severely impaired. In 2 patients a depressive condition was noted. It appeared before the brain damage in one, and afterwards in the case of the other.

Neurological examination

In contrast to the significant neuropsychological abnormalities seen in the patients, relatively few neurological physical signs were exhibited. Three patients had a mild parkinsonian-like syndrome, 1 of whom had tic-like movements; the other 5 had a normal neurological examination.

Summary of PET findings

1. The cortical *CMRglu values* were unremarkable, if Case 4, in whom the occipital metabolism was significantly elevated, is excluded. In the striatal area, however, the CMRglu was significantly reduced in 3/7 cases, while no changes were seen in the thalamic area.

2. The analysis of individual *cortical metabolic indices* was remarkable in the following respects. (1) The occurrence of significantly abnormal values (23 out of 185 analysed regional values or 12%) was higher than expected by chance alone. (2) Among the 23/185 significantly abnormal areas, 16 were frontal cortex areas (out of a total of 75 frontal cortex values) and 7 nonfrontal areas (out of 110 nonfrontal areas), a statistically significant distribution ($\chi^2 = 9.19$, $P < 0.01$). (3) Each of the 16 significant decreases were located within the frontal lobe, while each of the 7 significant increases were outside the frontal cortex, a distribution statistically significant by χ^2 ($\chi^2 = 18.94$, $P < 0.01$) (*see* fig. 10).

Among the 7 patients studied, 6 individually demonstrated at least one significantly decreased regional value in the frontal lobe, of whom 4 also showed a significantly increased index in nonfrontal posterior cortex. Among the 16 abnormally low frontal indices, 7 were located in the medial frontal cortex, 7 in

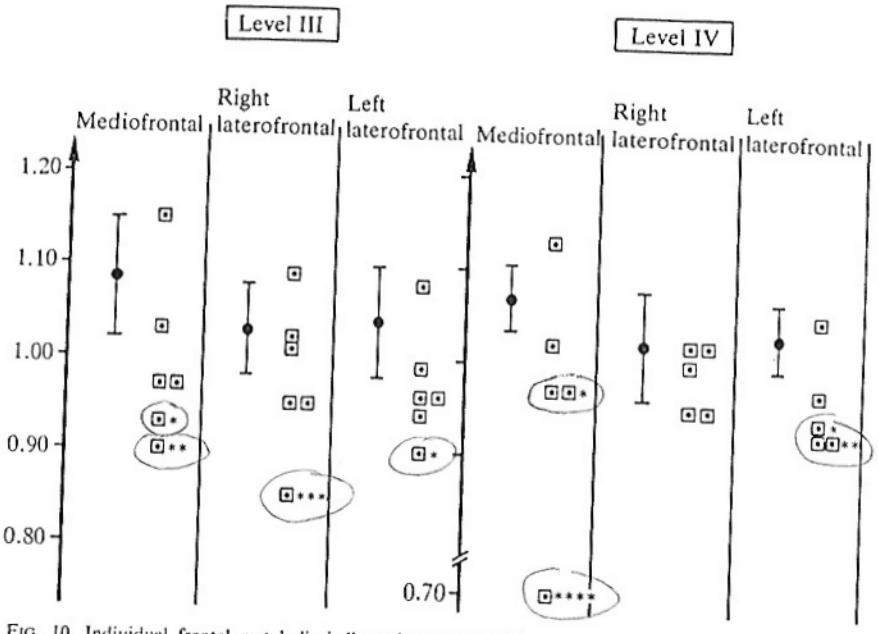

FIG. 10. Individual frontal metabolic indices (frontal CMRglu/mean cortical CMRglu, closed circles in squares), calculated separately for brain levels III and IV and for 3 regions (the mediofrontal and the right and left laterofrontal areas) in the 6 patients studied on the LETI camera (Cases 2, 3, 5, 6, 7 and 8; level IV was unavailable in Case 8). The mean (±1 SD) corresponding values in control subjects are also shown (closed circles). $^{*}P < 0.05$; $^{**}P < 0.02$; $^{***}P < 0.01$; $^{****}P < 0.001$.

the lateral prefrontal cortex, and 2 in the laterobasal frontal cortex, without any noticeable clustering either among these 3 anatomofunctional subdivisions, or in the vertical (axial) direction. Of the 7 significant increases in nonfrontal cortex metabolic indices, 5 were located in the occipital area and 1 each in the temporal and the temporo-parieto-occipital cortices.

3. *Subcortical metabolic indices.* Among the 14 striatal metabolic indices, 6 were significantly abnormally low and none abnormally high; these changes occurred in 4 of the 7 patients. No significant abnormality was found in the analysis of the thalamic metabolic indices.

For illustration, fig. 11 depicts the CMRglu images (plane III) of each of the 6 patients investigated with the LETI camera (Cases 2, 3, 5–8), as well as for a typical control subject.

Mean regional metabolic data

Table 2 shows the *mean rCMRglu* and the *mean regional metabolic indices* for all cortical areas analysed (after combining the right and left original cortical regions as the individual results did not show any trend for lateralized metabolic

TABLE 2. MEAN (±1 SD) REGIONAL CORTICAL GLUCOSE UTILIZATION (rCMRglu) AND CORRESPONDING METABOLIC INDICES IN 6 PATIENTS AS COMPARED WITH 13 CONTROL SUBJECTS

	Cortical area																					
	Mediofrontal			*Laterofrontal*						*Temporal*			*Parietal*			*Temporo-occipital*			*Parieto-occipital*	*Occipital*	
Level[a]	II	III	IV	V	II	III	IV	V	II	III	IV	V	III	IV	V	III	IV	V	V	III	IV
Controls[c]																					
rCMRglu (mg/100 g/min)	6.86 ±1.66	6.81 ±1.48	6.68 ±1.22	7.14 ±1.80	6.24 ±1.29	6.48 ±1.38	6.45 ±1.39	6.90 ±1.60	5.43 ±0.97	6.74 ±1.18	6.24 ±1.47	6.65 ±1.58	5.50 ±0.95	5.90 ±1.20	6.60 ±1.45	6.31 ±1.02	7.34 ±1.13				
Metabolic index[b]	1.078 ±0.091	1.086 ±0.062	1.067 ±0.035	1.051 ±0.086	0.991 ±0.055	1.036 ±0.049	1.027 ±0.056	1.026 ±0.043	0.868 ±0.060	1.083 ±0.045	0.994 ±0.088	0.987 ±0.048	0.885 ±0.033	0.941 ±0.054	0.983 ±0.037	1.018 ±0.068	1.086 ±0.067				
Patients[d]																					
rCMRglu (mg/100 g/min)	5.90 ±1.34	5.70 ±0.88	5.65 ±1.03	5.64 ±1.00	5.59 ±0.91	5.72 ±1.13	6.11 ±0.61	5.95 ±1.49	5.21 ±0.68	6.56 ±0.90	6.30 ±1.09	6.08 ±1.02	5.58 ±1.32	5.88 ±0.80	6.14 ±1.47	6.94 ±0.88	7.34 ±1.13				
Metabolic index[b]	0.994 ±0.143	0.992** ±0.089	0.992 ±0.164	0.953 ±0.156	0.910** ±0.065	0.975* ±0.067	0.976* ±0.038	0.995 ±0.040	0.875 ±0.069	1.085 ±0.067	1.000 ±0.066	0.986 ±0.042	0.912 ±0.077	0.938 ±0.030	1.013 ±0.045	1.155† ±0.121	1.133 ±0.062				

[a] Brain level of PET scan, *see* fig. 1. [b] Calculated as regional cortical CMRglu/mean cortical CMRglu of same level (*see* Methods). [c] n = 13 subjects, but mean regional values based on 10–13 individual data because of occasional unavailability of 1 PET level. [d] n = 6 patients, but mean regional values based on 4–6 individual data (*see* c). * Significant decrease ($^{*}P < 0.05$, $^{**}P < 0.02$), relative to controls by ANOVA. † Significant increase ($P < 0.01$) relative to controls by ANOVA.

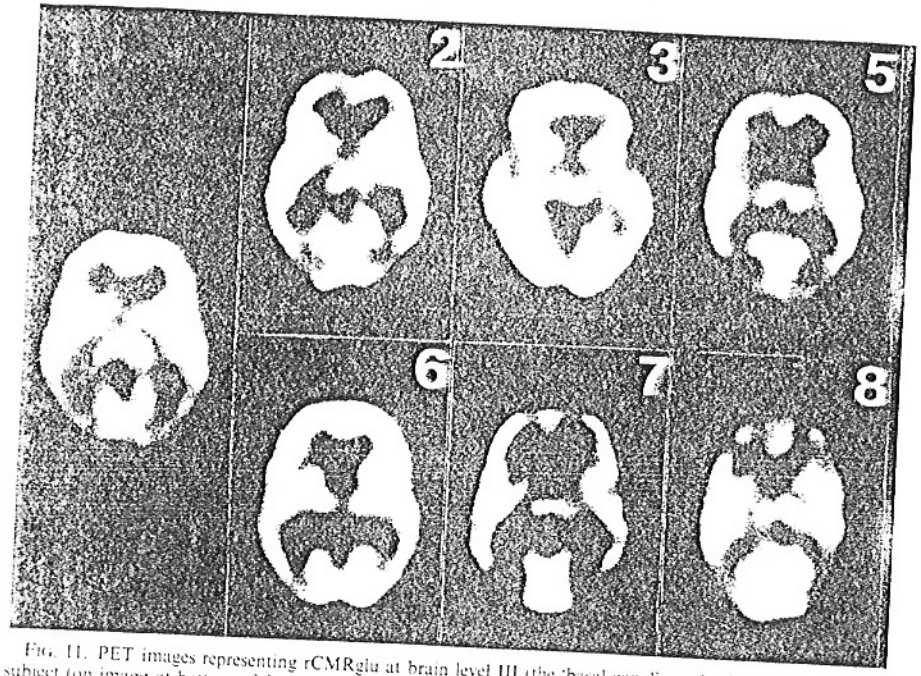

FIG. 11. PET images representing rCMRglu at brain level III (the 'basal ganglia cut') obtained in 1 control subject (on image at bottom of fig.) and in 6 patients (2, 3, 5, 6, 7, 8) studied with the LETI camera. In these images, anterior is uppermost and right is to the left; whiter shades of grey indicate higher metabolism. These images are not cross-scaled, so that differences in mean metabolic rate among patients are not apparent; this mode of display, however, allows visual assessment of the regional metabolic pattern. Compared with the control subject, whose image is typically normal, there is a mild degree of relative prefrontal cortex hypometabolism in all patients except Case 6; this effect was statistically significant on this brain level in Cases 2, 3, 5, and at a different brain level (not shown) in Cases 5, 7 (see PET results section 'Individual data analysis').

TABLE 3. MEAN (± SD) REGIONAL SUBCORTICAL rCMRglu AND CORRESPONDING METABOLIC INDICES IN 8 PATIENTS COMPARED WITH 13 CONTROL SUBJECTS

	Subcortical area	
	Striatal	*Thalamic*
Controls[a]		
rCMRglu (mg 100 g min)	6.85 ±1.13	6.31 ±1.01
Metabolic index[b]	1.107 ±0.098	1.018 ±0.093
Patients[a]		
rCMRglu (mg 100 g min)	5.05*** ±1.02	5.82 ±0.76
Metabolic index[b]	0.881**** ±0.098	0.950 ±0.045

[a] n = 8 *see* Table 1. Asterisks = significantly decreased relative to controls by ANOVA ***$P < 0.01$, ****$P < 0.001$.

effects). There was no significant abnormality of *mean rCMRglu values* although there was a trend for decreased rCMRglu in most frontal cortex areas. Of the 8 frontal regions analysed, 4 showed a significantly depressed *metabolic index* (the laterofrontal cortex of planes II, III, and IV and the mediofrontal cortex of plane III ($P < 0.02$, < 0.05, < 0.05 and < 0.02, respectively). In addition, the mean metabolic index in the occipital cortex was significantly increased ($P < 0.01$).

Table 3 shows the mean rCMRglu and the mean metabolic indices for *subcortical areas*. In the striatal region, both the CMRglu and the regional metabolic index were significantly decreased ($P < 0.01$ and 0.001, respectively). There were no significant changes in the thalamic areas.

DISCUSSION

Relationship to the frontal syndrome

Clinical studies

The first feature of note is the similarity of this syndrome to the frontal lobe syndrome, although here the lesions are at basal ganglia level, in the lentiform nuclei. It is difficult to find a neuropsychological definition of the frontal syndrome which is accepted by all authors. Several features are, however, considered as characteristic. Among the most significant is the loss of drive. All our patients had a decrease in spontaneous activity and drive. This was very marked in all patients except Cases 3 and 7 and was readily reversible under stimulation by the patients' relatives and friends. This is also the case with 'frontal' patients (Stuss and Benson, 1986). Consequently, this sign can be masked under test conditions. As emphasized by Eslinger and Damasio (1985), these disorders are more marked in day to day life than in artificial situations such as the neuropsychological examination. The decrease in verbal fluency is also frequently encountered in the 'frontal' syndrome. The finding of words belonging to a given semantic group was less altered than the listing of words beginning with a given letter. Such a dissociation has also been described in the 'frontal' syndrome (Stuss and Benson, 1986). Attention disorder, another frontal sign, was also present although less marked in our patients. Memory disturbances were marked in 2 patients (Cases 2 and 6). In Case 6, amnesia was a part of a global deterioration of cognitive function, suggesting the possibility of more diffuse lesions.

Responses to the Wisconsin Card Sorting test, often thought as the most sensitive test of frontal dysfunction, were markedly abnormal in most of our patients, and especially in Cases 3 and 7. They were, however, normal in Case 5. Qualitatively, results varied. Some of the patients exhibited severe perseverations, whilst others (Cases 1, 7) showed better control, perhaps because they had better insight into their disorder. Visuoconstructive tests primarily revealed difficulties in understanding an image pattern as a whole. Finally, the presence of affective disorder needs discussion. Patients showed a lack of concern regarding their own problems and those of their relatives. The absence of foresight suppressed anxiety.

Here also the severity of the disorder was variable, since for Cases 5 and 6, affect was not completely lost, and depressive thoughts and anxiety were present. The neuropsychological findings are thus similar to those observed following frontal lobe damage. The question arises as to whether there were frontal lobe lesions, associated with basal ganglia damage, but unidentified on morphological imaging of the brain.

From a clinical point of view, frontal-like syndromes have been described in basal ganglia disorders such as progressive supranuclear palsy (Cambier *et al.*, 1985) and Parkinson's disease (Taylor *et al.*, 1986; Gotham *et al.*, 1988). The present observations of frontal-like syndromes with bilateral lesions of the lentiform nuclei are more suggestive of this relationship since motor dysfunction, which sometimes complicates the interpretation of neuropsychological testing in the above mentioned diseases was, in our cases, absent or only mild.

PET studies

The PET studies, performed in 7 of the 8 patients reported here, revealed several noteworthy findings. First, there was evidence of unilaterally or bilaterally decreased striatal glucose utilization (absolute values and/or relative metabolic indices), in 5/7 patients. Secondly, the glucose utilization values in the cerebral cortex were essentially normal, as compared with control subjects of similar age. Thirdly, despite this lack of significant alteration in cortical rCMRglu, there was a significant reduction in glucose utilization in various parts of the frontal cortex *relative* to the whole cortex in 6/7 patients taken individually, as well as in 4/8 frontal cortex subdivisions (namely, two laterofrontal, one latero-fronto-basal and one mediofrontal area) when the whole group of patients was analysed; as a corollary to this relative prefrontal cortex hypometabolism, there existed a significant *relative* hypermetabolism of the occipital cortex in several patients individually, as well as on average in the whole sample. These results establish the occurrence in our patient sample of an imbalance between anterior and posterior cortex glucose use, resulting in an altered anteroposterior gradient of cortical metabolism, which will be referred to in what follows as a *relative prefrontal hypometabolism*.

The reduced glucose use in our 'striatal' areas presumably reflects the inclusion, within our ROIs, of the damaged part of the lentiform nucleus; due to the relatively low spatial resolution of our PET device, this damaged area could not be directly visualized, and in turn, could not have been excluded in the regional data sampling procedure (*see* fig. 1). It remains possible, however, that part of this striatal hypometabolism represents a remote effect of the actual lesion, for example, as a result of retrograde dysfunction along striatopallidal pathways.

The relative prefrontal hypometabolism found in our patients may be due to several mechanisms: a morphologically detectable loss of cerebral tissue, a neuronal loss without gross morphological alteration, or a deafferentation process.

A morphological loss of frontal cortex tissue is an unlikely explanation for this finding because all 5 patients in our group who did not show clear-cut cortical atrophy on the MRI scan had a significant relative prefrontal hypometabolism, while only 1 (Case 3) of the 2 patients with a substantial cortical (not especially frontal) atrophy exhibited this finding. Lesions of the white matter of the centrum semiovale are known to occur in some instances of anoxic encephalopathy (Lapresle and Fardeau, 1966; Ginsberg, 1985) and could possibly, if present, disconnect the frontal cortex; however, no significant abnormality of the MRI white matter signals was observed in our patients.

Two of our patients (Cases 4, 7) were former alcoholics, a condition associated with relative mediofrontal hypometabolism of unclear mechanism (Samson *et al.*, 1986); however, the relative prefrontal hypometabolism present in both was localized to the mediofrontal cortex in only 1 of these 2 cases (Case 7).

A microscopic neuronal loss in the frontal cortex without gross structural damage cannot be formally excluded as in none of our patients was histological examination available. Published detailed accounts of neuropathology in 22 cases of carbon monoxide encephalopathy, however, showed (in those dying later than 10 days after encephalopathy) no cortical damage in 5/9, minor cortical damage in 3/9 and noticeable damage in only 1/9; in addition, it is not indicated in this report that these scanty cortical lesions predominate in the frontal cortex (Lapresle and Fardeau, 1967). In the neuropathological study of one case of carbon monoxide poisoning, Kobayashi *et al.* (1984) indicated that 'the cytoarchitecture of the frontal cortex was unremarkable'. Similarly, damage to the cerebral cortex was not a feature in the detailed pathological study performed by Ginsberg *et al.* (1974) in 14 monkeys following experimental carbon monoxide intoxication. On the whole, therefore, although it is difficult to exclude the possibility that neuronal damage concentrated in the frontal cortex could have contributed to the observed metabolic abnormality, particularly in some of our cases, the radiological data as well as the neuropathological literature suggest it could hardly explain the consistency of our observation across 6 subjects of our sample. We would therefore favour a process of deafferentation of the prefrontal cortex to explain our findings, as a result of bilateral lesions in the area of the globus pallidus.

Such a mechanism has been generally implicated to explain the depression of glucose utilization and oxygen consumption in the cerebral cortex following subcortical lesions in other grey matter nuclei (Feeney and Baron, 1986; Perani *et al.*, 1987). Thalamic lesions of vascular or surgical origin often result in diffuse ipsilateral cortex hypometabolism which apparently underlies the neuropsychological impairment and has been ascribed to damage to the thalamocortical projection system (Baron *et al.*, 1986). Following stereotactic lesions of the nucleus basalis of Meynert in the baboon, there is a marked ipsilateral, predominantly frontal, cortical reduction of glucose utilization which is linearly correlated with the extent of cortical cholinergic deafferentation as measured by choline acetyl transferase activity (Kiyosawa *et al.*, 1987). In patients with large left putaminal haemorrhage,

Metter *et al.* (1986) observed temporal cortex hypometabolism which was proportional to the severity of aphasic symptoms. Finally, symptomatic Wilson's disease results in a marked but diffuse reduction in cortical glucose utilization (Hawkins *et al.*, 1987), in the development of which extralenticular pathology, especially cortical lesions, may however play a role.

This is the first report of cerebral glucose utilization in patients with bilateral lentiform lesions affecting predominantly or exclusively the globus pallidus. We are not aware of experimental bipallidal lesions studied with ^{14}C-deoxyglucose autoradiography. Although the lesions in some of our patients also affected part of the putamen, it is interesting to note that striatal lesions in rats do not result in significant frontal cortex hypometabolism (Kelly *et al.*, 1982; Kelly and McCulloch, 1984), suggesting that our findings in patients can probably be specifically ascribed to the pallidal lesions (it is possible, though, that any subpallidal extension of the lesion would have encroached upon the area innominata, and particularly the nucleus of Meynert, but the damage in our cases apparently spared this area). The only example of a pathological entity studied by PET which consistently involves the globus pallidus bilaterally, is progressive supranuclear palsy (PSP), where a conspicuous prefrontal cortex hypometabolism has repeatedly been demonstrated (D'Antona *et al.*, 1985; Leenders *et al.*, 1988) (although lesions of other systems are present in this degenerative disorder). The pathways linking the globus pallidus to the prefrontal cortex that would most likely be implicated in the development of the frontal dysfunction are the pallido-thalamo-cortical systems (*see* below); the process of prefrontal deafferentation in this case would therefore occur on a transneuronal basis.

It is tempting to implicate the observed frontal hypometabolism in the behavioural expression of bilateral pallidal lesions, which, by itself, is suggestive of dysfunction of the frontal cortex (*see* earlier discussion). Similarly, the intellectual impairment typical of PSP is characteristic of the frontal lobe syndrome and, as discussed above, is associated with a marked prefrontal hypometabolism. We searched for correlations between our frontal metabolic indices and the type and severity of the behavioural symptoms: there was no association between obsessive-compulsive features and/or psychic inertia on the one hand and the occurrence of significant frontal cortex hypometabolism and its topography within the frontal lobe on the other. For example, Baxter *et al.* (1987) recently reported a significantly increased glucose utilization in the left orbitofrontal cortex in obsessive-compulsive disorder. In addition to its small sample size, our study is made more difficult by the variability produced by the differing mechanisms of initial damage, ages of onset, and extensions of extrapallidal damage (Cases 3 and 6 had conspicuous cortical atrophy, and several cases showed putaminal damage).

At first sight, the dissociation between the severity of the behavioural impairment in our patients and the mildness of the metabolic changes, which affected the relative metabolic indices of the frontal lobe, may seem surprising. One hypothesis would be that the dysfunction of the cortical neurons, although present, had little consequence on the overall measured glucose utilization, because different neuronal populations are affected in opposite ways or because the neurotransmitter imbalance may not have disturbed the ionic gradients; a similar mechanism may explain the lack of significant cortical glucose hypometabolism in the dementia of Huntington's disease (although a slight relative frontal hypometabolism may be present in advanced cases; *see* Kuhl *et al.*, 1982; Young *et al.*, 1986). Alternatively, the significant prefrontal metabolic depression found here, although small, may nevertheless reflect a major disruption in the normal functional relationships between the prefrontal cortex and other interconnected cortical fields as well as with subcortical nuclei (Goldman-Rakic, 1987*a*) and, in turn, in a balance fundamental for normal behaviour. A similar rationalization would apply to the repeated observation of frontal cortex hypometabolism in patients with schizophrenic disorders (for review, *see* Buchsbaum, 1987). It is also possible that bipallidal lesions initially induce much larger effects on cerebral cortex metabolism, but that, as occurs in unilateral thalamic lesions, a progressive almost complete recovery occurs thereafter (Cambon *et al.*, 1987), in parallel with the clinical recovery. This would be consistent with the fact that the lowest CMRglu values were observed in the patient studied the earliest following the anoxic episode (2 months, Case 8). The recovery of clinical impairment, however, appears limited in bipallidal lesions.

On the other hand, it must be emphasized that the lack of significant reduction in cortical CMRglu in our patients is consistent with the overall preservation of global intellectual function. For example, the relative prefrontal cortex hypometabolism, characteristic of the 'subcortical' dementia of PSP, is actually superimposed on a significant depression of glucose utilization throughout the whole cortical mantle (D'Antona *et al.*, 1985; Leenders *et al.*, 1988): while the former may underlie the specific frontal lobe symptoms, the latter may be a counterpart to the global intellectual impairment found in this disease.

The prefrontal-basal ganglia-thalamocortical pathways

There have been conspicuous advances in the understanding of the anatomical relations between the basal ganglia and frontal associative cortex over the past decade. Recent anatomical and physiological findings have reinforced the general principle that some basal ganglia influences are transmitted only to restricted portions of the frontal lobe. Several segregated basal ganglia-thalamocortical pathways can be described, each of them including discrete, essentially nonoverlapping parts of neostriatum, pallidum or substantia nigra, ventral thalamus and cortex (Alexander *et al.*, 1986; Nauta, 1986). The 'motor' circuit, whose cortical target is the supplementary motor area, is the best documented from an anatomical and functional point of view, but the 'association' circuits are likely to be the anatomical basis of our patients' disorders. A dorsolateral prefrontal circuit has been proposed. The neostriatal input terminates within the dorsolateral head of the caudate and throughout a continuous rostrocaudal expanse that extends to

the tail of the caudate (Yeterian and Van Hoesen, 1978; Selemon and Goldman-Rakic, 1985). These specific sectors of caudate nucleus project to the globus pallidus and to rostral portions of the substantia nigra. With respect to the globus pallidus, several experimental studies indicate that the 'association' sectors correspond to rostral, medial and dorsal parts of the nucleus (Parent *et al.*, 1984; Percheron *et al.*, 1984). The pallidothalamic input of this association circuit terminates in the different parts of the ventral anterior and mediodorsal nuclei of the thalamus. Another circuit terminates in the lateral orbitofrontal cortex. It includes a ventromedial sector of the caudate nucleus and a dorsomedial sector of internal pallidal segment. The limbic circuit, which has been previously described and which includes the ventral striopallidal system (Heimer and Van Hoesen, 1979), could also be implicated.

It should be emphasized that the functional correlations are rather well documented for the motor circuits, but not yet for the associative circuits. It has been shown that bilateral lesions in primates restricted either to the lateral orbitofrontal area or to the portions of the caudate to which it projects appear to result in a perseverative interference with an animal's capacity to make appropriate switches in behavioural set (Divac *et al.*, 1967; Mishkin and Manning, 1978).

There was, however, an associated involvement of the motor systems channelled by the globus pallidus in some of our patients. Cases 1, 2 and 5 presented in milder degree the same extrapyramidal symptoms as those reported in the literature in cases of pallidal damage (Grinker, 1926; van Bogaert, 1946; Martin, 1965; Klawans *et al.*, 1982; Jellinger, 1986).

The anatomicoclinical correlations of these observations present further difficulties due to the fact that brain lesions of similar location may induce neuropsychological disorders that are somewhat variable from one patient to another, as shown in Table 1. For instance, in Case 3 spontaneous activity was relatively preserved but performance on the Wisconsin Card Sorting test was very poor, verbal fluency was altered, affect was decreased, and anxiety and depression were absent. In contrast, in Case 5, activity was dramatically reduced, performance on the Wisconsin Card Sorting test was normal, verbal fluency was intact and strong anxiety and depressive elements were present. In spite of the fact that all the case reports shared the same global pattern, a detailed analysis reveals obvious differences. These facts might be explained by the modular organization of the frontal cortex and by the interdigitation of these modules (Goldman-Rakic, 1987*b*). According to this functional concept, a slight displacement of the lesion could produce a change in the modules under stimulation, and thus induce different disorders.

Relationships with psychiatric diseases

It is certain that the inertia, akinesia, and slowness seen in major depressive conditions can closely resemble the frontal-like syndrome following lesions of the lentiform nuclei. Some of our patients, in fact, were thought for a time to be

depressed and diagnostic confusion between certain frontal syndromes and depressive states is well known. The strict application of the DSM III criteria without taking into account all clinical aspects may lead to such errors. The principal difference between our patients (and, by extension, all cases with frontal syndromes) and depressed patients is the subjective absence of sadness and of anxiety. The clinical impression of similarity between depressive states and 'lenticular' syndromes is reinforced by some metabolic PET studies which have shown, in endogenous depression, the existence of hypometabolism predominantly in the frontal region of the left hemisphere which disappears as the patient improves (Phelps *et al.*, 1984). Equally, the similarities between negative forms of schizophrenia and frontal syndrome have been underlined in the literature, and PET studies have confirmed the existence of frontal hypometabolism in cases of schizophrenia, in spite of occasional contradictory evidence (*see* Buchsbaum, 1987, for a review). The existence of obsessive-compulsive disorders, however, constitutes the most novel of our observations, although it must be noticed that not all our patients exhibited these. The occurrence of such abnormal behaviour after basal ganglia damage has already been reported amongst the sequelae of encephalitis lethargica (Jelliffe, 1929) and in Parkinson's disease (Schwab *et al.*, 1951). Furthermore, the obsessive aspects of some activities in Gilles de la Tourette syndrome are well known (Frankel *et al.*, 1986) and several arguments support the hypothesis of basal ganglia lesions in this disease (Devinski, 1983). In spite of the similarities between our patients' lesions, not all displayed such behaviour. The behavioural disorder was marked in Cases 1, 5, 6, 7 and in the 2 cases of Ali-Cherif *et al.* (1984), and fitted the DSM III definition of obsessions and compulsions. In Case 2 it consisted of simple mental stereotypies, without compulsive characteristics. Case 1, moreover, displayed abnormal movements very similar to those observed in Gilles de la Tourette syndrome. Case 5 also showed abnormal movements which were remarkable, in that once started, she was unable to stop a repeated movement unaided. In this latter case, the disorder might be attributed to a lack of motor program inhibition, as described by Luria (1965) in 'frontal' patients whose lesions extended to the basal ganglia. In our observations, it would seem that patients were unable to inhibit some programs that were either purely mental or both motor and mental. There seems to be in this series of patients a continuity between the motor stereotypies, some resembling tics, the mental stereotypies, and the obsessive-compulsive behaviours proper. Since motor stereotypies can be clearly related to basal ganglia disorder, this continuity represents an additional argument for attributing the behavioural syndrome to the lentiform nucleus lesions and not to other lesions undetectable on available imaging techniques. Finally it is worthy of note that frontal lobe dysfunction has also been found in obsessive-compulsive disorder by physiological (Malloy, 1987) and PET metabolic studies (Baxter *et al.*, 1987). To conclude, the findings reported here constitute a model of well-defined cerebral lesions which seem able to induce behavioural abnormalities mimicking some psychiatric symptoms. It may be

heuristic to propose that they provide anatomical and physiological clues to the origin of some of the clinical aspects of the major psychiatric disorders.

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