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Invited review

Emission tomography contribution to clinical neurology

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Abstract

The role of functional neuroimaging techniques in furthering the understanding of pathophysiological mechanisms of neurological diseases and in the assessment of neurological patients is increasingly important. Here, we review data mainly from emission tomography techniques, namely positron emission tomography (PET) and single photon emission computerized tomography (SPECT), that have helped elucidate the pathophysiology of a number of neurological diseases and have suggested strategies in the treatment of neurological patients. We also suggest possible future developments of functional neuroimaging applied to clinical populations and briefly touch on the emerging role of functional magnetic resonance imaging (fMRI) in clinical neurology and neurosurgery.

Keywords: Positron emission tomography; Single photon emission computerized tomography; Neurological diseases; Pathophysiology

1. Introduction

Emission tomography techniques, i.e. positron emission tomography (PET) and single photon emission computerized tomography (SPECT) can effectively and non-invasively measure cerebral metabolism (CMR) and cerebral blood flow (CBF). Their role in advancing our understanding of pathophysiological mechanisms of neurological diseases and in the clinical assessment of patients with these disorders is expanding.

PET provides a quantitative assessment of the main physiologic variables directly involved in the coupling of CMR and CBF in health and disease and it also provides information on other important physiologic variables in the central nervous system, such as neurotransmitters, receptors, pH and neuronal density. Also, neuronal functions can be studied with PET by means of activation of cerebral areas with sensory, motor, or cognitive tasks (Frackowiak et al., 1997).

SPECT can measure the distribution of CBF, cerebral blood volume (CBV), and receptor activity and is based on tomographic principles akin to PET. However, the spatial resolution is coarser than PET and the use of single-photon emitters (e.g. ^{133}Xe, ^{99m}Tc, ^{123}I) hampers the exact quantitation, due to their particular energy spectrum and their propensity to be scattered or attenuated. Furthermore, the fact that isotopes used in SPECT are not those of naturally occurring elements (e.g., N, O, C) makes it difficult to incorporate these isotopes into compounds so that they behave in a natural biochemical fashion in the nervous system. SPECT, however, is a simpler and more widely available technique than PET and can be applied to clinical populations more easily than PET.

The tracers most frequently used in PET are $H_2^{15}O$, measuring regional CBF, ^{18}F-2-deoxyglucose (^{18}FDG-PET), measuring cerebral glucose metabolism, and receptor ligands of dopamine, benzodiazepines, and opiates. In SPECT, the most widely used tracers to study CBF are perfusion agents such as ^{99m}Tc-hexamethylene-propylene-amine-oxime (^{99m}Tc-HMPAO) and ^{99m}Tc-bicisate (ECD).

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Receptor ligands for dopaminergic, benzodiazepine and muscarinic receptor are also used.

The goal of the present review is to focus on the contribution to clinical neurology of PET and SPECT. We will mainly summarize PET and SPECT data that are relevant to the understanding of the pathophysiological basis of neurological diseases, and may be useful for designing therapeutical interventions. We will briefly refer to studies using functional magnetic resonance imaging (fMRI), a rapidly evolving technique that may find wide and useful clinical application in the near future. Methodological issues, that have recently been summarized elsewhere (Toga and Mazziotta, 1996), will not be addressed here.

2. Cerebrovascular diseases

2.1. Brain Ischemia

In physiological conditions there is a matching of local values of CBF, CMR for oxygen ($CMRO_2$), and cerebral blood volume (CBV), according to linearly proportional relationships. The local CBF reliably reflects the prevailing local $CMRO_2$ (Lebrun-Grandie et al., 1983; Sette et al., 1989). This perfusion-to-metabolism coupling also applies to CMR for glucose (CMRGlu), with a stoichiometric relationship that indicates an almost exclusive oxidative glycolysis.

When the cerebral perfusion pressure (CPP) falls and there is a reduction of CBF, compensatory mechanisms are activated, with increases in CBV and in the oxygen extraction fraction (OEF). This has been termed 'misery perfusion' (Baron et al., 1981), and indicates cerebral tissue that maximally extracts nutrients from the reduced blood flow. This initial phase of 'oligoemia' is clinically silent. It becomes brain 'ischemia' when the compensatory mechanisms are exhausted. The $CMRO_2$ therefore falls precipitously, with first a reversible impairment of neuronal function (the 'ischemic penumbra'), then an irreversible one (Fig. 1).

Since the phenomenon of autoregulation is based on vasodilatation of resistance vessels to counteract reductions in CPP, altered CBV would be expected to accompany such changes in cerebrovascular resistance. Imaging both CBF and CBV allows computation of a ratio that reliably reflects the CPP and provides an index of the 'haemodynamic reserve', i.e. the capacity of the resistance vessels to vasodilate in response to a decrease in CPP, as in stenosis or occlusion of the major cerebral arteries (Gibbs et al., 1984). To assess the vasodilatory capacity of the brain, agents such as CO_2 (inhalation of 5% CO_2 in air) and acetazolamide (Vorstrup et al., 1987) can be used. Both PET and SPECT have been used to evaluate the changes in CBF after injection of acetazolamide, that in normal brain induces marked CBF increases. A blunted or even absent response indicates brain regions with an already vasodilated (autoregulated) vascular bed, despite normal perfusion at rest. Paradoxical decreases in CBF may even occur in areas that have an already exhausted reserve (so-called 'haemodynamic steal').

PET studies have indicated CBF and $CMRO_2$ thresholds separating structurally intact areas from necrotic ones. Gray matter with $CMRO_2$ below 1.4 ml/100 g per min, when assessed more than 2-6 h after stroke, is generally associated with infarction. Above this threshold, however, the tissue is ischemic but viable, a phenomenon called 'reversible ischemia' or 'ischemic penumbra', that may represent a pathophysiological counterpart of the 'therapeutic window' (Lassen et al., 1991). Finally, the tissue can be relatively hyperperfused and is characterized by an oxygen supply, through the local blood flow, in excess of demand: the OEF is thus reduced. This type of uncoupling has been termed 'luxury perfusion', and, in contrast to 'misery perfusion', indicates re-establishment of perfusion, and hence of the CPP, through the spontaneous (or therapeutically induced) lysis of an embolus that caused the ischemia. CBF may be increased (true hyper-perfusion) or normal or even decreased, but is consistently in excess of $CMRO_2$. CBV is also increased in hyperperfused areas (Frackowiak, 1985; Marchal et al., 1996).

Accordingly, three main CBF-$CMRO_2$ patterns have been observed with PET in acute stroke patients. Pattern 1 is characterized by a large area of profoundly depressed CBF and $CMRO_2$, suggesting established extensive infarction or necrosis. Pattern 2 is characterized by a moderately to markedly reduced CBF but a normal or relatively preserved $CMRO_2$, except possibly in a small and often deeply seated area; this pattern reflects ongoing ischemia with limited infarction, possibly as a result of adequate cortical collaterals. Pattern 3 is characterized by hyperperfusion with either normal $CMRO_2$, or a very limited area of profound hypometabolism; this pattern reflects early spontaneous reperfusion with only limited damage during arterial occlusion (presumably due to adequate collaterals). Patterns 1 and 3 invariably predict poor and good outcome, respectively. The outcome of Pattern 2 is unpredictable, ranging from tissue death to full recovery. The predictive value of PET findings has been shown to be superior to that of neurological scales, especially so for intermediate severity scores (Marchal et al., 1995). In particular, the volume of non-infarcted penumbral tissue strongly correlates with subsequent neurological recovery (Furlan et al., 1996) (Fig. 2).

These PET findings are relevant to the planning of therapeutic trials. Indeed, patients presenting with pattern 1 are expected to show poor clinical outcome regardless of therapy, so that erroneous conclusions may be drawn about potential efficacy. These patients may, however, benefit from anti-oedema therapy, because oedema itself will cause a decrease in perfusion around an ischemic core. In contrast, patients with pattern 3 show a good outcome even without therapy, e.g. in a 'placebo' arm of a trial, causing a 'ceiling' effect that again affects statistical evaluation of the

treatment. Pattern 2, i.e. high OEF and low CBF with relatively preserved $CMRO_2$, characterizes patients who would be expected to benefit maximally from therapy with neuroprotective agents. Since this pattern has been rarely observed up to 18 h after stroke onset, the concept of a rigid (for instance, < 6 h) therapeutic window may have to be reconsidered (Baron et al., 1995).

Acute stroke has been investigated with SPECT and ^{99m}Tc-HMPAO. In the vast majority of patients focally reduced tracer uptake has been observed, the extent of which is proportional to the severity of neurological deficit. Marked hypoperfusion correlates with large infarctions and poor neurological outcome (Limburg et al., 1991; Giubilei et al., 1990; Hanson et al., 1993). SPECT studies in acute stroke have been used in clinical trials to evaluate thrombolysis (Alexandrov et al., 1997). Extensive reperfusion of previously hypoperfused tissue at 24-36 h has generally been associated with better outcome, although not all reperfused cases necessarily show a good outcome, whereas all cases without reperfusion have poor neurological outcome.

Finally, patients with transient ischemic attack (TIA) have been studied with PET and SPECT both during and after attacks. Outside the attack, a reduced CBF with misery-perfusion was observed in a patient with previously documented carotid artery occlusion that was later corrected by external carotid artery (EC-IC) bypass surgery, with reversal of the metabolism-to-blood flow imbalance (Baron et al., 1981). During the phase of clinical signs and symptoms, patients with TIA have shown depression of cerebral perfusion with SPECT (Perani et al., 1987). However, the percentage of TIA patients with chronic misery-perfusion is small, thus substantiating the notion that the large majority of stroke patients do not have persistent near ischemic CPPs (Hartmann, 1985).

2.2. Remote effects of brain ischemia

Remote effects, i.e. focal or diffuse coupled metabolic and perfusion decreases far from the site of lesion, are frequently described in stroke patients. These remote effects are commonly explained by depression of synaptic activity at sites distant from, but neurally connected with (either directly or transneurally) the damaged area. Although they are often referred to collectively as ‘diaschisis’, this term conceals a variety of cellular derangements, from reversible hypofunction to evolving degeneration, with similar PET and SPECT expressions (Feeney and Baron, 1986). Since some of these effects may represent purely functional (i.e. potentially reversible) trans-synaptic derangement, and thus may participate in both the acute clinical expression of, and the subsequent recovery from stroke, they have attracted considerable interest over the years.

The first, and best known, ‘remote effect’ is crossed cerebellar hypoperfusion-hypometabolism (CCH), also termed ‘crossed cerebellar diaschisis’ (Baron et al., 1980). This depression of both CBF and $CMRO_2$ occurs in about 50% of cases following either cortical or subcortical stroke, in the cerebellar hemisphere contralateral to a supratentorial lesion (Pantano et al., 1986). It is due to damage of cortico-ponto-cerebellar pathways, inducing transneural functional depression. CCH is loosely correlated with both the presence and severity of hemiparesis. Although CCH shows no consistent tendency for recovery, it does recover in a fraction of stroke patients (Perani et al., 1987). Clinical correlates of CCH have been demonstrated both in the acute and in the chronic phase of stroke. All patients without CCH in the acute phase of stroke had a good clinical outcome at 2 months (Serrati et al., 1994). In patients studied up to a year after stroke, CCH was still present in many patients with poor recovery due to prolonged muscular flaccidity (Pantano et al., 1995; Pantano et al., 1996).

In patients with acute stroke, a depression of contralateral hemisphere metabolism (and blood flow) has been correlated with the patients’ level of consciousness (Lenzi et al., 1982; Heiss, 1983), but seems not predictive of recovery (Iglesias et al., 1996). Subcortico-cortical diaschisis has been reported in patients with aphasia and small, deep infarcts. Different, independent studies have reported a correlation between the severity of language impairment and the severity of hypometabolism, and that the recovery of language is paralleled by improvement of cortical metabolism and perfusion (Baron et al., 1986; Metter et al., 1988; Vallar et al., 1988). A similar pattern has been observed in patients with left hemineglect due to subcortical lesions (Vallar et al., 1988).

2.3. Recovery after stroke

Many PET and SPECT studies have addressed the mechanisms of recovery after stroke (Chollet et al., 1991; Weiller et al., 1992; Weiller et al., 1993; Pantano et al., 1996), all these approaches aimed at establishing relationships between the individual lesion, the amount of recovery and the pattern of effective reorganization. These reports are improving our understanding of neural plasticity and may eventually be of use in the daily management of stroke patients in the recovery phase. For instance, the emerging role of the ipsilesional hemisphere in functional recovery from stroke may have significance for developing new rehabilitation procedures, and for selecting patients for different rehabilitation strategies according to specific blood flow patterns.

2.4. Haemodynamics

PET and SPECT studies have clearly documented that a tight stenosis or the occlusion of the internal carotid artery (ICA) (or of the middle carotid artery (MCA)) may have haemodynamic consequences on the distal cerebral vascular bed that are related to the efficacy of the compensatory blood supply from the circle of Willis. The haemodynamic effects observed extend from a reduced vasodilatory capa-

city to CO_2 or acetazolamide, to true oligemia with abolished vasodilatory capacity and occasional hemodynamic steal. All these effects are, as expected, perfusion pressure-dependent.

The clinical correlates of these haemodynamic changes are sometimes straightforward, but in most cases it is difficult to establish their relationship to clinical events. Haemodynamic abnormalities can affect asymptomatic subjects or the asymptomatic hemisphere. Several controversies have surrounded the assessment of the clinical efficacy of EC-IC bypass (Samson et al., 1985). However, recent studies have indicated that when cerebrovascular reactivity is severely impaired, there is an increased risk of ipsilateral stroke, despite the 'best available' medical treatment (Webster et al., 1995). It has been shown that successful cerebral revascularization by means of either carotid endarterectomy or EC-IC bypass reverses, fully or in part, the pre-operative haemodynamic impairment, when present (Baron et al., 1981; Gibbs et al., 1987; Muraishi et al., 1993; Schmiedek et al., 1994). This observation shows that impairment results largely from arterial obstruction and not from distal bed disease such as in watershed micro-embolic angiopathy. It is important to take into account that a long-lasting severe impairment of autoregulation of the cerebral circulation will be a risk factor for poor clinical outcome in both surgically and medically treated patients. In particular, the occurrence of systemic hypotension should be avoided, be it due to surgical procedures or to medical therapy. Conversely, because embolic events may have more serious tissue consequences in a dysregulated vascular bed than they would in a normal brain, medical measures to prevent embolism should be considered, together with careful evaluation of compliance to therapy in patients who are often cognitively impaired.

3. Migraine

The pathophysiological aspects of migraine headache have been extensively investigated with techniques measuring regional CBF changes. The relevance of CBF studies in migraine headache with respect to the two main pathophysiological theories, the vascular theory and the spreading depression theory, will be addressed in this section.

Most of the early CBF observations were made on patients in whom a migraine attack was induced by carotid artery puncture (Olesen et al., 1981). The pattern of blood flow changes during an induced attack of migraine, was typically described as follows. A decrease in CBF is first observed in posterior regions of the brain. The CBF decrease generally precedes the beginning of the symptoms (aura) and spreads anteriorly at the rate of approximately 2–3 mm/min (Olesen et al., 1981; Lauritzen et al., 1983). This 'spreading oligaemia' continues while the aura symptoms disappear and migraine headache develops. Eventually, after 2–6 h from the onset of hypoperfusion, some previously hypoperfused cerebral areas show increased blood flow, outlasting headache (Olesen et al., 1990). This pattern of hypoperfusion has been typically observed in patients with migraine headaches and aura, and the magnitude of CBF decrease was estimated in these early studies around 20–25%, with some small areas of greater hypoperfusion, almost reaching ischemic levels. The side of the headache generally corresponds to the side of blood flow changes, whereas the aura symptoms are typically contralateral to the hypoperfusion. Note that the pattern of spreading oligaemia, as observed by these early studies (Olesen et al., 1981; Lauritzen et al., 1983), does not match large artery territories. Note also that both normoperfused and hypoperfused territories show intact autoregulation mechanisms, i.e. variations in arterial blood pressure do not affect CBF. Taken together, these findings argue against the notion that CBF changes during migraine are due to arterial vasospasm.

Although the symptomatology of an induced migraine attack is similar to the symptomatology of spontaneous migraine, some minor differences might, in principle, suggest that the underlying pathophysiological mechanisms are not identical and therefore, the blood flow changes during induced attacks may not be generalizable to spontaneous occurrences of migraine. Indeed, patients rushed to hospital at the onset of a spontaneous migraine attack are reported to show large areas of hypoperfusion that do not spread (Lauritzen and Olesen, 1984). These data suggest caution in associating spreading hypoperfusion observed in induced migraine with the pathophysiological mechanism of spontaneous migraine headache. However, a simple explanation for the lack of spreading hypoperfusion in spontaneous attacks, is that patients with spontaneous migraine were studied much later than patients with induced migraine, relative to the onset of symptoms.

A much more robust objection to the spreading pattern of hypoperfusion in migraine headache is that, as observed in the early investigations (Olesen et al., 1981; Lauritzen et al., 1983), it can be influenced by technical artifacts, in particular Compton scatter (an overestimation of hypoperfusion due to neighbouring normoperfused areas) (Skyhøj-Olsen and Lassen, 1989). Although Compton scatter may be an important factor in rCBF estimates using the ^{133}Xe intracarotid technique (but see Dalgaard et al., 1991 for a challenge to this objection), it is likely that scattered radiation has minimal, if any, influence on rCBF estimates obtained with PET. The high resolution and sensitivity of PET has always been considered ideal to study CBF changes during migraine. Practical considerations, however, have limited its use in migraine investigations. Recently, some PET evidence has provided new insights into the pathophysiology of migraine headache (Diener and May, 1996).

During a PET activation study, investigating visual recognition processes in the normal brain, a volunteer developed a spontaneous migraine (Woods et al., 1994). The symptoms came on after the sixth of twelve planned PET

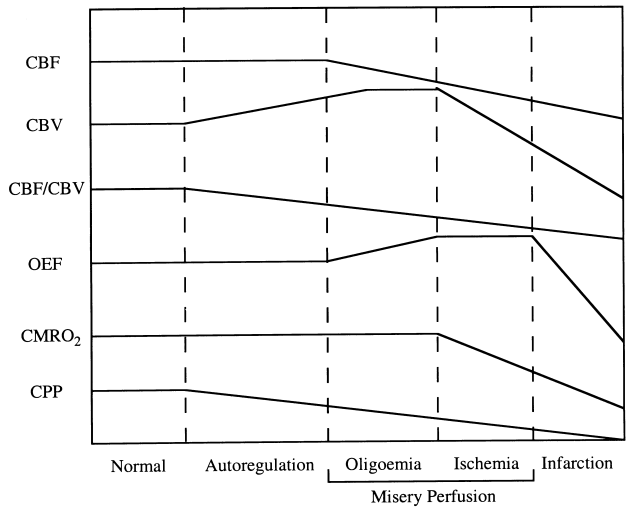


Fig. 1. Qualitative changes during brain ischemia in cerebral blood flow (CBF), cerebral blood volume (CBV), CBF/CBV ratio, oxygen extraction fraction (OEF), cerebral metabolic rate for oxygen ($CMRO_2$), and cerebral perfusion pressure (CPP). The graph should not be interpreted quantitatively. Dashed lines divide the stages of normal blood flow, metabolism coupling, autoregulation, misery perfusion comprising oligoemia and ischemia (or penumbra), and infarction. OEF increases when vasodilation no longer compensates at CBF/CBV ratio of about 5-6 (Gibbs et al., 1984).

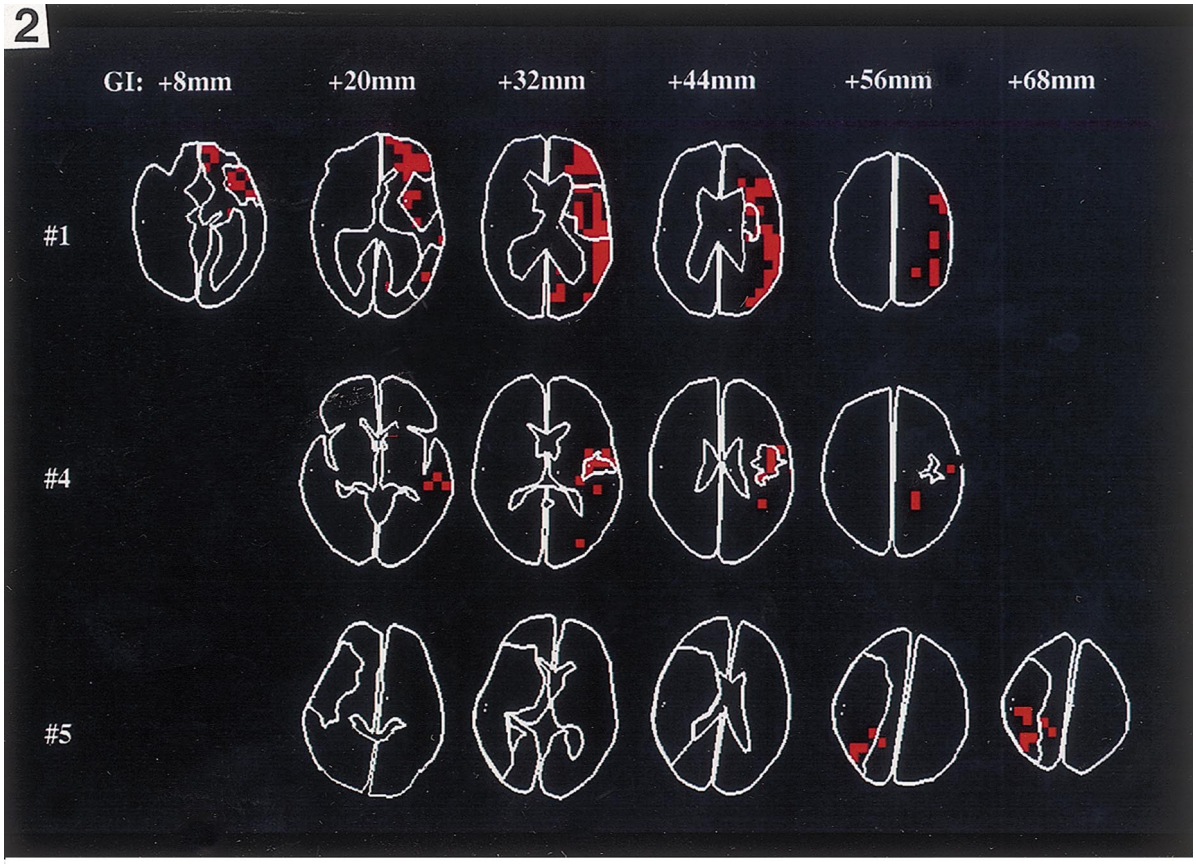
scans, made every 15 min. The headache was described as a sharp pain in the back of the head, that worsened over the next hour and that was associated with photophobia and nausea, but not with a clear aura. The seventh scan showed the first measurable rCBF decreases, starting in visual association areas and spreading anteriorly in subsequent scans at an estimated rate of ~1–2 mm/min, compatible with the spread of symptoms in patients with migraine and aura (Lashley, 1941), with the spreading oligaemia observed in early studies (Lauritzen et al., 1983), and with cortical spreading depression (CSD) (Leão, 1944; Leão, 1945). The spreading hypoperfusion encompassed the territory of four major cerebral arteries, sparing some cerebral structures within the same arterial territories, such as the basal ganglia, the thalamus, and the cerebellum. The magnitude of rCBF decrease was estimated around 40%, approaching ischemic levels. These decreases were, however, short-lasting and gradual reperfusion was observed starting from the scan following maximal rCBF decrease (Fig. 3).

Two features of these PET observations are important for understanding the pathophysiology of migraine headache. First of all, given the characteristics of the PET methodology used in the study (Woods et al., 1994), there is no basis for invoking technical artifacts as the cause of the observed pattern of spreading hypoperfusion. Second, the patient did not report symptoms resembling a typical aura. Note that the early rCBF studies showed that a spreading pattern of hypoperfusion was generally not seen in patients with migraine without aura. This observation suggests that spreading hypoperfusion is a common feature of migraine with or without aura, and that the most likely phenomenon underlying the spreading rCBF decreases is CSD. The only typical feature of CSD that was not observed by Woods et al. (1994) was the narrow band of hyperperfusion that generally precedes spreading hypoperfusion. However, given that this hyperperfused band can be as narrow as a few millimeters, PET spatial resolution limitations may have prevented such observation. fMRI techniques may be able to experimentally address this issue. For instance, they have been used to effectively visualize propagating waves of CSD in animals (Gardner-Medwin et al., 1994; Hasegawa et al., 1995) and to detect changes in CBF and CBV during spontaneous migrainous aura (Cutrer et al., 1998). The latter study, however, failed to show a narrow band of hyperperfusion preceding hypoperfusion and also failed to show a spreading pattern of hypoperfusion in 3 out of 4 patients. This may suggest that fMRI sensitivity in detecting blood flow changes associated with CSD is magnetic field-dependent. Indeed, the studies in animals (Gardner-Medwin et al., 1994; Hasegawa et al., 1995) were performed at higher magnetic fields than the 1.5 T used by Cutrer et al. (1998).

In another PET study, rCBF during spontaneous migraine (within 6 h of onset of symptoms), after the relief of headache by sumatriptan, and in a headache-free period, have been compared in 9 patients (Weiller et al., 1995). Higher rCBF during migraine was observed contralaterally to the side of the hemicrania in the nuclei of the dorsal raphe and in the locus coeruleus, than during a headache-free interval and after relief from headache. These findings suggest that the brain-stem nuclei showing rCBF increases are ‘migraine generator nuclei’ and that cortical spreading hypoperfusion might be mediated by the extensive serotonergic projections supplying small cortical blood vessels (Reinhard et al., 1979; Edvinsson et al., 1983). This hypothesis, however, predicts a topographical correspondence between dorsal raphe nuclei and cortical areas. In contrast, retrograde-labeling techniques seem to suggest only a coarse topographic relationship between dorsal raphe nuclei and cerebral cortex (Wilson and Molliver, 1991). Further, the PET study of Weiller et al. (1995) was performed much later than the study of Woods et al. (1994), relative to the onset of the symptoms, and it is not clear whether the rCBF increases in

Fig. 2. The volume of non-infarcted penumbral tissue correlates with neurological recovery. Three patients with good (top row), intermediate (middle row) and poor (bottom row) neurological recovery. Reprinted with permission from Furlan et al., 1996.

Fig. 3. Spreading of hypoperfusion as observed in serial PET scans. Initial involvement in red. The graph shows the time-activity profiles of the areas showing maximal blood flow decreases in each scan. Gradual reperfusion is observed after maximal decrease. Reprinted with permission from Woods et al., 1994.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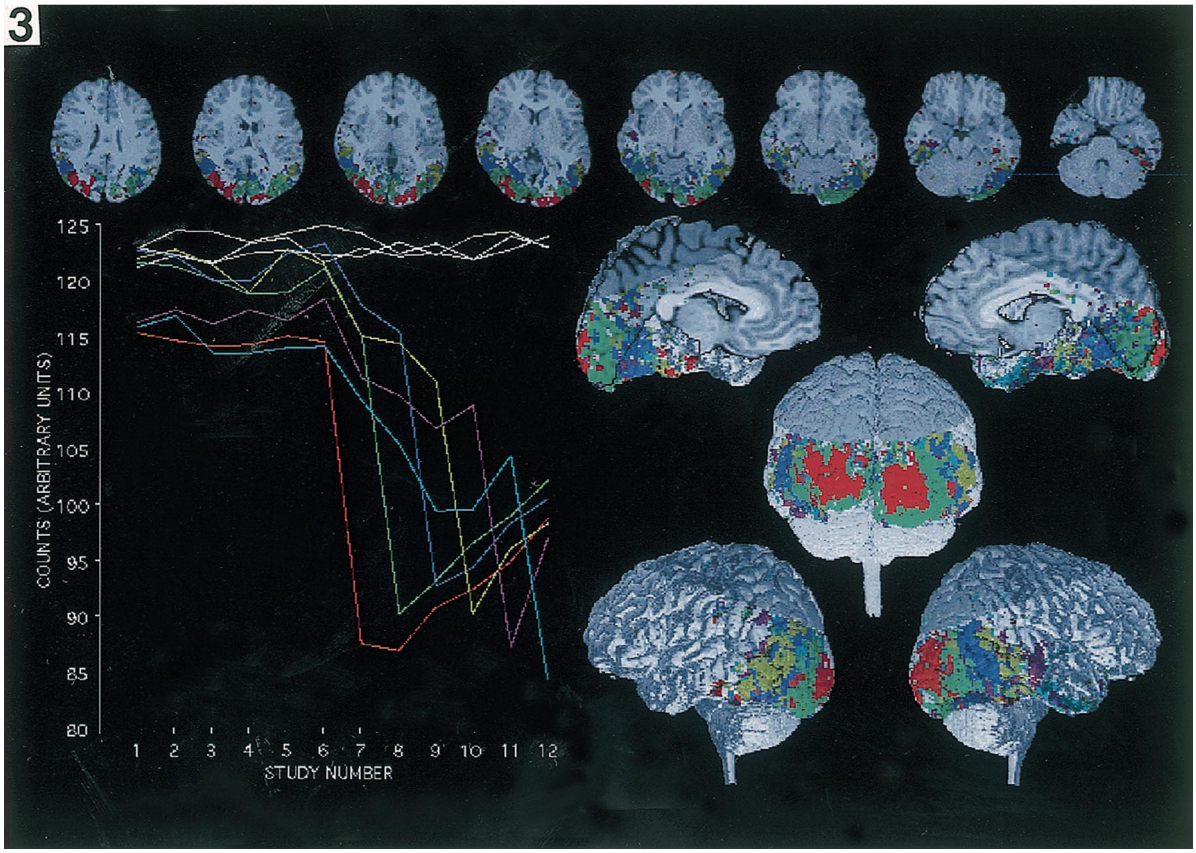
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brain-stem nuclei occur at the very beginning of a migraine attack.

In summary, new insights into pathophysiological mechanisms of migraine headache have been provided by emission tomography techniques that measure CBF changes. New techniques with better spatial and temporal resolution than PET, such as fMRI, can now provide further evidence that will help our understanding of the pathophysiology of migraine and most importantly, assess experimentally the mechanisms of action of anti-migraine drugs. This ability might be of use in selecting specific treatments for individual migrainous patients.

4. Tumors

PET and SPECT have found clinical applications in the non-invasive assessment of cerebral neoplasms. Tumors have an accelerated rate of glycolysis that co-exists with adequate oxygenation. There is also a correspondence between the rate of tumour metabolism and the growth rate of individual malignant cells (Weber, 1977). ^{18}FDG-PET has confirmed this finding in human gliomas: in virtually all grade III and IV gliomas there are 'hot spots' of hypermetabolism, while such areas are only rarely seen in low-grade (I and II) tumors (Di Chiro et al., 1982; Di Chiro et al., 1987). Given that tumour histology correlates with survival, the metabolic grading of gliomas has prognostic value. In keeping with this finding, in a series of 45 consecutive patients with high-grade gliomas, the PET findings were effective in predicting survival time (Patronas et al., 1985). A high uptake of ^{18}FDG-PET, however, can also be observed in mass lesions that are not neoplastic.

PET has been utilized for studying other aspects of intracerebral neoplasms, such as alterations of the blood–brain barrier (BBB) (Yen et al., 1982), amino-acid uptake, pharmacokinetics of chemotherapeutic agents, and the effects of steroids and whole brain irradiation on BBB functions (Jarden, 1994). However, how the daily clinical management of tumour patients can benefit from such studies is still unclear. Alternative PET tracers such as labelled amino acids and fluorodeoxyuridine are of interest for non-invasive characterization of cerebral tumors. For instance, fluorodeoxyuridine has been used to differentiate high and low grade gliomas in a series of 16 patients (Kameyama et al., 1995).

Thallium-201 SPECT has been shown to correlate better with glioma grade, residual high grade glioma, and tumour recurrence than computerized tomography or MR imaging (Kim et al., 1990). Thallium-201 uptake is proportional to tumour malignancy, thus making it possible to differentiate high grade from low grade gliomas and recurrences from radiation necrosis. An increase in Thallium uptake with time indicates degeneration of low-grade to high-grade gliomas. However, Thallium uptake is also seen with other malignant cerebral tumors or non-neoplastic lesions with large inflammatory infiltrates and is not specific to gliomas.

PET and SPECT have also been utilized in presurgical mapping, in particular when a lesion is in close anatomical relationship with functionally important regions of the cortex. This has been done for arteriovenous malformations (Grafton et al., 1994) as well as in cases of low-grade gliomas (Sabatini et al., 1995). In presurgical mapping, however, fMRI seems to be the most promising technique. Indeed, the wide availability of MR scanners, the increasing use of echo-planar imaging, and the better spatial resolution of fMRI, when compared with PET and SPECT, are all factors in favour of fMRI as the blood flow technique of choice for presurgical mapping of tumour patients.

5. Epilepsy

PET and SPECT have been widely applied to epileptic populations to study metabolic and blood flow aspects of ictal and interictal pathophysiology, to investigate the effect of antiepileptic treatments, to detect epileptogenic foci for surgical localization, to map cortical representations of cognitive functions to be spared by surgery, and to predict the outcome of surgical resections in epileptic patients.

The assessment of rCBF changes with bolus injections of $H_2^{15}O$ in PET has the advantage of good temporal (less than 60 s) and spatial resolution (less than 1 cm along the 3 spatial axes). The main disadvantage is that the short half-life of the tracer makes it logistically difficult to perform ictal studies. Ictal studies are difficult to interpret with ^{18}FDG-PET, because of very poor temporal resolution, given that tracer uptake occurs over 30–40 min after injection. In contrast, PET interictal studies are frequently and effectively performed with both tracers.

The ^{99m}Tc-HMPAO SPECT technique can effectively investigate rCBF changes related to seizures. Indeed, the tracer, after intravenous injection and subsequent uptake (nearly 70% in a min) is stable for several hours. The main logistic problem with the tracer is its instability after preparation. To circumvent this problem, a preparation with cobalt chloride, that stabilizes the tracer for about 6 h, can be used. Alternatively, ^{99m}Tc-ECD which has better cerebral retention and greater stability (many hours) can be used (Lancman et al., 1997).

5.1. Ictal pathophysiology

5.1.1. Generalized epilepsy

The ^{18}FDG-PET hallmark of ictal activity in generalized idiopathic epilepsy is a diffuse increase in glucose metabolism, ranging from 30 to 300%. The greatest increases are observed in children and in absences (Engel et al., 1982; Engel et al., 1985). This is probably due to differences in average metabolic rate over the time of tracer uptake that includes both ictal and post-ictal activity, given that generalized convulsive seizures are associated with post-ictal metabolic depression and absences are not.

The use of bolus injection of $H_2^{15}O$ in patients in whom absences were induced with hyperventilation showed a mean rCBF global increase of ~15% and a local thalamic rCBF increase from 4 to 8%. No focal decreases or increases of cortical rCBF were observed (Prevett et al., 1995a). Although this evidence suggests an important role of the thalamus in the pathophysiology of absence seizures, it is unclear whether the initiation of ictal activity is localized to the cerebral cortex or in the thalamus. Unfortunately, even functional neuroimaging techniques with a better temporal resolution than PET, such as fMRI, still rely on blood flow responses secondary to changes in neural activity, and are unlikely to differentiate between cortex and thalamus as the locus of the initial ictal activity.

Receptor ligand studies provide a complementary type of information that may help the understanding of ictal pathophysiology in generalized epilepsy. The cortical binding of the central benzodiazepine ligand [^{11}C]flumazenil is not affected by absence seizures (Prevett et al., 1995b). In contrast, the opioid receptor ligand [^{11}C]diprenorphine, which binds with similar affinity to different subtypes of opioid receptors, shows a reduction in binding to neocortical association areas during absences, whereas no changes in the binding to thalamus, basal ganglia, and cerebellum have been observed (Bartenstein et al., 1993). These findings suggest that a neocortical release of endogenous opioids may be implicated in the pathophysiology of absence seizures, although it may also be an epiphenomenon.

5.1.2. Partial epilepsy

Partial seizures are generally associated with increases in glucose metabolism and blood flow in the epileptogenic focus (Engel et al., 1983; Chugani et al., 1994). In a recent PET study with $H_2^{15}O$, ictal activity in partial seizures was associated with large (70–80%), bilateral rCBF increases involving the temporal lobes, the thalamus, and the basal ganglia. Ictal lateral temporal blood flow was elevated compared with interictal lateral temporal blood flow, but reduced, when compared with ictal mesial temporal blood flow (Theodore, 1996). These PET blood flow data are in line with SPECT data, showing a characteristic initial temporal hyperperfusion, followed by lateral temporal hypoperfusion and mesial temporal hyperperfusion (Newton et al., 1995). The post-ictal activity is generally characterized by hypoperfusion that gradually returns to baseline (Theodore, 1996). Interestingly, ^{18}FDG-PET shows a persistence of relative increases in glucose metabolism for 24 or even 48 h after partial seizures (Leiderman et al., 1994). This observation suggests that blood flow and metabolism are uncoupled in epileptic foci.

In temporal lobe seizures, SPECT evidence suggests that dystonic postures are generally associated with rCBF increases in the contralateral basal ganglia, that are ipsilateral to an epileptogenic focus (Newton et al., 1992). In frontal lobe seizures, SPECT ictal rCBF increases in the dorsolateral frontal cortex are associated with contralateral head and eye movements, contralateral clonic jerking and asymmetry in tonic posturing (Harvey et al., 1993).

Ictal SPECT is highly accurate in localizing the site of ictal onset in patients with extratemporal epilepsy (Ho et al., 1994). In patients with supplementary sensori-motor area epilepsy, ictal SPECT showed unilateral hyperperfusion in all patients. The heterogeneity of clinical features correlated with propagation to, and activation of, specific cortical structures such as ipsilateral premotor and motor cortices or contralateral mesial frontal cortex (Laich et al., 1997). Finally, SPECT shows focal rCBF increases in epilepsia partialis continua even in the absence of focal EEG epileptic activity (Katz et al., 1990).

Recently, the better spatial and temporal resolution of fMRI have been used to further the understanding of ictal pathophysiology of partial seizures, especially when combined with simultaneous EEG recording. For instance, in a study combining fMRI and EEG, activity coupling left ventrolateral thalamus and left frontal cortex has been described in a patient with frequent partial seizures (Detre et al., 1996).

5.2. Interictal pathophysiology

5.2.1. Generalized epilepsy

Typically, the ^{18}FDG-PET interictal pattern in patients with idiopathic generalized epilepsy is normal (Duncan, 1997). In contrast, receptor ligand studies have found a variety of abnormal patterns in patients with idiopathic generalized epilepsy. Unfortunately, the consistency of these patterns across different studies is disappointingly low. Indeed, central benzodiazepine receptor ligands such as [^{11}C]flumazenil were originally reported to show a reduction in cortical binding (Savic et al., 1990), and in the thalamus (Savic et al., 1994), and increased binding in the cerebellum (Savic et al., 1994) in patients with generalized seizures. In contrast, a later study found no difference between patients and control subjects in the binding of the benzodiazepine receptor ligand in cerebral cortex, thalamus and cerebellum (Prevett et al., 1995b). The same group subsequently found higher binding in patients than in normals, ranging from 11 to 14%, in cerebral cortex, thalamus, and cerebellum (Duncan, 1997). The diversity of results could, in principle, be reconciled by invoking differences across groups in selection criteria and methodological approaches. However, it unequivocally indicates that the results of central benzodiazepine ligand binding studies are difficult to generalize.

In patients with secondary generalized seizures, interictal ^{18}FDG-PET studies have been more useful. In children with infantile spasms, PET has shown that the lenticular nuclei and brain-stem are often associated with hypermetabolism, regardless of the presence or type of cortical abnormality (Chugani et al., 1992). This finding is consistent with the clinical observation that infantile spasms are generally symmetric even if associated with unilateral cortical lesions, suggesting that infantile spasms may result from the com-

plex interaction of cortical abnormalities with abnormally active subcortical structures (Chugani et al., 1992).

5.2.2. Partial epilepsy

Typically, the interictal epileptogenic focus is a focal area of decreased glucose metabolism and blood flow, that is usually larger than the corresponding structural abnormality (Duncan, 1997). This pattern is likely due to deafferentation of neighbouring neurons around the epileptogenic focus. In epileptic foci, metabolism is reduced to a greater extent than rCBF, suggesting that interictal neural activity rather than vascular supply is primarily depressed (Gaillard et al., 1995b).

The pathophysiological mechanisms producing hypometabolism and hypoperfusion in epileptic foci are still unclear. Studies of functional-structural correlation have produced diverging results. Temporal lobe hypometabolism measured with ^{18}FDG-PET was found to be significantly associated with the degree of hippocampal volume loss as measured by MRI (Gaillard et al., 1995a). Others, however, have failed to observe a significant correlation between regional interictal ^{18}FDG-PET hypometabolism and neuronal density of resected hippocampi, suggesting that other mechanisms must be invoked to explain regional interictal hypometabolism in temporal lobe epilepsy (Henry et al., 1994). Note that in temporal lobe epilepsy, the area of hypometabolism is often not limited to the temporal structures. Indeed, thalamus, basal ganglia, and frontal lobe can show foci of hypometabolism in 30–50% of patients (Henry et al., 1993). It is possible that regional temporal hypometabolism is the result of neuronal losses in a variety of areas that are functionally and anatomically connected. It is also possible that other mechanisms rather than neuronal loss, may account for, or at least contribute to, regional interictal hypometabolism (Sloviter, 1994). In fact, areas of interictal glucose hypometabolism show a greater increase in metabolic activity than the brain as a whole after administration of the $GABA_A$-receptor agonist THIP (4,5,6,7-tetrahydro - isoxazolo(5,4,-c)-pyridin-3-ol) (Peyron et al., 1994). This result suggests that $GABA_A$ receptors are still functionally active in epileptogenic foci.

Receptor ligand investigations have shown a greater consistency across studies in partial epilepsy than in generalized epilepsy. The binding of [^{11}C]flumazenil to central benzodiazepine receptors in epileptogenic foci is generally reduced (Savic et al., 1993) and the area of reduced binding is smaller than the area of hypometabolism in temporal lobe epilepsy (Henry et al., 1993; Savic et al., 1993). Similar results have been reported using [^{123}I]iomazenil and SPECT (Sjoholm et al., 1995; Tanaka et al., 1997). The area of benzodiazepine receptor abnormalities seems to correspond well with structural lesions as shown by MRI (Koepp et al., 1996). However, areas of reduced [^{11}C]flumazenil binding can be found in cortical sites that do not show an abnormality on MRI (Richardson et al., 1996). The pathophysiological and clinical significance of these findings is in need of further investigation.

5.3. Surgical localization

The neuroimaging techniques measuring blood flow and metabolism that are most effective in localizing epileptic foci for surgical resection and for predicting outcome after surgery are ^{18}FDG-PET in the interictal phase and SPECT in the ictal phase. Quantitation techniques are generally helpful in preventing false localization in ^{18}FDG-PET, that, at any rate, are rare and occur in less than 1% of patients with temporal lobe epilepsy (Sperling et al., 1995) but somewhat more frequently in patients with extra-temporal epilepsy (Radtke et al., 1993). With regard to ^{99m}Tc-HMPAO SPECT, the main confounding localizing factor is the rapid spread of activity to other areas, that may also be interpreted as areas of onset of a seizure.

Studies with ^{18}FDG-PET in patients with temporal lobe epilepsy have shown a 60–90% incidence of focal hypometabolism in the temporal lobe (Duncan, 1997). When ^{18}FDG-PET and MRI were compared in the same series of patients with temporal lobe epilepsy, hypometabolism and structural abnormalities were concordant in about 60% of patients, but hypometabolism was also found in an additional 30% of patients not showing structural abnormalities (Gaillard et al., 1995a). This finding suggests that ^{18}FDG-PET has a much better sensitivity than MRI in detecting epileptogenic foci candidates for potential surgical resection.

Ictal ^{99m}Tc-HMPAO SPECT has shown, in a recent series, an excellent sensitivity for both temporal and extra-temporal foci (Newton et al., 1995). The latter are generally harder to localize with imaging techniques. However, ictal SPECT has shown a 92% sensitivity in these cases (Newton et al., 1995). A recent cross-comparison of ictal ^{99m}Tc-HMPAO SPECT, interictal ^{18}FDG-PET and MRI, has shown better sensitivity for the two functional neuroimaging techniques, that provide complementary information when MRI fails to localize an epileptogenic focus (Ho et al., 1995) (Fig. 4).

In terms of predictive value, the magnitude and size of hypometabolism in the temporal lobe has been shown to correlate with seizure outcome following surgery (Radtke et al., 1993). A later study, however, seems to suggest that hypometabolism in the mesial temporal lobe, but not in the lateral temporal lobe, correlates with outcome after surgery (Manno et al., 1994). Finally, interictal ^{18}FDG-PET has good predictive value in infantile spasms. When a single focus of hypometabolism is detected by ^{18}FDG-PET and EEG, and the seizures are intractable, surgery results in seizure control and partial or complete reversal of the developmental delay generally associated with such disease (Chugani et al., 1990). In contrast, patients with infantile spasms and bitemporal glucose metabolism are not good candidates for cortical resection, with generally a poor long-term outcome and autism (Chugani et al., 1996).

In the future, we believe, there will be more use of fMRI combined with EEG in localizing seizure foci with high spatial and temporal resolution. fMRI already seems more accurate than electroencephalography recorded from subdural grids in indicating the site of successful surgical therapy (Detre et al., 1995; Bookheimer, 1996).

6. Extrapyramidal disorders

Extrapyramidal disorders have been extensively investigated with functional neuroimaging techniques. In this section we will mainly focus on PET studies using ^{18}FDG, $H_2^{15}O$, ^{18}F-6-fluoro-L-dopa ([^{18}F]dopa), and dopamine receptor ligands to investigate the functional integrity of basal ganglia structures in patients with a variety of extrapyramidal disorders. Some SPECT evidence in patients with movement disorders will be also discussed.

6.1. Parkinsons disease

PET studies have described patterns of altered metabolism in Parkinson's disease (PD) and in syndromes mimicking the clinical features of PD. Uncomplicated, early PD is associated with a normal global glucose metabolism, with increased regional metabolism in the thalamus and lentiform nucleus, and decreased regional metabolism in the lateral and medial wall of the frontal lobe, inferior parietal lobe and parietooccipital areas. The metabolic profile of these structures in individual patients has been shown to correlate with the progression of disease as measured by the Hoehn and Yahr score, and with quantitative ratings for rigidity and bradykinesia (Eidelberg et al., 1994). When applied to a cohort of early PD patients, typically showing clinical asymmetries, a statistical covariate approach disclosed basal ganglia and thalamic asymmetry patterns that correctly discriminated early PD patients from atypical PD patients with drug-resistance in the early stage. This method seems to show better sensitivity in discriminating early PD from atypical PD than imaging techniques, such as [^{18}F]dopa, that measure presynaptic nigrostriatal function directly (Eidelberg et al., 1995a).

The validity of this covariate statistical approach has been subsequently confirmed when the method was applied to the study of surgical outcome following unilateral pallidotomy in advanced PD patients. A series of patients undergoing unilateral pallidotomy were studied pre- and post-operatively with ^{18}FDG-PET. The post-surgical improvement in contralateral motor functions was observed to correlate with lentiform metabolic activity in the pre-operative study. After surgery, metabolic increases were observed in primary motor, lateral premotor, and dorsolateral prefrontal cortices

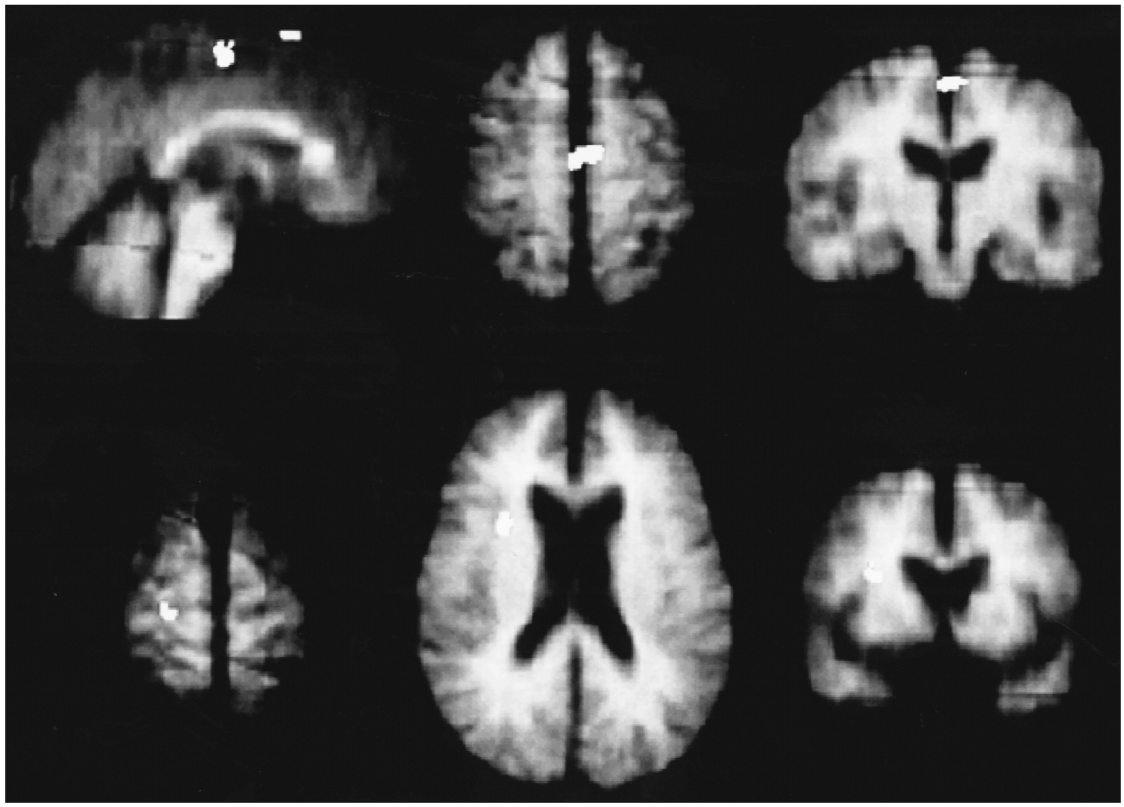

Fig. 4. Areas with significant post-pallidotomy blood flow increases during movement are shown in white, superimposed on patients' average MRI. Increases are seen in SMA (top row), premotor cortex and anterior insula (bottom row). Reprinted with permission from Grafton et al., 1995.

of the hemisphere ipsilateral to surgery. The improvement in post-operative motor performance in the limb contralateral to pallidotomy was found to correlate with the post-operative decrease in thalamic metabolism and the post-operative increase in cortical metabolism of the lateral wall of the frontal lobe. Further, the post-operative metabolic decrease in the lentiform nuclei (note that the current resolution of ^{18}FDG-PET does not allow a reliable discrimination between external and internal pallidal activity) and the thalamus ipsilateral to surgery covaried with the increase in glucose metabolism of medial premotor cortex (SMA) bilaterally, and the individual profile of post-operative metabolic changes in this network of covarying cerebral structures was correlated with post-operative improvements in both ipsilateral and contralateral limb performance (Eidelberg et al., 1996).

These findings are largely consistent with animal models of basal ganglia-thalamo-cortical circuitry and with the notion that the effect of unilateral pallidotomy is basically to remove uncontrolled pallidal inhibition of the ventrolateral thalamus, that produces reduced thalamocortical input and depression of cortical activity. This abnormality occurs in PD patients because nigrostriatal dopamine deficiency produces a decrease of inhibitory putaminal activity into the internal globus pallidus that is associated with preserved excitatory inputs from the subthalamic nucleus to the globus pallidus pars interna (Alexander and Crutcher, 1990). Findings from a recent PET study using $H_2^{15}O$ and a motor activation paradigm in patients who underwent ventrolateral pallidotomy are consistent with this view (Grafton et al., 1995). Patients were imaged during a simple prehension task before and after surgery. When compared with pre-operative values, rCBF changes related to movement in the post-operative PET scans showed significant increases in both lateral premotor cortex and SMA (Fig. 5). Behaviorally, there was no difference in completed prehension movements and total movement time before and after surgery. Thus, the differences observed in blood flow during the movement task between post-operative and pre-operative PET studies cannot be attributed to differences in actual movement. Recent blood flow measurements during stimulation of chronically implanted electrodes in PD patients are also consistent with this model of basal ganglia-thalamo-cortical circuitry (Limousin et al., 1997)

Presynaptic dopaminergic terminals can be assessed with [^{18}F]dopa and PET, showing significant relationships between impaired putaminal [^{18}F]dopa uptake and the most affected side, severity of bradykinesia and rigidity but not tremor; caudate uptake is only mildly reduced in the early stages of idiopathic PD (Brooks, 1997). Recently, this technique has been applied to study the rate of disease progression in PD patients. Two general models of progression of disease have been proposed in PD. One assumes that a transient exposure to an insult damaging the substantia nigra is associated with an approximately linear cell loss due to the ageing processes (Koller et al., 1991). The other model assumes that the onset and progression of disease are triggered by a relatively recent degenerative process with exponential decay (Fearnley and Lees, 1991). Two recent [^{18}F]dopa-PET studies have addressed this issue.

In the first study, the annual rate of progression, as measured by the decrease of striatal [^{18}F]dopa uptake, was observed to be only 0.78% greater than in normals. This led to an estimated preclinical period of about 40-50 years

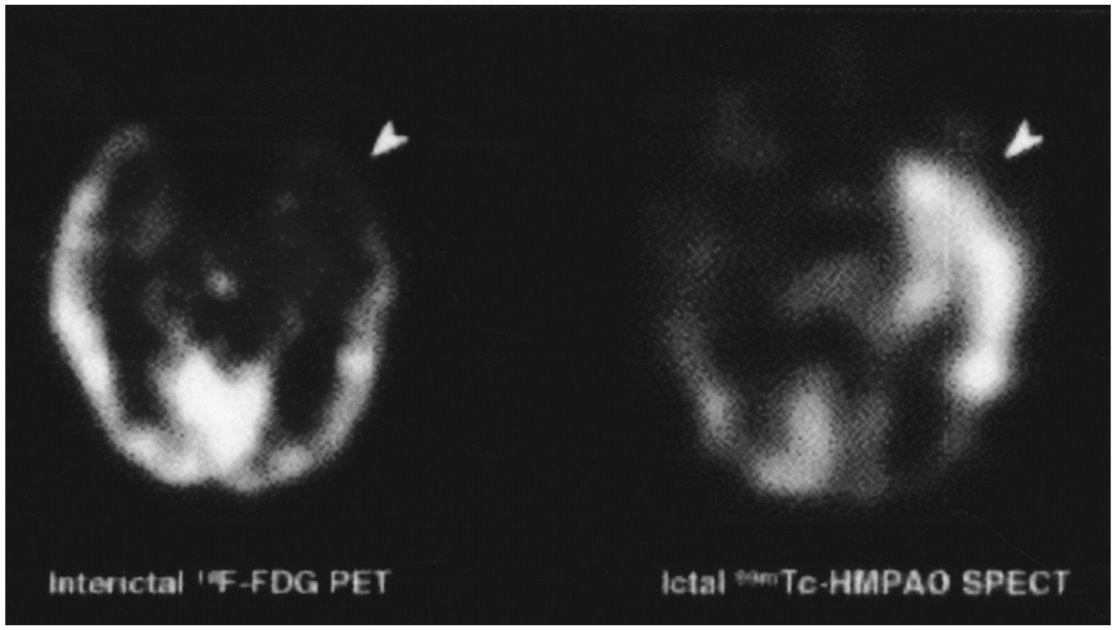

Fig. 5. Focal hypometabolism on interictal PET and focal hyperperfusion on ictal SPECT in a patient with left temporal lobe epilepsy. Reprinted with permission from Ho et al., 1995.

(Vingerhoets et al., 1994). In this study, however, the regions of interest used for estimating the loss in [^{18}F]dopa uptake were large, encompassing putamen, caudate and surrounding tissue. A second study, in which the [^{18}F]dopa influx constant (K_i) of different basal ganglia structures was correlated with the severity of disease in PD patients, demonstrated that the putaminal K_i is a more sensitive measure of function than caudate or overall striatal K_i. Most importantly, this second study demonstrated a mean putamen K_i reduction of 12.5% per annum in PD patients, with a more rapid rate of reduction in putaminal K_i in recent onset PD patients than in established PD patients (Morrish et al., 1996).

This finding suggests that the rate of progression in PD may be non-linear. An exponential fit of the empirical data would estimate the duration of the preclinical period to be less than 3 years (Morrish et al., 1996). The appealing aspect of an exponential fit is that it can also account for longer estimates of the preclinical period in studies in which patients with longer duration of disease were enrolled (Vingerhoets et al., 1994).

[^{18}F]dopa-PET studies can also be used to assess the functional aspects of embryonic mesencephalic tissue containing dopamine cells implanted in PD patients (Lindvall et al., 1989). Post transplantation increases in striatal [^{18}F]dopa uptake have also been repeatedly observed, with corresponding meaningful clinical benefit (Freed et al., 1992; Freeman et al., 1995). In a recent series, [^{18}F]dopa uptake in the grafted putamen has been found to correlate with the percentage of time spent ‘on’ and with contralateral finger dexterity (Remy et al., 1995). Finally, it has been documented that the post-graft increase in [^{18}F]dopa uptake corresponds to actual reinnervation of the host striatum by the graft as found by different histological techniques in a case who incidentally went to post-mortem several months after grafting (Kordower et al., 1995).

Compensatory mechanisms, however, may make the interpretation of data from single tracers quite difficult and may lead to models that are too simplistic. For instance, the loss of putaminal dopaminergic nerve terminals may be offset by the sprouting of alternate terminals, thus resulting in a functional imaging pattern that may not reflect the reality of an underlying dramatic neural reorganization and progression of disease.

PET receptor ligand studies have also been used in PD. In early PD, there is increase in D_2 receptor binding in the putamen contralateral to the most clinically affected side, indicating up-regulation of post-synaptic receptors due to reduced synaptic dopamine (Antonini et al., 1995; Rinne et al., 1995). Putamen D_1 receptor binding, in contrast, appears normal (Rinne et al., 1990). To explore changes in synaptic dopamine levels, changes in striatal binding of [^{11}C]raclopride, a dopamine D_2 receptor antagonist has been frequently used with highly reproducible results (Volkow et al., 1993). Note that the degenerative process in PD seems to affect the ventrolateral substantia nigra more than the dorsomedial substantia nigra. The ventrolateral substantia nigra projects mainly to the posterior putamen, whereas dorsal and medial cells of substantia nigra project preferentially to the caudate (Fearnley and Lees, 1991). In a recent study, the acute administration of levodopa in PD patients produced a reduction in striatal [^{11}C]raclopride binding that follows the same rostro-caudal gradient of the degenerative process in PD, with the greatest reduction in the posterior putamen, an intermediate reduction in the anterior putamen and a less pronounced reduction in the caudate (Tedroff et al., 1996). The magnitude of the levodopa-induced [^{11}C]raclopride binding reductions was correlated with drug-free rating scores of disability. Further, in hemiparkinsonian PD patients, the reduction of [^{11}C]raclopride binding was found only in the putamen contralateral to clinical symptoms. Taken together, these data suggest that levodopa increases its ability to displace [^{11}C]raclopride binding where dopaminergic denervation is greater, implying that as a compensatory mechanism amine turnover increases with dopaminergic degeneration in PD. In keeping with this notion, when levodopa was given to healthy monkeys, no change in striatal [^{11}C]raclopride binding was observed (Antonini et al., 1994).

Another important aspect of PD concerns its neuropsychological manifestations. Even at early stage, idiopathic PD may be accompanied by subtle impairments in shifting cognitive strategy and in mental manipulation of items. Such a mental ‘slowness’ is often collectively termed ‘dysexecutive syndrome’. These deficits seem to worsen with time, although it is not clear whether they anticipate dementia. In non-demented idiopathic PD patients, PET has shown that the dysexecutive syndrome correlates negatively with glucose metabolism in thalamic medio-dorsal nucleus and positively with glucose metabolism in dorsolateral prefrontal cortex. This fits the striato-frontal models that assume that caudate dopamine denervation would induce hyperactivity in the pallido-thalamic GABAergic pathway which would in turn deactivate the thalamo-prefrontal system (Marie’ et al., 1995).

Summing up, this brief review indicates that PET studies can be helpful in the differential diagnosis of early PD, in understanding the pathophysiological mechanisms of PD, and in monitoring the effects of surgical treatments. Clearly, the combined use of different tracers that index different aspects of neural activity is the most promising approach and should be pursued in future PET studies of PD. Some PD SPECT data will be discussed below with regard to issues of differential diagnosis in akinetic-rigid syndromes.

6.2. Huntington’s disease

Early PET observations in Huntington’s disease (HD) patients demonstrated a reduction in glucose metabolism in the striatum, regardless of the type of symptom displayed, even when structural abnormalities due to striatal atrophy were not detected (Kuhl et al., 1982). These findings have

been confirmed and refined in later studies. The caudate metabolic rate in HD patients has been found to correlate with the general functional status, with the cognitive profile and with motor abnormalities, but notably, not with dystonia. Putaminal metabolism, however, was found to correlate better with motor symptoms than caudate metabolism, although the latter showed an overall better sensitivity to the presence of disease (Young et al., 1986). Thalamic metabolism is either increased (Young et al., 1986), in the normal range (Kuwert et al., 1990), or decreased (Holthoff et al., 1993). This finding may reflect dynamic changes in the functional aspects of basal ganglia connectivity during the course of the disease. In early stages, thalamic metabolism may change because of the loss of presynaptic input to pallido-thalamic neurons. In later stages, pallidal output to the thalamus may also be affected by the disease to produce further changes in thalamic metabolism due to direct denervation.

An alternative model would predict thalamic hypermetabolism in patients displaying the choreic form of HD, where preferential damage of the indirect output pathway from the striatum to the pallidum, via subthalamic nucleus, is assumed to reduce pallidal inhibition of the ventral thalamus and results in increased thalamic and thalamocortical activity. Akinetic-rigid forms, in contrast, show non-selective loss of striatal inputs to the pallidum in both direct and indirect pathways, that may not affect thalamic metabolism (Hallett, 1993). The combined PET studies of metabolism and receptor binding may directly test these models in the future.

PET has also been shown to be sensitive in pre-clinical at-risk populations. Asymptomatic subjects at risk of developing HD were found to show caudate hypometabolism in a percentage of subjects consistent with the probability of having clinically unexpressed genetic marker of the disease (Mazziotta et al., 1987) (Fig. 6).

In a subsequent study, caudate hypometabolism as measured with PET, showed a 75% sensitivity in a sample of subjects with positive genetic test results or phenotypic expression of the disease (Grafton et al., 1990). When positive versus negative genetic testing of at-risk individuals were compared, a 3.1% loss of caudate glucose metabolism and a 3.6% increase in caudate atrophy per annum was observed in the gene positive group, compared with those without the HD gene (Grafton et al., 1992).

D_1 and D_2 receptor binding PET studies have also been applied to HD. D_1 and D_2 binding were reduced in HD patients, irrespective of phenotype (choreic or akinetic form), although HD patients with rigidity showed a greater reduction in D_1 and D_2 binding than HD patients without rigidity (Turjanski et al., 1995). In a recent study, [^{11}C]raclopride binding PET measurements showed a 50% sensitivity in detecting abnormalities in asymptomatic gene-carriers (Weeks et al., 1996). Finally, a combined approach of ^{18}FDG-PET and [^{11}C]raclopride has shown 83% sensitivity and 100% specificity in asymptomatic gene carriers of HD (Antonini et al., 1996).

6.3. Other syndromes

Functional neuroimaging has been applied to extrapyramidal disorders in an attempt to characterize the different patterns of functional anatomy in syndromes that share clinical features, and in an attempt to further the understanding of pathophysiological mechanisms of movement disorders. For instance, multiple system atrophy (MSA) can be divided into a parkinsonian-like form, striatonigral degeneration (SND), and a cerebellar-like form, sporadic olivopontocerebellar atrophy (OPCA). Glucose metabolism as assessed by ^{18}FDG-PET has shown predominant lentiform hypometabolism in SND patients, and predominant cerebellar hypometabolism in OPCA patients (Perani et al., 1995). In this PET study of MSA, a negative correlation was also observed between glucose metabolism in the caudate and putamen and the severity of parkinsonism, a negative correlation with cerebellar metabolic activity and cerebellar symptomatology, and, finally, a negative correlation between thalamus, frontal and temporal hypometabolism, and the degree of autonomic dysfunction.

Early PET observations described marked bilateral frontal hypometabolism in patients with progressive supranuclear palsy (PSP), the degree of which was linearly correlated to the severity of the clinical frontal lobe syndrome (Blin et al., 1990). It is unclear whether this hypometabolism results from disconnection phenomena due to primary neuronal loss in subcortical centers or from a primary degenerative processes in the neocortex. Presumably, both mechanisms contribute to the marked reduction in frontal glucose metabolism observed with PET. This frontal hypometabolism in PSP is present from the early stages of the disease (Blin et al., 1990), which, together with marked striatal hypometabolism in PSP patients (Blin et al., 1990) may help in the differential diagnosis from idiopathic PD in uncertain cases. Also, striatal opioid receptor binding has been used to differentiate between PD, PSP and SND. A recent [^{11}C]diprenorphine PET study has shown normal binding in the putamen and caudate of PD patients, reduced binding in the putamen but not in the caudate of SND patients and reduced binding in both putamen and caudate in PSP patients (Burn et al., 1995).

Wilson's disease has been studied less frequently with PET. A ^{18}FDG-PET study has shown a diffuse reduction in glucose metabolism, with the exception of the thalamus. Glucose metabolism was particularly reduced in the lentiform nucleus (Hawkins et al., 1987). PET has also been used to investigate the pathophysiology of idiopathic and acquired dystonia. A covariate statistical approach with ^{18}FDG-PET has shown bilateral increases in glucose metabolism in lateral and medial premotor cortex, associated with lentiform hypermetabolism contralateral to sustained muscle contractions (Eidelberg et al., 1995b). Motor activation PET studies have been performed in both idiopathic and acquired dystonia (Ceballos-Baumann et al., 1995a; Ceballos-Baumann et al., 1995b). When compared with normals,

patients with idiopathic dystonia showed an increased activation in contralateral premotor cortex, rostral SMA, anterior cingulate and bilaterally in the lentiform nuclei. Decreased activation was found in primary motor areas, caudal SMA and medial parietal cortex. In patients with acquired dystonia, a similar activation pattern was observed in premotor cortical areas, suggesting that regardless of its etiology, dystonia is produced by frontal disinhibition due to the disruption of basal ganglia inhibitory control.

Finally, glucose metabolism as measured with PET is increased in the pallidum and precentral gyrus of schizophrenic patients with tardive dyskinesias (Pahl et al., 1995). Such a pattern was not observed in a comparable group of schizophrenic patients without tardive dyskinesias. This finding suggests that pallidal overactivity may generate tardive dyskynesias. However, the long-held hypothesis that tardive dyskinesia may be due to increased D2 receptor density in the striatum is not supported by PET data currently available (Blin et al., 1989).

7. Dementia

Since the original PET reports on glucose and oxygen

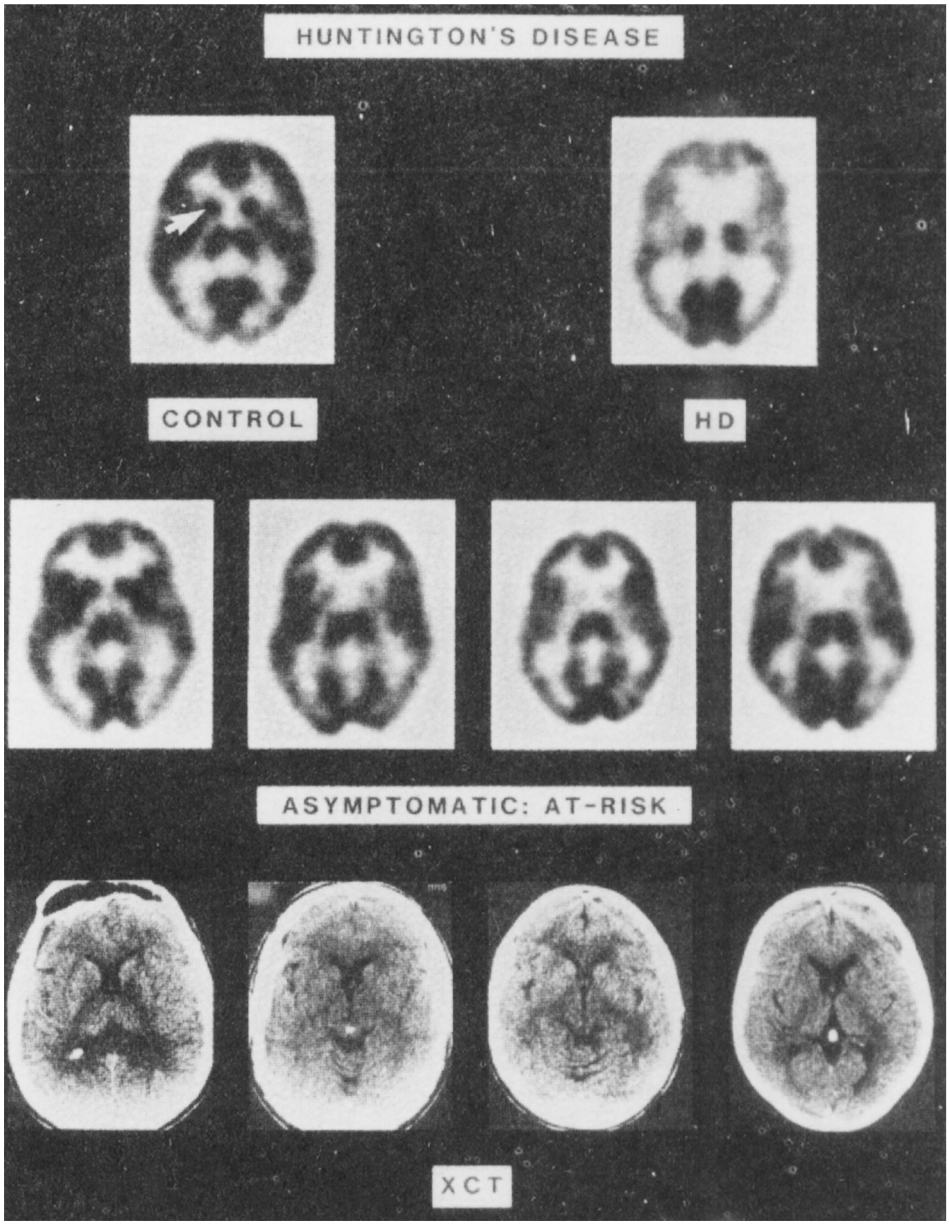

Fig. 6. Glucose metabolism in a control subject (upper left), in a patient with HD (upper right) and in 4 asymptomatic at-risk individuals (middle row). The 4 subjects show degrees of metabolic patterns in the caudate, from normal (leftmost) to severely hypometabolic (rightmost). CT scans were normals in all 4 of these asymptomatic at-risk subjects (bottom row). Reprinted with permission from Mazziotta et al., 1987.

metabolism abnormalities in Alzheimer's disease (Benson et al., 1983; Frackowiak et al., 1981), a variety of functional neuroimaging techniques have been applied to the study of dementia. With PET, glucose metabolism, blood flow and receptor binding measurements have been used in studies on demented patients and at-risk individuals. SPECT, although less informative than PET, has the advantage of allowing prospective studies of large populations of demented or 'pre-demented' patients, that may define patterns of altered brain function that are associated with cognitive impairment. Functional imaging techniques may also be utilized for the evaluation of changes in cerebral metabolism due to therapeutic agents both in large clinical trials on dementia as well as for pre-trial screening of new compounds.

7.1. Alzheimer's disease

The pattern of metabolism in Alzheimer's disease (AD) is typically characterized by temporoparietal metabolic reduction, associated with a relative preservation of metabolic activity in primary sensorimotor and visual cortex, thalamus, basal ganglia and cerebellum (Frackowiak et al., 1981; Benson et al., 1983). As the disease progresses, metabolism in the frontal lobe tends to decrease too.

The temporoparietal metabolism tends to correlate with the severity of dementia. This is not specific to AD and has been observed also in other types of dementia. From a quantitative standpoint, absolute rates of temporoparietal metabolism are less effective for correlation purposes than relative rates, with reference to metabolism of cerebral regions that are relatively spared, since absolute rates, especially of glucose metabolism, show a large variability in both normals and demented patients (Herholz, 1995).

Asymmetries in glucose hypometabolism are often seen in the early stages of the disease, and may be present even in the later stages of AD (Grady et al., 1986). PET may even demonstrate a reduction in glucose metabolism well before detectable neuropsychological deficits (Haxby et al., 1986). When AD patients with early-onset and late-onset forms of the disease are compared, early-onset AD patients tend to show lower parietal metabolic ratios than late-onset AD patients (Small et al., 1989). Recently, it has been shown that at-risk individuals for familial AD, carriers of the apolipoprotein E type 4 allele, have comparably lower parietal glucose metabolism than individuals without the apolipoprotein E type 4 allele. Patients with dementia have parietal metabolism lower than at-risk individuals with positive genetic testing (Small et al., 1995). These findings have been replicated and expanded (Reiman et al., 1996), while others have documented that the posterior cingulate gyrus and nearby medial parietal area 7 may be affected metabolically even earlier than posterior lateral area 7 in pre-symptomatic AD (Minoshima et al., 1997) (Fig. 7). This finding suggests that glucose metabolic assessment with PET can be used to measure the effectiveness of experimental treatments at a very early stage in the disease.

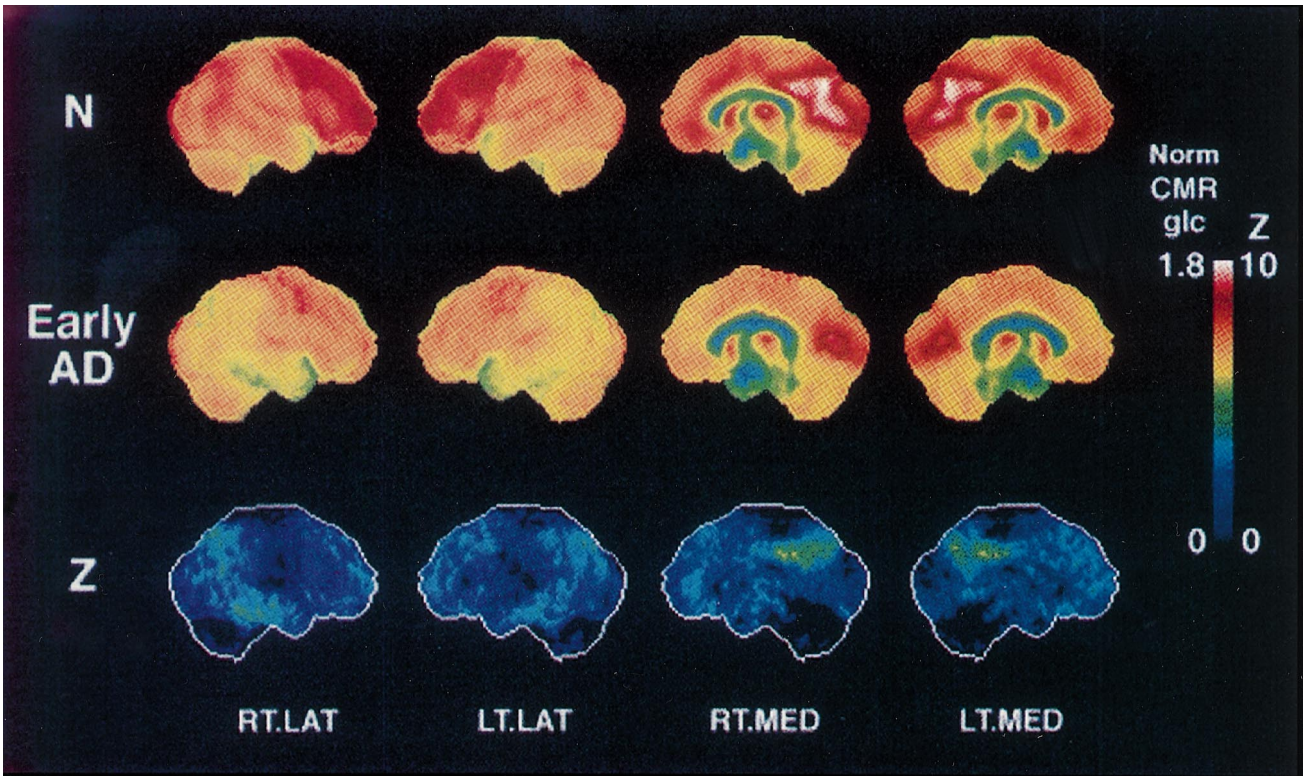

Fig. 7. Patterns of altered metabolic activity in very early AD, compared with normals. Metabolic reductions are seen in the posterior cingulate and left medial parietal regions. N, normals; Z, Z images. Reprinted with permission from Minoshima et al., 1997.

A theoretically and pathophysiologically important question related to glucose hypometabolism in AD is whether this is due to a neuronal and synapse loss (with resulting tissue atrophy), or to a reduction in synaptic activity in the remaining neurons, or both. Recent data, comparing rates of glucose metabolism with that of [^{11}C]methionine accumulation in AD patients, as measured with PET, seem to suggest that regional tissue loss cannot completely account for the glucose hypometabolism observed in AD, which may partly reflect reduced synaptic activity (Salmon et al., 1996).

A central and early symptom of AD, episodic memory impairment, seems to be associated with reduced metabolism in the hippocampus, cingulate gyrus and basal frontal cortex. These structures, in a series of patients with global amnesia due to different etiologies, showed a reduction in metabolic activity similar to AD patients. Global amnesics, however, did not show the typical temporoparietal hypometabolism of AD patients (Perani et al., 1993a). PET observations have suggested that the network of cortical structures whose metabolic impairment is associated with verbal episodic memory deficit in AD is task-dependent, with some tasks relying more on dorsolateral prefrontal cortex and others on parieto-temporal association cortex in addition to the hippocampal and posterior cingulate areas (Desgranges et al., 1998). Left parietotemporal hypometabolism at rest seems also correlated with writing disorders in AD (Penniello et al., 1995).

Activation studies have been performed in AD patients using both $H_2^{15}O$ and ^{18}FDG. The latter, is a tracer with a very poor temporal resolution, limiting the interpretation of results in activation tasks. During an ^{18}FDG-PET study using a visual recognition task, smaller activations have been observed in temporoparietal structures of AD patients relative to normals (Kessler et al., 1991). Others, in contrast, using $H_2^{15}O$ a tracer that, due to its short half-life has a much better temporal resolution than ^{18}FDG, have observed no differences between AD patients and normals in the activation of occipitotemporal striate cortex during a face matching task (Grady et al., 1993). Moreover, AD patients showed a greater activation of frontal and occipital cortex than normal controls. These additional activations presumably reflect the increased difficulty of the task for AD patients, due to their reduced cognitive ability. A different cognitive approach between AD patients and normal controls in a face matching task can also be observed by means of correlation analyses of blood flow changes in different cortical regions (Horwitz et al., 1995).

The diagnostic accuracy of ^{99m}Tc-HMPAO-SPECT has been tested in AD patients in two recent studies. A ^{99m}Tc-HMPAO-SPECT study has shown a 42% sensitivity in mild AD patients, a 56% sensitivity in moderate AD patients and a 79% sensitivity in severe AD patients, when specificity is set at 90% (Claus et al., 1994). Further, a diagnostic gain of 34% was observed in mild AD patients, when the prior probability of disease was around 50%. This suggests that SPECT is a useful tool in AD when there is still considerable diagnostic doubt. In keeping with this conclusion, in a follow up study of a heterogeneous group of patients with suspected dementia, including AD, multi-infarct dementia (MID), and psychiatric disorders, progressively impaired CBF was observed in 85% of patients with AD, and improved CBF was observed only in the psychiatric population (Golan et al., 1996).

Receptor studies have shown reduced serotonin 5HT-2a receptor densities, predominantly affecting the frontal cortex, in moderate to severe AD (Blin et al., 1993). Regarding the muscarinic system, both reduced presynaptic cholinergic terminals (Kuhl et al., 1996) and reduced muscarinic receptor densities in cortical areas (Wyper et al., 1993) have been reported, but the lack of selective M1 or M2 ligands has hampered the study of clinical correlations thus far.

7.2. Other dementias

An increasingly recognized cause of dementia is the nosological entity known as diffuse Lewy body disease (DLBD) (Gibb et al., 1987). A recent ^{18}FDG-PET study on 3 patients with DLBD and 3 patients with combined DLBD and AD has shown that, in addition to the typical pattern of hypometabolism previously described associated with AD, all patients showed hypometabolism in primary and associative visual cortical areas (Albin et al., 1996). The distribution of Lewy bodies, the characteristic pathological hallmark of the disease, surprisingly, was not correlated with hypometabolism. Strikingly, glucose metabolism in the anterior cingulate cortex, a region usually associated with a high density of Lewy bodies, was substantially preserved. In contrast, the occipital cortex showed hypometabolism without evident major pathology. The hypometabolism in cerebral regions without major pathological involvement can be, in principle, explained by invoking diaschitic mechanisms. Normal metabolism in regions with major pathology may be explained as reflecting inputs from distant areas unaffected by disease.

Typically, Pick's disease is associated with bilateral frontal and anterior temporal hypometabolism (Herholz, 1995). Other frontal lobe dementias, that are probably more frequent than Pick's dementia, are associated with hypometabolism in the frontal lobe. This pattern, however, is largely non-specific, given that a number of conditions may be associated with frontal hypometabolism, such as PSP (D'Antona et al., 1985), depression (Baxter et al., 1989), and schizophrenia (Buchsbaum et al., 1992).

Among prion diseases, two entities have been studied with functional neuroimaging techniques. Creutzfeld-Jakob disease is associated with multifocal reductions in blood flow and metabolism and a highly heterogeneous pattern that correlates well with the distribution of the underlying pathological processes. This suggests that both PET and SPECT may be useful in providing clues for diagnostic brain biopsy (Goldman et al., 1993; Aharon-Peretz et al.,

1995). In patients with fatal familial insomnia (Lugaresi-Gambetti Disease), when symptomatology is restricted to dysautonomia and insomnia, selective thalamic hypometabolism is observed. When multiple neurological signs are present, however, diffuse cortical metabolism, associated with a reduction in glucose metabolism in the basal ganglia and cerebellum, is found (Perani et al., 1993b).

In vascular dementia, multifocal reductions in blood flow and metabolism are observed in both cortical and subcortical structures (Frackowiak et al., 1981; Metter et al., 1985; Herholz, 1995). A fundamental question is whether the cortical hypometabolism observed in vascular dementia patients is due to primary effects of cortical ischemic lesions or to remote effects due to subcortical vascular lesions. In a recent study, vascular dementia patients with no MRI evidence of cortical lesions, were studied with PET (Sultzer et al., 1995). In spite of a substantial heterogeneity of results, this study seems to suggest that more severe subcortical lesions are associated with a greater reduction in glucose metabolism of the cortical mantle. Moreover, frontal hypometabolism seems to be associated with lacunar infarcts in the basal ganglia or thalamus. These findings suggest that remote effects of focal brain lesions, generally termed diaschisis (Feeney and Baron, 1986), are present in vascular dementia patients and may play a major role in the pathophysiology of the disease.

8. Multiple sclerosis

The role of PET and SPECT in the clinical management of multiple sclerosis (MS) patients has been minor thus far, in particular in comparison to MRI. However, since nearly 50% of MS cases have cognitive disorders, PET and SPECT evaluation can be utilized to substantiate the metabolic and/or perfusion deficits related to cognitive features, the basic mechanism being a deafferentation due to the subcortical white matter lesion(s). PET observations of a decrease of both oxygen metabolism and blood flow that correlated with cognitive impairment (Brooks et al., 1984) have been confirmed with SPECT (Pozzilli et al., 1991). In keeping with this finding, patients with primary progressive multiple sclerosis, who have relatively preserved cognition, show a relative lack of brain lesions on conventional MRI and of focal hypoperfusion with SPECT (Thompson et al., 1997).

Another aspect of MS that has been investigated with emission tomography and that may be relevant for management is the depressive disorder that affects MS patients more frequently than the general population or patients with various other medical and neurological diseases. While data on the relationships between MRI lesions and depression are still unclear, a significant association between CBF asymmetry in the limbic system as measured with SPECT and the severity of depression in MS patients has been reported (Sabatini et al., 1996).

9. Conclusions

Functional neuroimaging 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 and to our understanding of the neurobiology of disease, but also to a more complete understanding of the strengths and weaknesses of functional neuroimaging techniques as applied to clinical populations.

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