

Review articles

Clinical contribution of PET neurotransmission imaging in neurological disorders

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Abstract

Imaging neurotransmission in vivo using positron emission tomography (PET) is a rapidly expanding clinical science. The present review summarizes the actual contribution of PET imaging to clinical problems in movement and seizure disorders and dementia.

Key words : Positron emission tomography ; dopamine ; serotonin ; acetylcholine ; GABA ; movement disorders ; seizure disorders ; dementia.

1. Introduction

Neurotransmitter systems can be directly imaged *in vivo* in humans using positron emission tomography (PET). PET involves introduction, usually via an intravenous injection, of a radioactive tracer into the human body. A tracer is essentially a biological compound of interest labelled with a positron emitting isotope, such as ^{11}C , ^{18}F , and ^{15}O . These isotopes are used because they have relatively short half-lives (minutes to less than two hours). The tracer used ideally has very high specific activity (ratio of radioactive to cold compound) such that only a very small amount (in the range of nanomoles to picomoles per gram) is administered. Therefore, the tracer will have minimal effect on the subject's biological system. Acquisition of data in the three dimensional (3D) mode using a state-of-the-art scanner greatly increases the spatial resolution of PET images (Spinks *et al.* 2000). The improved signal-to-noise ratio and the accompanying enhanced sensitivity of 3D PET scanners also allow a lower effective dose of radiation to be administered to subjects (1–5 mSv per scan compared with around 4 mSv administered in a head computed tomography (CT) scan). PET images taken with most modern scanners have a reconstructed spatial resolution of about 4 millimetres. Coregistration of PET images to high-resolution anatomical magnetic resonance images enables the accurate anatomical localisation of functional changes displayed on PET.

In addition to PET, single photon emission computerized tomography (SPECT) and magnetic resonance spectroscopy (MRS) can also be used to measure neurotransmitters activity *in vivo*. SPECT and MRS are less costly but the spatial resolution of these techniques is coarser than PET. MRS also has a low sensitivity in comparison with methods using radioactive tracers and it is clear that MRS has not yet reached the technical maturity of PET and SPECT.

This review mainly focuses on the clinical contribution of PET imaging in movement and seizure disorders and dementia. The usefulness of dopaminergic, serotonergic, cholinergic and GABAergic PET biomarkers to clinical problems is discussed. Although they might be considered as non-specific markers of neurotransmission, we do not address the clinical utility of cerebral glucose metabolism or blood flow measurements.

2. Movement disorders

2.1. PARKINSON'S DISEASE AND PARKINSONIAN DISORDERS

Although some aspects are still debated (Ravina *et al.* 2005), we review below evidence suggesting that neurotransmission imaging can be used for diagnosis, therapeutic monitoring and differential diagnosis of PD and parkinsonian disorders. Before turning to the various imaging types in detail and considering how these may be used it is useful to briefly consider the underlying pathology. The main pathology of the early stages of Parkinson's disease (PD) is the loss of the dopaminergic neurons that project from the lateral ventral tier of the substantia nigra *pars compacta* in the midbrain (Fearnley and Lees 1991) to the caudal part of the putamen in the forebrain (Kish *et al.* 1988). Hence, an imaging method with sensitivity to show degeneration in the nigrostriatal pathway, either cell body loss in the midbrain or terminal loss in the striatum will, in theory, identify abnormal dopaminergic innervation of the striatum. Patients with essential

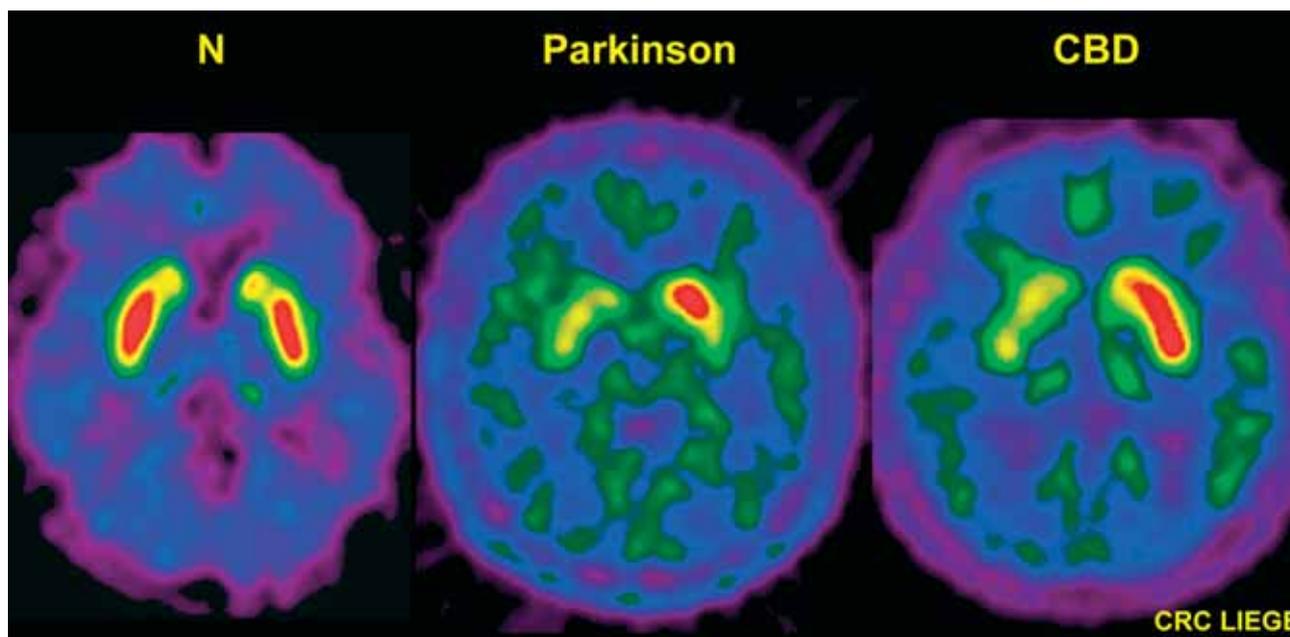


FIG. 1. — Presynaptic dopaminergic innervation of the striatum as assessed using ^{18}F -DOPA PET in a healthy subject (N), a PD patient (Parkinson) and a patient clinically diagnosed with corticobasal degeneration (CBD).

In both patients, the decrease in activity is more pronounced in the caudate and putamen contralateral to the most clinically affected body side. In the PD patient, there is also a loss of dopaminergic innervation in the posterior part of the ipsilateral putamen.

tremor (ET), “vascular”, drug-induced or psychogenic parkinsonism, or Alzheimer’s disease (AD) will have normal presynaptic dopaminergic innervation of the striatum. Thus, imaging techniques that distinguish normal from abnormal nigrostriatal innervation should help to rule out PD, but normal imaging does not differentiate between normality, ET, vascular parkinsonism, drug-induced parkinsonism, psychogenic parkinsonism and AD. By contrast, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), MPTP-induced parkinsonism and diffuse Lewy body dementia (DLBD)(with akinetic rigid features) – that share nigrostriatal degeneration as a common pathological feature – will have abnormalities in nigrostriatal pathway imaging. Imaging abnormal nigrostriatal innervation will thus differentiate PD, PSP, MSA, CBD, MPTP-induced parkinsonism and DLBD from normality. As a corollary, the use of dopaminergic neuroimaging to distinguish these disorders from each other is more complex (Fig. 1).

2.1.1. Early detection of PD

Of particular interest for patients, investigators, and pharmaceutical companies is the possibility of halting the process of degeneration and clinical deterioration. The first step is to detect PD at an early stage preferably prior symptoms onset. Because a pathological hallmark of parkinsonian disorders is a deficiency of DA (Hornykiewicz and Kish 1987), most imaging studies have focused on

studying the problem directly, using a variety of approaches. Dopaminergic neurons typically offer three sites to which biological compounds tagged with positron emitting isotopes can bind: 1) the dopamine transporter (DAT), which is mainly found on the plasma membrane of the dopamine terminal and is responsible for the reuptake of dopamine from the synaptic cleft; 2) the vesicular monoamine transporter 2 (VMAT2), which is located on the vesicular membrane and allows packaging of terminal dopamine into synaptic vesicles; and 3) the enzyme aromatic-amino-acid decarboxylase (AAAD), which is mainly inside the synaptic terminal and enables transformation of dopa to dopamine.

2.1.1.1. ^{18}F -DOPA PET

Measurement of 6- ^{18}F -fluoro-L-DOPA (^{18}F -DOPA) uptake is still regarded by many as the “gold standard” of DA imaging. As initially demonstrated by the group at McMaster University (Garnett *et al.* 1983), ^{18}F -DOPA is taken up by DA neurons, decarboxylated to fluorodopamine and stored in synaptic vesicles. Vesicular storage means that radioactivity is effectively “trapped” over the course of a scan lasting 90-120 minutes, and an influx constant (K_i) can therefore be calculated based on the relationship between activity in the tissue of interest (i.e. putamen) to the input function, derived either from arterial plasma or a region of reference tissue, typically occipital cortex (K_{occ}). It must, however, be remembered that K_i reflects a combination of processes, including tracer uptake

and passage across the blood-brain barrier, decarboxylation by the AAAD and vesicular storage. Furthermore, whereas the plasma radioactivity can be corrected for metabolites, this is not possible for the more widely used tissue input function, although this can be partially compensated for by administration of a catechol-O-methyltransferase (COMT) inhibitor prior to administration. Finally, there is some evidence to suggest that ^{18}F -DOPA uptake is not specific for DA neurons and can be taken up by other neurons expressing AAAD (Tison *et al.* 1991). Brown *et al.* (1999) carried out ^{18}F -DOPA PET studies in normal volunteers and concluded that, in addition to trapping of the compound in dopaminergic neurons, substantial accumulation in serotonergic and noradrenergic neurons occurred.

Despite any weaknesses in the method, the values derived from this approach have been shown to correlate with both nigrostriatal cell loss and striatal concentration of dopamine (Snow *et al.* 1993b ; Brooks *et al.* 2003).

Several studies have reported that by the time patients with sporadic PD present clinically, they have lost up to 50% of normal ^{18}F -DOPA uptake from the caudal putamen contralateral to the side with the most severe symptoms compared with 20-30% on the ipsilateral side (Morrish *et al.* 1995 ; Morrish *et al.* 1998). The caudate nucleus is affected later on (Rakshi *et al.* 1999). There is consistent evidence to suggest that the mean preclinical period of detectable ^{18}F -DOPA uptake reduction for the most affected part of the putamen is unlikely to be longer than seven years (Morrish *et al.* 1998 ; Nurmi *et al.* 2001 ; Hilker *et al.* 2005). Sectional studies in PD have shown a negative correlation between putamen ^{18}F -DOPA uptake and severity of some motor signs (Brooks *et al.* 1990b ; Otsuka *et al.* 1996).

Studies with 2D-PET have shown that ^{18}F -DOPA PET has an 85% sensitivity to detect early PD although there is an overlap between normal and abnormal putaminal uptake values (Morrish *et al.* 1995). In 3D-PET, there is a complete separation between normal and abnormal nigrostriatal values (Whone *et al.* 2002), particularly when absolute values in the caudal and dorsal putamen, the initial locus of striatal DA loss in PD, are compared. However, data providing positive and negative predictive values have not been published yet. The difference between normal and abnormal striatal uptake can be further proved by investigation of the asymmetry uptake between left and right putamen (Brooks 2000) and the degree of change of the putamen with that of the caudate (Rakshi *et al.* 1999).

When compared with patients with sporadic PD matched for clinical disease severity and duration, patients with familial PD have a similar reduction in posterior dorsal putamen ^{18}F -DOPA uptake but

generally have greater involvement of head of caudate and anterior putamen (Broussolle *et al.* 2000 ; Khan *et al.* 2002 ; Thobois *et al.* 2003). There is some evidence to suggest that at risk asymptomatic relatives of familial PARK6- and PARK2- linked early-onset PD patients have reduced striatal ^{18}F -DOPA uptake when compared to controls (Khan *et al.* 2002 ; Khan *et al.* 2005). Some of these patients went on to develop symptoms.

Clinical and ^{18}F -DOPA PET data are not always concordant. In the REAL PET study (Whone *et al.* 2003), 11% of previously untreated patients clinically classified PD with symptoms duration of 2 years or less had entirely normal ^{18}F -DOPA imaging. This level of discordance between early clinical diagnosis and dopaminergic imaging was also seen in another study (unpublished observations reported in (Piccini and Whone 2004)) and in a recent ^{123}I -beta-CIT SPECT investigation (Fahn *et al.* 2004). A further investigation into the clinical diagnosis of these patients is underway. As mentioned above, patients with ET or vascular parkinsonism would also be expected to have normal nigrostriatal innervation. To confirm that these patients do indeed have PD and that dopaminergic imaging was correct, post-mortem data would be required.

2.1.1.2. Other dopaminergic markers

As ^{18}F -DOPA, PET radiotracers that bind to either the DAT or the VMAT2 have been used as biomarkers of presynaptic dopaminergic activity. Most available DAT and VMAT2 ligands suffer from a relatively poor selectivity for DA transporters compared with other monoaminergic transporters. Nevertheless, these markers all display asymmetrical reduced striatal uptake in PD patients, with a rostro-caudal gradient as described above for ^{18}F -DOPA (Leenders *et al.* 1990 ; Frey *et al.* 1996 ; Davis *et al.* 2003).

It is important to emphasize that there is some evidence to suggest that DAT binding and ^{18}F -DOPA uptake are subject to compensatory changes in PD. In contrast VMAT2 does not appear to be subject to these potential confound (Vanderborgh *et al.* 1995 ; Wilson and Kish 1996). By performing concurrent scans with all three markers in patients with early PD, the Vancouver group found that DAT binding (as assessed using [^{11}C]-d-threo-methylphenydate) is reduced further than what would be expected from VMAT2 binding studies (as assessed using [^{11}C]-dihydrotrabazine)(Lee *et al.* 2000). In contrast, the degree of reduction in ^{18}F -DOPA uptake was not as great as would have been predicted by the decline in VMAT2 binding. These observations are compatible with compensatory upregulation of AAAD activity in early PD, as well as downregulation of DAT activity. Both changes would serve to maintain synaptic levels of DA in the face of nerve terminal degeneration. A

similar conclusion was reached by another group (Ribeiro *et al.* 2002). The corollary of these findings is that while PET scans with DAT ligands may be more sensitive to early changes in PD, they may overestimate the degree of dysfunction and may not be as helpful for studying disease progression, because of confounding compensatory changes. Similarly, ^{18}F -DOPA PET may underestimate the degree of dopaminergic denervation. Finally, the effect of antiparkinsonian medications themselves on ^{18}F -DOPA uptake and DAT binding is unclear (Zhu *et al.* 1993 ; Cho *et al.* 1997 ; Cumming *et al.* 1997 ; Nurmi *et al.* 2000 ; Guttman *et al.* 2001 ; Ceravolo *et al.* 2002).

2.1.2. Monitoring progression of PD

Imaging presynaptic dopaminergic activity can be used to monitor progression of PD (Brooks *et al.* 2003) and can be helpful in studies examining the effects of various interventions such as neuroprotective therapies or transplantation.

Morrish *et al.* (1998) estimated an annual rate of decline of 4.7% of the normal mean for ^{18}F -DOPA uptake in the putamen of 32 PD patients using a graphical analysis method when repeated scans were performed over an 18-month period. In a five year study, Nurmi *et al.* (2001) estimated reduced ^{18}F -DOPA uptake of 10.3, 8.3, and 5.9% of the baseline mean per year for posterior putamen, anterior putamen, and caudate, respectively. In addition to technical issues such as tomograph resolution, the ability to separate caudate from putamen, and the analysis method chosen, another factor that may influence this estimate is disease duration with more rapid decline observed in patients studied early after symptoms onset (Hilker *et al.* 2005).

However, clinical and imaging estimates of disease progression are not always concordant. In two longitudinal studies testing the neuroprotective effect of ropinirol and pramipexol against levodopa in PD – the REAL PET study (Whone *et al.* 2003) and the CALM-PD-CIT study (Parkinson Study Group 2002), respectively – imaging was used as a biomarker of the loss of nigrostriatal dopaminergic nerve-terminal function. In the REAL-PET study, there was a 13.4% reduction in ^{18}F -DOPA uptake at 2 years in the ropinirol group compared with the 20.3% in the L-DOPA group. Despite this apparent reduction in loss of presynaptic dopaminergic function, the motor Unified Parkinson's Disease Rating Scale (UPDRS) score increased by 0.7 in the ropinirol group compared to a reduction of 5.6% in the L-DOPA group. In the CALM-PD-CIT study, there was a reduced rate of decline of ^{123}I -beta-CIT uptake over the course of the study in the pramipexol group compared to the L-DOPA group. However, clinical severity scores were worse in the dopamine agonist group than in the L-DOPA group at 2 years, and similar at 4 years. Thus, in both

studies, there is a discrepancy between imaging and clinical findings, emphasizing the need for caution when interpreting studies with incongruous results.

^{18}F -DOPA PET has also been used in restorative trials as a biological marker of response to treatment. The clinical improvement seen in PD patients receiving human fetal mesencephalic tissue transplantation or intraputamenal infusion of glial cell line derived neurotrophic factor (GDNF) is accompanied by increases in striatal K_i (Brooks and Piccini 2000 ; Gill *et al.* 2003). At the post-mortem examination of two PD patients with transplants, who died from unrelated causes, increased striatal ^{18}F -DOPA uptake was associated with the survivals of grafts and dopaminergic reinnervation of the striatum (Kordower *et al.* 1995). "Off" phases of dyskinetic involuntary movements observed in some PD patients following transplantation procedures are not associated with abnormal increases in ^{18}F -DOPA uptake suggesting that this side effect does not result from excessive growth of grafted dopaminergic neurons (Hagell *et al.* 2002).

2.1.3. Dyskinesia in PD

It has been suggested for many years that the complications associated with long-term treatment of PD may reflect alterations in dopamine receptors. However, PET studies have in general substantiated the findings of post-mortem neurochemical analyses, which have failed to demonstrate significant differences associated with fluctuations in motor function or levodopa-induced dyskinesia (Turjanski *et al.* 1997b). When dyskinetic and nondyskinetic patients were studied with ^{11}C -diprenorphine PET, the former showed a significant reduction in striatal and thalamic opioid site availability suggesting a role for opioid transmission in motor fluctuations (Piccini *et al.* 1997). Recent findings from an ^{11}C -raclopride PET study of levodopa-induced changes in striatal dopamine levels suggest that presynaptic mechanisms may play a key role in the emergence of peak-dose dyskinesias in PD (Fuente-Fernandez *et al.* 2004).

2.1.4. Differential diagnosis of parkinsonian disorders

Differentiating various types of parkinsonian disorders clinically can be difficult especially in the early stages of the disease. In a clinico-pathological study, diagnosis accuracy for PD was around 75%, 25% of patients clinically diagnosed with PD had PSP, MSA, AD, or vascular disease on post-mortem exam (Hughes *et al.* 1992). More recently, a similar investigation by the same researchers found a higher diagnostic accuracy for PD (90%), suggesting that clinicians are becoming more adept at interpreting atypical clinical features (Hughes *et al.* 2001). In the more recent study, MSA

accounted for most false positives. However, the suggested 90% diagnostic accuracy for PD represents a best-case scenario. All of the patients had died, and the physicians making a prospective clinical diagnosis therefore had the benefit of witnessing end-stage disease. The number of false positive and false negative diagnoses is likely to remain significant, especially in the early stages of the disease, where the clinical features to discriminate parkinsonian disorders are mild or absent.

PD, PSP, MSA, CBD, and DLBD (with akinetic rigid features) share nigrostriatal degeneration. As described in more details below, the use of dopaminergic imaging to distinguish these disorders from each other is complex. The pattern of impaired cerebral glucose metabolism measured using ¹⁸fluorodeoxyglucose (¹⁸FDG) PET might also be useful to differentiate among parkinsonian disorders (Garraux *et al.* 2000) but this is beyond the scope of this review. It is important to emphasize that follow-up studies and series comparing *in vivo* imaging with subsequent post-mortem examination are mandatory to establish the exact sensitivity and specificity of neuroimaging findings in regard with the final diagnosis.

2.1.4.1. Changes in presynaptic dopaminergic function in parkinsonism

As described by Fearnley et Lees (1991), the pattern of pathological changes across the substantia nigra in PD is highly conserved and commences in the lateral ventral tier. Change in this nigral region will produce early dopaminergic loss in caudal putamen (Kish *et al.* 1988). In PSP and MSA, nigra cell body change is more extensive and nigral projections to the caudate nucleus become involved earlier in the course of the disease (Fearnley and Lees 1990 ; Daniel *et al.* 1995). The pathological difference in the degree of caudate nucleus involvement can be identified *in vivo* using ¹⁸F-DOPA PET. Several studies with this technique have shown that in patients with PSP, MSA and CBD, mean ¹⁸F-DOPA uptake in the posterior putamen is decreased to concentrations comparable to those of patients with PD with similar disease duration but that caudate nucleus uptake is more affected (Brooks *et al.* 1990a ; Sawle *et al.* 1991a ; Burn *et al.* 1994). We found, however, that some CBD patients studied at a relatively early stage may show, as in PD, reduced ¹⁸F-DOPA uptake in putamen with relatively preserved caudate uptake (Laureys *et al.* 1999).

Although the power of ¹⁸F-DOPA PET to differentiate between typical (e.g. Parkinson's disease) and atypical (e.g. parkinsonian syndromes) forms of parkinsonism has been suggested to be about 70% (Brooks *et al.* 1990a), overlap exists and more recent investigations indicate that ¹⁸F-DOPA measurements are not able to distinguish between different forms of parkinsonism (Antonini *et al.*

1997 ; Ghaemi *et al.* 2002).

2.1.4.2. Changes in postsynaptic dopaminergic function in parkinsonism

Since assessment of presynaptic dopamine terminal integrity within the putamen only partly differentiates between PD and other parkinsonian syndromes, radiotracers have been used in order to assess other indices of dopaminergic function. One difference in striatal pathology between PD and parkinsonism shown by post-mortem investigations is the presence of postsynaptic abnormalities in Parkinson plus syndromes.

Postsynaptic changes in the nigrostriatal pathway have traditionally been studied using ligands of dopaminergic receptors. Increased levels of ¹¹C-raclopride binding, a ligand of dopaminergic D2/D3 receptors, has been observed in early PD (Rinne *et al.* 1995). However, interpretation of studies performed using ¹¹C-raclopride, might be problematic as the binding of this particular ligand to the receptors is subject to competition with endogenous DA (Laruelle 2000). This means that the increased levels of ¹¹C-raclopride binding seen in early PD could reflect receptor upregulation in response to denervation, but could also be an artifact due to dopamine depletion. The former seems more likely, given that similar increases are seen following scans performed with [¹¹C]-N-spiperone, which is not prone to competition with dopamine (Kaasinen *et al.* 2000).

In contrast to the situation in PD, a significant reduction in D2 receptor binding is usually observed in PSP and MSA (Brooks *et al.* 1992 ; Ghaemi *et al.* 2002)(figure 2) and a 100% separation between PD and MSA was achieved by the use of putaminal ¹¹C-raclopride binding (Antonini *et al.* 1997). Despite the ability of D2 receptor binding to separate PD from PSP and MSA, decreased binding will be seen in both the latter 2 disorders and therefore D2 imaging alone will not separate these 2 parkinsonian syndromes from each other. Future studies should clarify the clinical utility of dopaminergic receptor binding measurements in extrastriatal regions using high affinity ligands.

2.1.4.3. Sympathetic cardiac innervation

Depending on the definition used, orthostatic hypotension (OH) occurs in 20-50% of PD patients (Micieli *et al.* 1987 ; Hillen *et al.* 1996 ; Senard *et al.* 1997). If OH is early and prominent with respect to the movement disorder, this may indicate a different disease such as a parkinsonian form of MSA (MSA-P). One way to distinguish PD from MSA-P has been to monitor the clinical response to levodopa but some patients with MSA-P do show improvement with levodopa (Wenning *et al.* 1997) so that in practical terms this distinction does not always suffice.

Many studies have shown that most patients

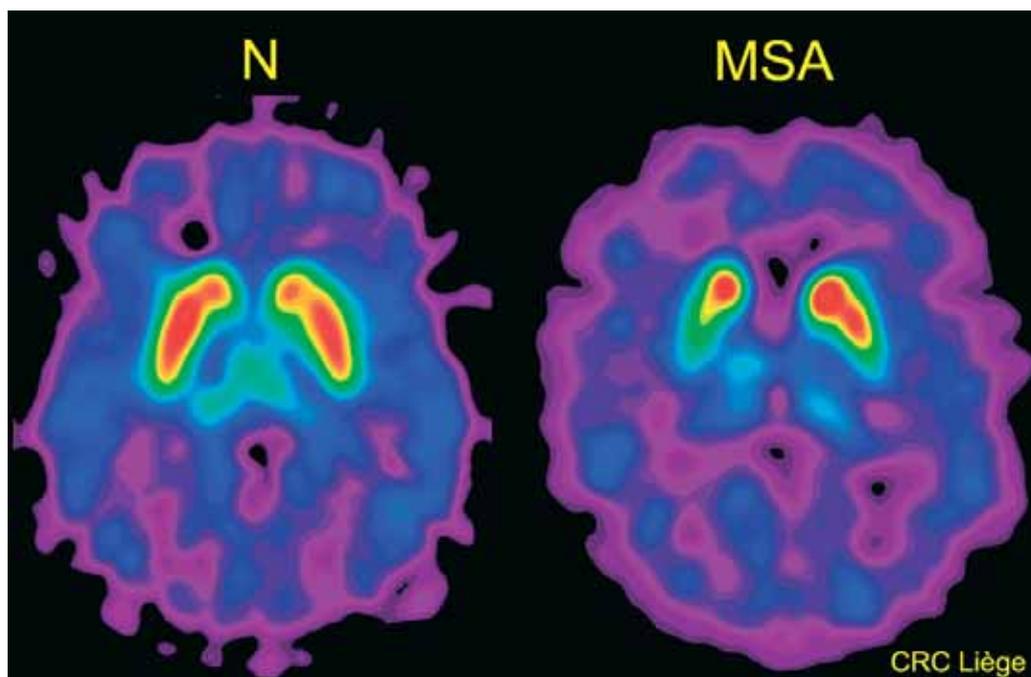


FIG. 2. — Postsynaptic dopaminergic innervation of the striatum as assessed using [^{18}F]-tropapride PET in a healthy subject (N) and a patient clinically diagnosed with multiple system atrophy (MSA). In the patient, D2 receptor binding is decreased in caudal putamen, bilaterally.

with PD have at least a partial loss of sympathetic innervation of the heart as indicated by low myocardial concentration of radioactivity after injection of sympathoneural imaging agents (Langer and Halldin 2002) such as ^{123}I -metaiodobenzylguanide (Sato *et al.* 1999) and ^{18}F -dopamine (Li *et al.* 2002). This occurs even in the absence of clinical features suggesting autonomic failure at an early stage of the disease (Takatsu *et al.* 2000). On the contrary, there is evidence to suggest that patients with MSA with or without orthostatic hypotension have intact cardiac sympathetic innervation, as measured by sympathetic neuroimaging (Braune *et al.* 1999). Hence, imaging cardiac sympathetic denervation can be used in differential diagnosis between PD and MSA.

Importantly, this has received validation by autopsy pathology (Orimo *et al.* 2001 ; Orimo *et al.* 2002). In addition to their diagnostic value, these findings support the hypothesis that PD features a postganglionic sympathetic noradrenergic lesion whereas MSA-P does not.

It has been suggested that reduced uptake of sympathoneural imaging agents is exclusive for PD (Sato *et al.* 1999 ; Taki *et al.* 2000) but this needs further evaluation as limited uptake might also occur in other movement disorders such as Machado-Joseph disease (Kazuta *et al.* 2000) and dementia with Lewy bodies (Saiki *et al.* 2004).

2.2. POSTTRAUMATIC AND POSTENCEPHALITIC PARKINSONISM

Posttraumatic encephalopathy (PTE) is charac-

terized by a combination of upper motor neuron, basal ganglia, cerebellar, and psychiatric disturbances. A “striatal” variant, with predominant post-traumatic parkinsonism (PTP), is uncommon and may be difficult to distinguish from idiopathic PD. When evaluated using ^{18}F -DOPA PET, PTP patients showed decreased striatal uptake with putamen and caudate equally affected as opposed to relative sparing of caudate function in PD (Turjanski *et al.* 1997a).

Results from ^{18}F -DOPA PET studies in postencephalitis parkinsonism are conflicting. Some have disclosed reduced striatal uptake with a rostro-caudal gradient similar to PD (Lin *et al.* 1995 ; Caparros-Lefebvre *et al.* 1998) whereas others have shown decreased striatal uptake with putamen and caudate equally affected (Ghaemi *et al.* 2000).

2.3. MPTP-INDUCED PARKINSONISM

The small group of drug addicts in the United States who injected a bad batch of “synthetic heroin” around 1982 had no idea that some of them would develop a Parkinson’s disease-like illness within weeks (Langston *et al.* 1983). It transpired that the chemist who had made the offending drug had unwittingly synthesised 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which proved to be a potent and specific nigral toxin (Przedborski and Vila 2003).

Clinically, MPTP-induced parkinsonism may be almost indistinguishable from PD with bradykinesia, rigidity, impaired postural reflexes, sometimes tremor, and a neuropsychological deficit similar

to PD (Stern *et al.* 1990). Some others who escaped from parkinsonism in the aftermath of their exposure have gone on to develop clinical parkinsonism years later, suggesting that a transient exposure to a toxin can cause progressive nigral pathology (Vingerhoets *et al.* 1994). Some clinical signs might be dopa-responsive, at least in the earlier stages of illness. A few incapacitated patients underwent fetal cell implantation (Widner *et al.* 1992). Aged monkeys treated chronically with MPTP have been reported to have inclusions in nigral dopaminergic neurons that are reminiscent of Lewy bodies (Forno *et al.* 1993). However, the post-mortem distribution of the striatal dopaminergic deficit in human MPTP parkinsonism has not yet been described in the literature (Langston *et al.* 1999).

In 1985, Calne and coll. were the first to demonstrate low striatal ^{18}F -DOPA uptake in subjects who had been exposed to MPTP (Calne *et al.* 1985). Using a higher resolution tomograph, Snow *et al.* (2000) reported an equal decrement of tracer uptake in the caudate and putamen. This contrasted with the greater putaminal loss seen in a group of patients with PD. They also found less asymmetry of uptake than in patients with PD. However, a complicating factor to consider when interpreting these data is the known variability in the pattern of striatal involvement in MPTP animal models according to the dosing schedule used.

2.4. CHOREA

Huntington's disease (HD) is an autosomal dominant disorder arising from expanded CAG repeats in the IT15 gene on chromosome 4. HD is predominantly characterized pathologically by a loss of medium spiny striatal neurons, which express dopamine D1 and D2 receptors. Striatal D2 binding, as measured using ^{11}C -raclopride PET, decreases by approximately 5% per year in HD, and the reduction correlates with the duration and clinical severity of the disease (Pavese *et al.* 2003). Assessment of VMAT2 binding in rigid and choreic patients showed reduced binding in both groups (Bohnen *et al.* 2000). However, much greater decreases in all areas of striatum were seen in rigid compared with choreic patients. The authors interpreted this as suggestive of nigrostriatal pathology in HD, particularly in the rigid type.

Although HD can be diagnosed accurately using genetic tests, there is, as yet, no reliable way to predict disease onset in presymptomatic carriers. Several PET studies have found reduced striatal D2 binding in some HD carriers (Weeks *et al.* 1996 ; Antonini *et al.* 1996). Large trials are ongoing to ascertain the accuracy of PET in identifying carriers nearing the onset of disease since intervention at this early stage with putative neuroprotective agents may be of greater benefit than treatment in later stages.

In neuroacanthocytosis, Brooks *et al.* (1991) reported normal caudate and anterior putaminal ^{18}F -DOPA uptake in 6 patients, but reduced uptake in posterior putamen. In this study, striatal D2 receptor binding was also reduced.

2.5. DYSTONIA

Dopa-responsive dystonia (DRD) or Segawa disease is a disorder of functional dopamine deficiency typically characterized by the onset of gait disorder in children with diurnal variations. Recognition of the genetic basis for the disorder has expanded the recognizable clinical phenotype to include onset of parkinsonism in adulthood or onset of focal dystonia such as writer's cramp. The disorder has been characterized by (most often) a deficiency of guanosine triphosphate (GTP) cyclohydrolase I (Ichinose *et al.* 1994). This results in the loss of tetrahydrobiopterin, which is a cofactor for tyrosine hydroxylase, required for the synthesis of dopamine. Many mutations exist. Patients usually demonstrate an excellent response to low-dose levodopa, and this response is often used as a diagnostic test.

Imaging the presynaptic dopaminergic system might be useful in differentiating DRD patients from PD patients, especially those with young-onset PD (YOPD). In contrast to PD, striatal uptake of ^{18}F -DOPA was found to be normal or moderately decreased in both symptomatic and asymptomatic DRD patients (Sawle *et al.* 1991b ; Nygaard *et al.* 1992 ; Snow *et al.* 1993a). An uncommon late onset parkinsonism clinical phenotype of DRD was found to have normal ^{18}F -DOPA uptake and thus could also be differentiated from PD (Takahashi *et al.* 1993). This reflects the fact that in DRD, the abnormality is upstream to decarboxylation of dopa, and suggest that vesicular storage of dopamine and nerve terminal themselves are intact.

D2 receptor binding has been measured in symptomatic DRD patients and asymptomatic gene carriers using ^{11}C -raclopride PET (Kishore *et al.* 1998). All patients showed elevated ^{11}C -raclopride binding in the striatum, with no differences between groups. Kunig *et al.* (1998) performed a similar study but found, in comparison with PD patients, elevation of binding in the caudate nucleus of DRD patients.

2.6. TOURETTE'S SYNDROME

Tourette's syndrome is characterized by motor and vocal/phonic tics with an onset usually prior to 21 years of age. Tics can be accompanied by emotional or behavioural disorders [(i.e. attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD)]. Many aspects of the pathophysiology of TS remain unclear and both the site(s) and nature of the initial dysfunction are

still unknown. Because patients typically respond to medications that deplete or block dopamine receptors, it has been assumed that there may be a relative increase in dopaminergic innervation of the striatum. Increased right ventral striatal ^{14}C -dihydrotrabenazine binding to VMAT2 has been recently demonstrated in patients with TS (Albin *et al.* 2003) but this abnormal ventral striatal dopaminergic innervation in TS should receive validation by other studies.

3. Seizure disorders

Complex partial seizures remain uncontrolled in a significant proportion of patients despite optimal medical therapy. Surgical removal of epileptic foci in partial seizures such as medically intractable temporal lobe epilepsy (TLE) results in significant improvement in the control of seizures and quality of life. The main clinical use of functional neuroimaging in epilepsy is the localisation of the epileptogenic foci in potential surgical candidates with intractable focal epilepsy and corroborating findings from other investigational modalities such as electroencephalographic recordings (Sadzot 1996). Although one of the most widely used imaging approach in preoperative evaluation of such patients is periictal perfusion SPECT and the technique of composite ictal subtraction perfusion SPECT coregistered to MRI (SISCOM)(Van Paesschen 2004), this review rather focuses on the clinical usefulness of measuring specific neurotransmitter systems.

3.1. TEMPORAL LOBE EPILEPSY

The majority of patients referred for epilepsy surgery have TLE, and 60% of these have hippocampal sclerosis (Babb *et al.* 1984). MRI has been reported to be normal in 15–30% of patients with TLE, even when histopathological examination of resected specimens detects hippocampal sclerosis, focal cortical dysplasia or other pathologies (Chugani *et al.* 1990 ; Kuzniecky *et al.* 1991 ; Desbiens *et al.* 1993). In the absence of identifiable pathology on imaging, surgery in TLE patients has a less favourable outcome (Berkovic *et al.* 1995). Thus, while patients with TLE and normal MRI represent a relatively large and important group in epilepsy centres, they are less likely to undergo surgery.

PET imaging has been employed to evaluate various neurotransmitter systems in patients with epilepsy. Initial studies focused on benzodiazepine receptor imaging. GABA is the principal inhibitory neurotransmitter in the brain, acting at the GABA_A receptor complex. Flumazenil (FMZ) is a specific, reversibly bound high-affinity antagonist at the benzodiazepine site of the GABA_A receptor (Olsen *et al.* 1990), which is expressed by most neurones.

^{11}C -FMZ was shown to be a useful *in vivo* marker of GABA_A receptor binding (Maziere *et al.* 1984).

In TLE patients who have hippocampal sclerosis on MRI, Koepp *et al.* (1997) have shown that ^{11}C -FMZ binding is reduced (Fig. 3) over and above hippocampal volume loss. Correlation analysis of autoradiography and quantitative neuropathology in resected hippocampi also revealed a greater reduction in FMZ binding than in neuronal cell density (Hand *et al.* 1997) and good correlation between *in vivo* ^{11}C -FMZ PET and ^3H -FMZ autoradiography (Koepp *et al.* 1998). Collectively, these results suggest that ^{11}C -FMZ PET may be more sensitive than MRI in the identification of subtle hippocampal abnormalities.

In practice, ^{11}C -FMZ-PET is most useful in situations where MRI is equivocal or normal. Hammers *et al.* (2002) recently investigated 18 patients with refractory temporal lobe epilepsy and normal MRI using ^{11}C -FMZ-PET. Sixteen patients showed abnormalities in temporal lobe ^{11}C -FMZ binding, in seven of whom the findings were concordant with clinical and EEG data. Three patients subsequently underwent anterior temporal lobe resection with significant clinical improvement. Neuropathological findings from the surgical specimens from these patients suggest that some abnormalities seen on ^{11}C -FMZ PET are likely to be due to microdysgenesis, which is not often detected with optimal anatomical MRI.

Studies in experimental models have suggested a potential role for serotonergic transmission in epilepsy. Central 5-HT_{1A} receptors are found in high density in the brainstem raphe and in regions important for TLE, including the hippocampus and temporal neocortex (Varnas *et al.* 2004). Clinical interest in this research has been increased by the development of PET ligands that can be used to study 5-HT_{1A} receptors such as [^{18}F]FCWAY (Carson *et al.* 2000) and [^{18}F]p-MPPF (Plenevaux *et al.* 2000). Results from 2 independent PET studies using these ligands provided some evidence to suggest that TLE patients including those with medically intractable TLE show decreased temporal 5-HT_{1A} binding (Toczek *et al.* 2003 ; Merlet *et al.* 2004). However, further validation and development is needed to establish the potential clinical value of this imaging approach in such patient groups (Theodore 2003).

3.2. EXTRATEMPORAL LOBE FOCAL EPILEPSY

Individuals with medically intractable extratemporal lobe epilepsy (ETLE) represent groups of especially challenging patients in whom the success of cortical resection is highly dependent on the accurate presurgical delineation of the region(s) responsible for generating seizures. With advanced MRI techniques, malformations of cortical development (e.g., cortical dysplasia) are being increas-

ingly recognized as structural substrates of epileptogenicity in neocortical epilepsy. Despite this, MRI results are considered as normal in a considerable number of potential candidates for epilepsy surgery. In such cases, especially when surface EEG is poorly localizing, failure to delineate the epileptogenic cortex accurately leads to suboptimal surgical results.

As in patients with TLE, functional neuroimaging techniques are widely used to lateralize and localize epileptogenic cortical areas when no focal lesion can be detected using anatomical MRI. ^{11}C -FMZ PET was found to be significantly more sensitive than ^{18}F FDG PET in detecting cortical regions of seizure onset and frequent interictal spiking (as defined by intracranial EEG) in children with extratemporal lobe epilepsy (Muzik *et al.* 2000). Importantly, decreased ^{11}C -FMZ binding was highly correlated with the seizure onset zone (Muzik *et al.* 2000; Arnold *et al.* 2000). In another study, resection of cortex with ^{11}C -FMZ binding abnormalities in the lobe of seizure onset was associated with excellent outcome even in the absence of a structural lesion whereas extensive cortical abnormalities on ^{11}C -FMZ PET predicted poor outcome (Juhász *et al.* 2001). Furthermore, in the same study it has been shown that in some ETLE patients with normal MRI and nonlocalizing scalp EEG findings, ^{11}C -FMZ PET can be successfully used to guide placement of intracranial EEG electrodes.

PET using [^{11}C]-alpha-methyl-L-tryptophan (AMT), a tracer developed to measure serotonin synthesis, has been found clinically useful in some patients after an initial failed epilepsy surgery for medically intractable ETLE. Reoperation in such patients can alleviate seizures provided that previously nonresected epileptic regions are accurately defined and removed. The clinical value of ^{11}C -AMT PET to detect nonresected epileptic foci was examined in a recent study conducted in 33 young patients with a previously failed neocortical resection (Juhász *et al.* 2004). All 7 patients with localizing ^{11}C -AMT PET, who underwent reoperation, became seizure free or showed considerable improvement of seizure frequency suggesting that ^{11}C -AMT PET can assist in planning reoperation of patients with previously failed neocortical epilepsy surgery.

4. Dementia

Alzheimer's disease (AD), which remains the most common cause of dementia in all age groups, is a progressive neurodegenerative disorder that is characterized from a neuropathological viewpoint by the presence of amyloid deposition and neurofibrillary tangles together with the loss of cortical neurons and synapses (Terry *et al.* 1991). Postmortem studies suggest that the hippocampus and entorhinal cortex are the first brain areas to be affected – at

least by neurofibrillary pathology – with cortical association areas being increasingly involved as the disease progresses (Hyman *et al.* 1984; Braak and Braak 1991; Hyman *et al.* 1991; De Lacoste and White, III 1993). Recent serial brain imaging during longitudinal neuropsychological studies indicate that significant neuronal and synaptic loss might already occur from an early stage. In addition to these cortical changes, subcortical neuronal loss occurs, for example in the nucleus basalis of Meynert, raphe nucleus and in the locus coeruleus, resulting in a decrease in cortical levels of cholinergic, serotonergic and noradrenergic markers, respectively (Bondareff *et al.* 1982; Whitehouse *et al.* 1982; Mann *et al.* 1984; Francis *et al.* 1999; Lyness *et al.* 2003; Hendricksen *et al.* 2004).

Individuals with mild cognitive impairment (MCI) have memory impairment of unknown etiology, but their general cognitive function is normal and activities of daily living are intact. Amnesic MCI patients are at risk for developing dementia, and the rate of conversion to dementia (usually to AD) has varied between 6% and 25%, being usually around 12–15% annually (Petersen *et al.* 2001). Thus, a considerable number of people with MCI may have early AD changes in the brain.

Neurochemical imaging techniques for detecting dementing disorders are currently far from use in the average day-to-day clinical practice. In fact, the oldest and most prevalent “metabolic imaging” of the brain, ^{18}F FDG PET, can detect a very early stage of AD (Minoshima *et al.* 1997) (figure 4) and does allow certain differential diagnoses among dementing disorders (Salmon *et al.* 1994).

Because of the involvement of the cholinergic system in AD, tracers developed to measure changes in presynaptic and postsynaptic cholinergic functions have been intensively studied (Volkow *et al.* 2001). Acetylcholine (ACh) is synthesized by condensation of acetyl-CoA and choline mediated by the enzyme choline acetyltransferase (ChAT). Following synthesis, ACh is transported into synaptic vesicles via the vesicular ACh transporter (VAcHT). After release in the synaptic cleft, ACh signalling is terminated by enzymatic breakdown to choline and acetate by acetylcholinesterase (AChE). Microscopically, there are some non-cholinergic neurons that express AChE, but for the purpose of *in vivo* imaging of the brain, AChE activity serves as an indicator of cholinergic neurons and terminals.

Although there are no currently available radiotracers for ChAT, there are radiotracers for VAcHT and AChE, both having been shown to map acetylcholine cells in the brain and to have a reasonable correspondence with ChAT (Mesulam and Geula 1992; Weihe *et al.* 1996). Cortical binding of [^{125}I]IBVM, an analog of vesamicol that binds to the VAcHT, was reduced in AD patients, and the reduction predicted dementia severity (Kuhl *et al.*

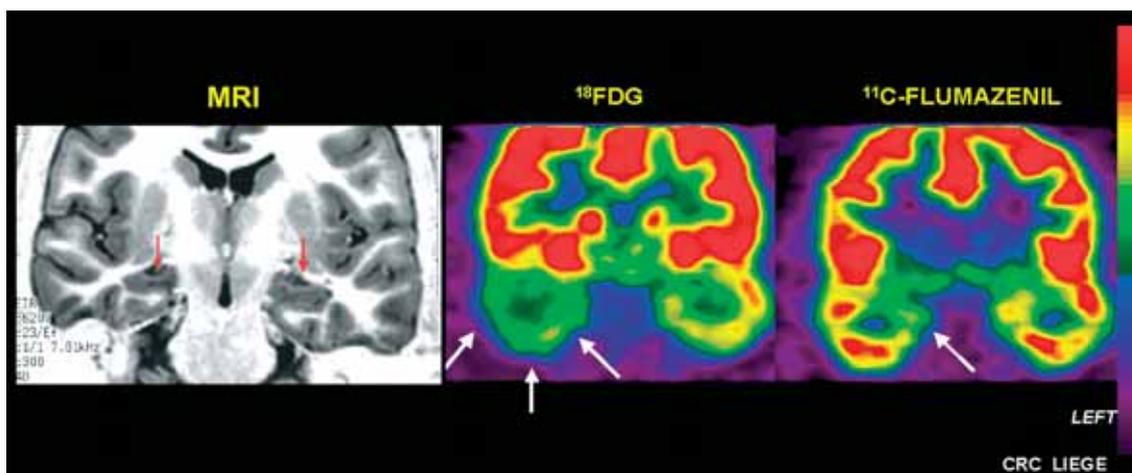


FIG. 3. — Brain imaging in a patient with right TLE.

T1-weighted MRI, interictal ^{18}F -FDG- and ^{11}C -flumazenil- PET data are displayed in coronal view. On PET images, note that the area of decreased activity is restricted to right medial temporal lobe structures on ^{11}C -flumazenil-PET whereas it spreads to the lateral part of the temporal cortex on ^{18}F -FDG-PET (white arrows). The pseudocolor scale corresponds to the relative activity measured on PET images (Courtesy Prof. B. Sadzot).

1996). The binding levels were also related to the age of disease onset ; patients with an age of onset of < 65 years had reductions throughout the cortex and hippocampus (approximately 30%), whereas patients with an age of onset of > 65 years had reductions only in the temporal cortex and hippocampus.

Cortical AChE activity has been mainly evaluated using labelled ACh analogs that serve as substrates for AChE and are hydrolyzed to a hydrophilic product that is trapped in the cell (Kuhl *et al.* 1999 ; Herholz *et al.* 2000). Using ^{11}C -PMP-PET, a piperidyl derivative, one group showed *in vivo* that AChE activity was reduced in moderate AD. The cortical distribution of changes was homogeneous, however, and did not correlate with ^{18}F -FDG PET findings (Kuhl *et al.* 1999). In MCI patients, findings are somewhat controversial. Rinne *et al.* (2003) reported only modest reduction of AChE activity in the hippocampus, which was not statistically different from that of controls. Using the same compound, Vandenberghe *et al.* (2004) found a decrease in AChE activity in left medial temporal cortex and this was considered statistically significant. These controversial findings would be consistent with recent post-mortem measurements, which indicated that cholinergic depletion might not be a major feature of very early AD (Davis *et al.* 1999 ; Tiraboschi *et al.* 2000 ; Dekosky *et al.* 2002). Alternatively, AChE is located in both cholinergic and cholinergic (non-cholinergic) neurones and it has been noted that people with AD may display an almost normal density of acetylcholinesterase-rich cholinergic perikarya in regions of the cortex that show severe loss of acetylcholinesterase-rich axons (Mesulam 2000). Thus, in early AD, ligands reflecting ACh

synthesis could be more useful in the early diagnosis than those reflecting AChE activity.

ACh exerts its signalling action at two major classes of receptors, the muscarinic (MACHR) and nicotinic (NACHR) cholinergic receptors. MACHR predominates in the CNS. *In vivo* studies have included measures of both muscarinic and nicotinic receptors (Nordberg *et al.* 1990 ; Yoshida *et al.* 1998 ; Zubieta *et al.* 2001) but this has not yet been shown to be of clinical use.

Serotonergic cells in the brain stem are lost in AD (Lyness *et al.* 2003 ; Hendricksen *et al.* 2004). To the best of our knowledge, there are no available *in vivo* neuroimaging studies in AD patients on serotonin transporter (SERT), which allow to visualize the density of serotonergic axon terminals. A PET study of serotonergic 5-HT₂ receptors in AD using ^{18}F -setoperone showed a significant loss of 5-HT₂ receptors in the cerebral cortex, particularly in the frontal and temporal cortices (Blin *et al.* 1993). PET of 5-HT₂ receptors using ^{18}F -altanserin showed a significant loss of binding in AD in comparison to late-life depression (Meltzer *et al.* 1999) and possible correlation with behavioural aspects of the disease (Meltzer *et al.* 1998). Because relatively high or very high densities of 5-HT_{1A} receptors are found in pyramidal cells of the hippocampal formation and in entorhinal cortex (Varnas *et al.* 2004) and that these areas are affected earlier and more severely by AD compared to other regions, future studies should test the clinical utility of [^{18}F]FCWAY or [^{18}F]p-MPPF PET in assessing dementia.

Observations of postmortem specimens indicated the presence of immune responses in AD brains (McGeer *et al.* 1989). The involvement of a complement pathway and microglial activation was

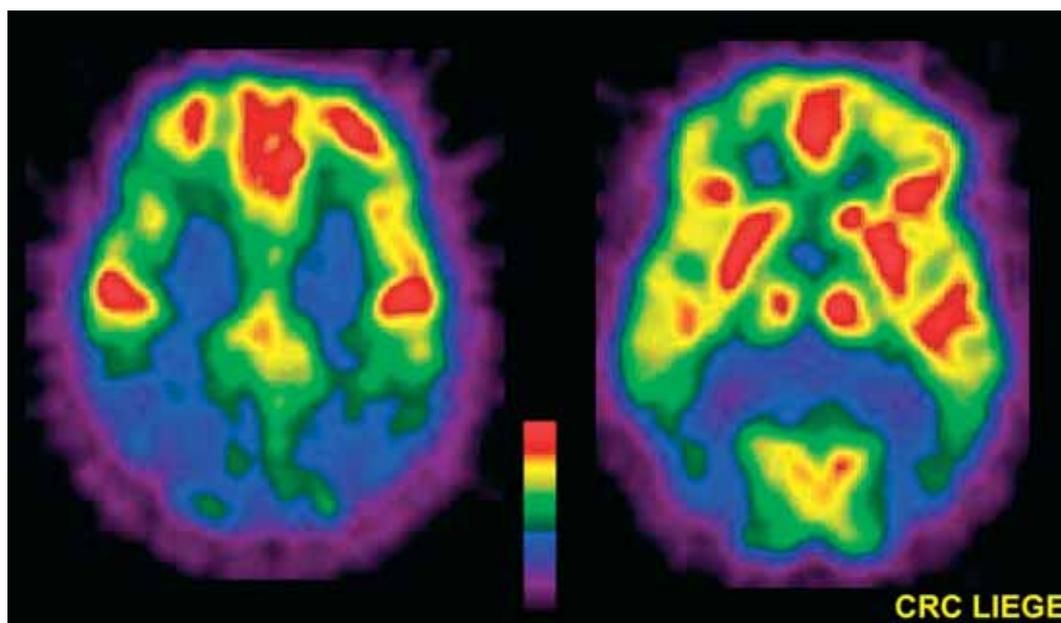


FIG. 4. — ^{18}F FDG-PET in an AD patient.

These 2 axial slices illustrate the characteristic decrease in glucose metabolism in posterior association cortices (including posterior cingulate areas) and middle prefrontal regions. Note that the metabolism in primary (sensori-motor and visual) cortices and basal ganglia is relatively preserved. The pseudocolor scale corresponds to the relative activity measured on PET images.

speculated to be one of the possible mechanisms of neuronal death in AD (McGeer *et al.* 1987 ; McGeer and Rogers 1992). PK11195 is a specific ligand for a receptor known as the peripheral benzodiazepine binding site. Whereas only a small number of peripheral benzodiazepine receptors are expressed in normal brain parenchyma, this receptor can be expressed on activated microglia in the brain (Banati *et al.* 1997). Labelled with carbon-11, PK11195 can be used as a ligand for PET. An initial PET study using ^{11}C -PK11195 showed no detectable alteration in patients with mild-to-moderate AD (Groom *et al.* 1995). However, a subsequent study using the enantiomer, (R)-PK11195, showed significantly increased binding in the entorhinal cortex, temporoparietal cortices, and posterior cingulate cortex in patients with mild and early AD (Cagnin *et al.* 2001a). This tracer thus provides an exciting opportunity for investigators to examine immune responses in AD as well as in other neurodegenerative (Gerhard *et al.* 2001 ; Gerhard *et al.* 2004 ; Turner *et al.* 2004) and neuroinflammatory disorders (Banati *et al.* 2000 ; Cagnin *et al.* 2001b) and possible responses to anti-inflammatory drug treatments of these disorders.

Another development in functional imaging relates to the final pathological hallmark of AD : amyloid plaques. All of the genetic mutations that have so far been associated with autosomal dominant AD modulate amyloid metabolism. This suggests that amyloid metabolism is an important pathogenic factor in AD and, as such, amyloid imaging might be an important biomarker for trials

of disease-modifying agents. Several compounds have been developed for the imaging of amyloid : radiolabelled amyloid-peptide (A) antibodies and peptide fragments ; small molecules (such as derivatives of Congo red, thioflavin, stilbene, and acridine) for PET and SPECT imaging ; and compounds for MRI. The first *in vivo* human study of the novel amyloid-marking tracer 'Pittsburgh Compound-B' (PIB) was recently published and suggested a similar pattern of cerebral uptake to the distribution of amyloid deposition in histopathological studies (Klunk *et al.* 2004). In cortical areas, PIB retention correlated inversely with cerebral glucose metabolism determined with ^{18}F FDG PET. Further studies evaluating the longitudinal changes in amyloid deposition and its topographical distribution *in vivo* are awaited with interest. In the future, amyloid imaging as a biomarker might provide presymptomatic detection and allow studies of disease progression and should be used to assess the effectiveness of anti-amyloid therapy, such as vaccination. However, there are still limitations to amyloid-imaging technology and further validation and development is needed for routine clinical assessment.

5. Conclusions

Imaging neurotransmission is a rapidly expanding clinical science and its application to clinical problems is increasing at a fast pace. These are exciting times for both the clinical neurologist and the functional neuroimaging scientist. A growing

exchange of information between clinicians and specialists in imaging will be of benefit not only to neurological patients but also to a more complete understanding of the strengths and weaknesses of molecular imaging techniques as applied to clinical populations.

Acknowledgements

GG is research associate at the 'Fonds National de la Recherche Scientifique' (FNRS). This work was also supported by grants from the 'Fonds Medical Reine Elisabeth' (FMRE).

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