Behavioural Neurology (1992), **5**, 139 - 147

REVIEW

Single-photon emission computerized tomography (SPECT) in neuropsychiatry: a review

B.K. Puri[1] and S.W. Lewis[2]

[1] Department of Psychiatry, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, and [2] Academic Department of Psychiatry, Charing Cross and Westminster Medical School, St Dunstan's Road, London W6 8RP, UK

Correspondence to: B.K. Puri at above address

Cranial single-photon emission computerized tomography (SPECT or SPET) can now give regional cerebral blood flow images with a resolution approaching that of positron emission tomography (PET). In this paper, the use of high resolution SPECT neuroimaging in neuropsychiatric disorders, including Alzheimer's disease, multi-infarct dementia, Pick's disease, progressive supranuclear palsy, Korsakoff's psychosis, Creutzfeld-Jakob disease, Parkinson's disease, Huntington's disease, schizophrenia, mood disorders, obsessive-compulsive disorder, HIV infection and AIDS is reviewed. Finally, further potential research and clinical uses, based on ligand studies, are outlined.

Keywords: Ligand studies – Neuroimaging – Neuropsychiatric disorders – PET – SPECT – SPET

INTRODUCTION

This paper begins by outlining the basic principles underlying the use of cranial single-proton emission computerized tomography (SPECT). The uses and applications of SPECT in neuropsychiatric disorders are then reviewed. The paper ends with an appraisal of the potential developments in the rapidly progressing field of the application of SPECT in ligand studies.

BASIC PRINCIPLES

The study of cerebral blood flow (CBF) and cerebral metabolism in neuropsychiatry began after the Second World War with the development of a technique by Kety and Schmidt (1948) involving the inhalation of nitrous oxide. This early method simply gave an index of total cranial CBF. It entailed sampling the arterial blood supply to the brain and the internal jugular venous flow from the brain.

The nitrous oxide inhalation technique was superseded by methods based on the radioactive gases ^{85}Kr (krypton-85) and ^{133}Xe (xenon-133) which allowed the measurement of regional cerebral blood flow (rCBF). Initially the radioactive gas was administered intra-arterially (Lassen and Ingvar, 1963), but, with the advent of better scintillation counter technology, inhalation became the most popular route of administration.

The combination of the measurement of gamma ray photons emitted through the scalp, following inhalation of ^{133}Xe, with computerized tomography, gave birth to SPECT. The "single-photon" in the name refers to the fact that the radioactive tracers used emit single photons (of gamma ray electromagnetic radiation). One major disadvantage of ^{133}Xe SPECT is its low resolution. In addition, only cortical areas could be imaged in initial studies. Another disadvantage of ^{133}Xe SPECT is that clearance curves recorded over the scalp by scintillation counters on either side of the head are contaminated by photons emanating from the contralateral cerebral hemisphere, a phenomenon referred to as cross-talk (Sakai *et al.*, 1979). Furthermore, scalp clearance curves may also be contaminated by leakage from the face mask of the ^{133}Xe being inhaled. When compared with the same subjects during leak-free runs, it has been found that even small leaks of ^{133}Xe from the face mask lead to significant differences in the rCBF values, particularly in those regions nearest the face mask, that is, the frontal lobes (Mathew *et al.*, 1988).

The difficulties of scalp clearance curve contamination and relatively poor image spatial resolution with ^{133}Xe SPECT have largely been overcome by two recent developments: the use of ^{123}I (iodine-123) and ^{99m}Tc (technetium-99m) radiolabelled tracers; and the use of more

sophisticated photon detector systems. In contrast to the freely diffusible (or dynamic) radiotracer ^{133}Xe, the newer ^{123}I and ^{99m}Tc radiolabelled (static) tracers are retained in the brain for longer (allowing more accurate photon detection over a longer period) and display a more fixed regional cerebral distribution (thus allowing better resolution rCBF images); these properties allowed static SPECT imaging to take place using the rotating head gamma camera. The first of the newer static tracers to be widely used in neuropsychiatric studies was the radiopharmaceutical [^{123}I]*p*-iodo-*N*-isopropylamphetamine (^{123}I-IMP), which had the distinct advantage that the kinetics of its cerebral uptake are such that initially the latter is approximately proportional to the rCBF (Kuhl *et al.*, 1982). However, major disadvantages of ^{123}I-IMP include its relatively long half-life, of approximately 13 h, and the fact that it is relatively expensive since, as with radiotracers used in positron emission tomography (PET), a cyclotron is needed for its generation. These difficulties have been overcome with the development of the comparatively inexpensive radiopharmaceutical [^{99m}Tc]*d, l*-hexamethyl-propyleneamine oxime (^{99m}Tc-HMPAO). In comparison to ^{123}I-IMP, the chemical structure of ^{99m}Tc allows its incorporation in a relatively large variety of molecules. ^{99m}Tc-HMPAO displays rCBF dependent uptake with little redistribution over time. The lipophilic ^{99m}Tc complex has been demonstrated, *in vitro*, to convert slowly to a secondary complex, and this may underlie the relative lack of cerebral redistribution (Neirinckx *et al.*, 1987); after crossing the blood-brain barrier on first pass, ^{99m}Tc-HMPAO enters brain cells where the pH change renders the molecules lipophobic. The half-life of ^{99m}Tc-HMPAO is only approximately 6 h and the radioisotope ^{99m}Tc is easily obtainable from nuclear medicine department generators. Following the formation of the cerebral lipophilic ^{99m}Tc complex, a relatively high proportion of the radioactivity left in the blood is trapped in erythrocytes, possibly by a similar mechanism to that causing cerebral retention. However, since the total volume of blood in the adult brain is of the order of 0.031 l, the contribution of photons from the blood to the total photon count from the brain is very small, being less than 2% at 1 h postinjection (Neirinckx *et al.*, 1987).

So far as the detection of photons is concerned, the conventional rotating gamma camera used in most clinical nuclear medicine departments has been technically superseded by high resolution, multidetector systems using a head-dedicated ring of focused detectors which move around the source, known as single-photon ring tomography (SPRINT), which give a higher sensitivity and resolution (Mountz *et al.*, 1991).

SPECT of the brain was until recently regarded as a poor relation to PET. The main difference is that whereas in PET the radiotracers used emit positrons which in turn react with electrons to yield two photons (of gamma radiation) per reaction, the radiotracers used in SPECT decay with the emission of a single photon, so that in theory locating the source of the emission in SPECT is less precise and hence spatial resolution is limited. However, by using SPRINT with ^{99m}TC-HMPAO, SPECT can now give rCBF images with a resolution of 7-8 mm at the detector, which approaches that of PET (Lewis, 1992). Moreover, as mentioned above, compared with PET, ^{99m}Tc-HMPAO SPECT is much cheaper; the radiotracers used in PET, having relatively short half-lives, require the presence of an on-site cyclotron for their generation. It should be noted that PET allows absolute measurement of rCBF in ml/min, whereas SPECT is semiquantitative, measurements being expressed as a ratio (for example, cerebral to cerebellar radiotracer uptake).

In the following discussion of the use and applications of SPECT in neuropsychiatric disorders, whenever possible the studies reviewed generally do not include low resolution studies and those involving the use of ^{133}Xe. In determining relative cerebral perfusion in neuropsychiatric disorders that do not affect the cerebellum, the ratio of cerebral to cerebellar radiotracer uptake is often used.

NEUROPSYCHIATRIC DISORDERS

Dementia

To date, the majority of SPECT studies in dementia have been concerned with Alzheimer's disease, either on its own or in comparison with other causes of dementia. The most consistent finding in Alzheimer's disease is that patients have a bilateral decrease in rCBF in the posterior temporal and parietal regions, adjacent to the occipital lobe; occasionally decreased rCBF is also found in the frontal lobes, although the basal ganglia tend to be unaffected (Geaney and Abou-Saleh, 1990). These findings are consistent with earlier PET studies which also demonstrated decreased rCBF and reduced oxygen and glucose metabolism in the temporo-parietal and frontal regions (Frackowiak *et al.*, 1981; Benson *et al.*, 1983). Moreover, the finding in right-handed subjects with Alzheimer's disease, using PET, that a reduced rCBF and reduced cerebral metabolic rate (CMR) occur in the right parietal lobe of those with apraxia, and in the left temporo-parietal region in those with aphasia (Foster *et al.*, 1983) has been mirrored by similar SPECT findings (for example, Burns *et al.*, 1989) which indicate that praxis is related to posterior non-dominant parietal activity, memory to dominant temporal activity, and language functions to activity throughout the dominant cerebral hemisphere. Cerebral protein biosynthesis, measured with ^{11}C methionine, has also been demonstrated to be reduced in parietal and frontal regions (Bustany *et al.*, 1983) and may be related to a greater vul-

nerability in these regions to oxidative impairments, possibly leading in turn to decreased activity of the ketoglutarate dehydrogenase complex, and so causing impaired glutamate metabolism and selective neuronal death (Blass and Gibson, 1991).

Although most studies conclude that ^{99m}Tc-HMPAO SPECT may be useful in diagnosing Alzheimer's disease, most of these studies have been retrospective with patient selection based on the diagnosis confirmed at the time of SPECT neuroimaging (Holman *et al.*, 1992). Furthermore, reduced rCBF in the bilateral temporo-parietal regions does not always occur in Alzheimer's disease (Neary *et al.*, 1987), and false positive results may also occur (Hoffman *et al.*, 1990). These difficulties have been addressed in a recent prospective study of 132 consecutive patients with cognitive dysfunction who were neuroimaged using ^{99m}Tc-HMPAO SPECT (Holman *et al.*, 1992). The conclusion of this study was that ^{99m}Tc-HMPAO SPECT is indeed useful in the diagnostic evaluation of patients with cognitive dysfunction, with the presence of bilateral posterior cortical rCBF defects indicating a high probability, of the order of approximately 0.8, of the presence of Alzheimer's disease; unilateral posterior rCBF defects and frontal rCBF defects were not found to be predictive of this disorder.

Case studies of patients with Down's syndrome who were clinically diagnosed as suffering from the neuropathological changes of Alzheimer's disease have demonstrated the SPECT changes seen in Alzheimer's disease (Nakayasu *et al.*, 1991; Rae-Grant *et al.*, 1991). Therefore it may be possible to use SPECT to detect presymptomatic and early cases of dementia in this common cause of mental retardation.

Multi-infarct dementia has not been found to be associated with any particular pattern of rCBF deficits (Deisenhammer *et al.*, 1989; Geaney and Abou-Saleh, 1990). As would be expected, therefore, most studies have demonstrated that SPECT correctly distinguishes Alzheimer's disease from multi-infarct dementia in the majority of cases, for example in 80% of cases in a large study of 160 consecutively imaged elderly patients with suspected dementia (Launes *et al.*, 1991). One recent study that did not find a statistically significant decrease in ^{99m}Tc-HMPAO uptake in the temporo-parietal region in Alzheimer's disease compared with multi-infarct dementia was based on a sample of just 27 demented patients (Weinstein *et al.*, 1991).

Tohgi *et al.* (1991) carried out a study of 18 patients with vascular dementia of the Binswanger type compared with 25 patients with Alzheimer's disease. It was found that moderate dementia of the Binswanger type was significantly associated with a reduced bilateral uptake of ^{123}I-IMP in the basal grey region (that is, the thalamus and basal ganglia) and the frontal area. In the more severe cases of the vascular dementia the rCBF was significantly decreased in all areas. Moreover, the decrease in the mean value of the rCBFs was significantly correlated with clinical severity as measured by psychometric testing.

Using ^{99m}Tc-HMPAO as the radiotracer and Alzheimer's disease as a comparative group, both Habert *et al.* (1991) and Neary *et al.* (1987) have studied patients with Pick's disease and progressive supranuclear palsy. Both causes of dementia were found to be associated with frontal hypoperfusion, with the pattern of frontal deficits differing between the two disorders. A marked hypoperfusion was found to affect the superior and inferior cortices in Pick's disease while progressive supranuclear palsy was associated with a smaller, but still significant, decrease in the rCBF in only the superior frontal cortex (Habert *et al.*, 1991). In the earlier study by Neary *et al.* (1987) progressive supranuclear palsy was associated with an intact rim of frontal cerebral perfusion, which would be consistent with subcortical dysfunction. A study by Miller *et al.* (1991) of eight patients with Pick's disease, using ^{123}I-IMP SPECT, demonstrated frontal and temporal hypoperfusion, with relative sparing of parietal and occipital blood flow; this finding is in accord with the known distribution of neuropathological changes in this cause of dementia.

In contrast to patients with Alzheimer's disease, in Korsakoff's psychosis posterior temporal rCBF has been reported to be maintained, although a trend has been found to reduced ^{99m}Tc-HMPAO uptake in other cortical areas which in turn was correlated with impairment of neuropsychological function (Hunter *et al.*, 1989a).

In two separate case reports of patients with Creutzfeld-Jakob disease, the diagnosis being proved by biopsy, ^{99m}Tc-HMPAO SPECT demonstrated either perfusion defects in the left frontal and right temporo-parietal regions (Cohen *et al.*, 1989) or throughout the cerebral cortex (Hunter *et al.*, 1989b). That these apparently differing findings may be part of the same picture at different times is suggested by the fact that both focal and generalized reductions in the rCBF were found in a third case study, using ^{123}I-IMP and ^{99m}Tc-HMPAO, in which decreased accumulation of both radiotracers occurred, localized initially in focal regions and then progressing eventually to the whole brain (Ono *et al.*, 1989). The clinical value of SPECT over X-ray computerized tomography (CT) in the investigation of this condition is highlighted by the finding of a normal brain CT scan in all three cases. In an earlier report of two cases of clinically diagnosed (but not pathologically proved) Creutzfeld-Jakob disease, ^{123}I-IMP SPECT demonstrated decreased rCBF in all cortical areas, while CT and magnetic resonance imaging (MRI) showed no abnormality apart from slight cortical atrophy (Momose *et al.*, 1988).

Since it is generally accepted that Parkinson's disease is

caused by depletion of dopaminergic neurones of the substantia nigra that project to the corpus striatum (Adams and Graham, 1988), it might be expected that SPECT neuroimaging in this disorder would reveal a reduced rCBF in the basal ganglia. This has indeed been found to be so in a SPECT study, using ^{123}I-IMP, of 20 patients with Parkinson's disease (Hayashi *et al.*, 1989) in which rCBFs in the basal ganglia and frontal cortex were reduced by a quarter compared with normal controls. In a larger Japanese study, with ^{123}I-IMP SPECT, of 159 patients with Parkinson's disease, Morimatsu (1991) found a reduction in the rCBF in the frontal and temporal lobes which was correlated with the severity of the disease using Yahr staging. Furthermore, scores on the Mini-Mental State and Hasegawa's Dementia Scale showed a highly significant correlation with the blood flow in the frontal and parietal lobes, leading the author to suggest that dementia in this condition may be caused by dysfunction in these regions. On the other hand, a small number of studies has demonstrated bilateral posterior hypoperfusion. For example, in a study of 30 patients with Parkinson's disease by Spampinato *et al.* (1991) a comparison of rCBF, evaluated by ^{99m}Tc-HMPAO SPECT, was carried out in 15 patients with dementia and 15 without dementia. It was found that rCBFs in non-demented Parkinson's disease patients did not differ from a further set of control subjects. In the demented patients with Parkinson's disease, however, a significant rCBF reduction was found in the parietal, temporal and occipital cortices, although not in the frontal cortex. The above studies on Parkinson's disease have demonstrated bilateral haemodynamic changes. In order to test the effects of lateralized parkinsonian symptoms on cognition and rCBF, a cognitive battery and SPECT study by Agniel *et al.* (1991) was carried out on 23 right-handed patients with lateralized idiopathic Parkinson's disease, comparing 13 patients with predominantly right-sided symptoms with 10 having predominantly left-sided symptoms. No correlation was found between laterality of motor parkinsonian symptoms and cognitive or haemodynamic asymmetry scores. Changes in rCBF with respect to the "one-off" syndrome have also been evaluated. Using ^{99m}Tc-HMPAO SPECT, Costa *et al.* (1988) studied patients with Parkinson's disease during an "on" phase (under levodopa therapy) and on a separate occasion after withdrawal of the levodopa ("off" phase). A significant change was found in the radiotracer uptake in the caudate nucleus, in which the ^{99m}Tc-HMPAO uptake was lower during the "off" phase, and in the thalamus, in which uptake was higher during the same phase.

In general, the SPECT findings in Huntington's disease are consistent with its known neuropathological changes, with bilaterally decreased radiotracer uptake in the basal ganglia, involving the heads of the caudate nuclei and adjacent structures (Nagel *et al.*, 1991; Geaney and Abou-Saleh, 1990). Although parallel findings are generally found using MRI, the rCBF deficit in SPECT may be greater than that expected from MRI (Smith *et al.*, 1988).

Dementia occurring in AIDS is considered in the section on HIV infection and AIDS below.

Schizophrenia

Both PET and SPECT have shown cortical abnormalities in schizophrenia, as described below. It can be argued that these are best demonstrated under conditions of cognitive activation, whereby differences from normal controls are greatest when imaging is carried out while subjects are engaged in a cognitive task known to be mediated by the cortical region of interest (Lewis, 1992).

Left dorsolateral frontal deficits have been shown in right-handed patients with schizophrenia in ^{133}Xe inhalation SPECT studies (Weinberger *et al.*, 1986), as has left temporal overactivity (Mathew *et al.*, 1988) which has also been shown with ^{18}F-deoxyglucose PET (DeLisi *et al.*, 1989), as well as with ^{123}I-IMP SPECT in a single case study of an hallucinating patient (Matsuda *et al.*, 1988). Right parietal deficits were reported by Cleghorn *et al.* (1989) and found to correlate with deficits on a range of neuropsychological tests.

The most consistent finding using ^{99m}Tc-HMPAO SPECT is hypofrontality. Thus in a report of six paraphrenic patients by Podreka *et al.* (1987), half showed hypofrontality. Similarly, in a case report by Hawton *et al.* (1990) involving neuroimaging on three occasions in a right-handed 42-year-old woman suffering from schizophrenia, marked hypofrontality, possibly entering into the temporo-parietal region, was shown during an acute psychotic phase of the illness. During remission the scintigrams were within normal limits, but some return of the original deficit was subsequently noted during a relapse.

The first comparative study of rCBF in schizophrenia and heathly controls using ^{99m}Tc-HMPAO SPECT was reported by Rubin *et al.* (1991). Nineteen patients newly diagnosed as suffering from schizophrenia or schizophreniform psychosis were compared with seven healthy volunteers. The patients were either neuroleptic drug naive or else had received neuroleptics for only a few days. Following neuroimaging at rest, activation was carried out using the Wisconsin card sorting test, a problem-solving and abstract-reasoning test known from previous studies to be a sensitive indicator of frontal function in humans (Weinberger *et al.*, 1986). A significant relative activation deficit in the left inferior prefrontal region and impaired left striatal suppression were found during activation in the patient group. The authors speculate that the inability to suppress striatal activity may result from a lack of corticostriatal feedback during prefrontal activation.

Lewis *et al.* (1992) also carried out a similar comparative study, again using ^{99m}Tc-HMPAO SPECT. The rCBF

was measured during a word fluency cognitive task, which selectively activates frontal regions (particularly on the left side), in 25 male, right-handed, medicated patients with schizophrenia and in 25 age-matched male, right-handed healthy volunteers. Compared with the controls, in subcortical regions patients showed increased rCBF in the caudate and thalamus; this was probably secondary to pharmacotherapy with neuroleptic medication, as indicated by previous PET studies (for example, DeLisi *et al.*, 1985; Szechtman *et al.*, 1988). In the cortex, patients showed a patterned abnormality comprising: markedly decreased rCBF in left mesial, inferior and dorsolateral frontal regions; possibly decreased right parietal rCBF; and increased rCBF in left superior temporal and occipital regions. Similar cortical deficits have been reported in previous studies, as mentioned above. The overall pattern of the cortical abnormalities was highly reminiscent of that reported by Buchsbaum *et al.* (1990) which used ^{18}F-deoxyglucose PET to examine regional brain glucose uptake in 13 medication-free patients with schizophrenia and 37 healthy controls, while carrying out a cognitive activation task. The fact that these two studies differed with respect to whether the patients were medication-free would tend to suggest that the similar changes seen in both are robust to medication status. Other findings by Lewis *et al.* (1992) were that lateralized patterns of left-sided frontal rCBF dominance in controls were reversed in patients, as were normal patterns of right-sided parietal rCBF dominance. Also, negative symptom score correlated inversely with mesial frontal rCBF, particularly on the left. This suggests that mesial frontal dysfunction might be at least as important as dorsolateral frontal dysfunction (Weinberger *et al.*, 1986; Liddle, 1987) in explaining the neuropsychological deficits which underlie negative symptoms of schizophrenia. In a PET study of 30 patients with schizophrenia by Liddle *et al.* (1992), the syndrome of psychomotor poverty was also found to be associated with left dorsolateral prefrontal dysfunction, with the region of hypoperfusion extending to the medial prefrontal cortex and contiguous anterior cingulate cortex.

Mood disorders

The vast majority of the relatively few studies published to date on the measurement of rCBF with SPECT in patients with mood (affective) disorders have used inhaled ^{133}Xe as the radiotracer. They may therefore suffer from some of the artefacts of inhalation ^{133}Xe SPECT outlined above, and this may account, at least in part, for the conflicting results so far. While Mathew *et al.* (1980) and Gustafson *et al.* (1981) found a decrease in rCBF in depressed patients at rest, Uytenhoef *et al.* (1983) found an increase in rCBF in the left frontal lobe and a decrease in right posterior areas in such patients, and other studies have shown no difference in rCBF between depressed patients and controls (Risberg, 1980; Gur *et al.*, 1982, 1984; Silfverskiöld and Risberg, 1989).

In a study of 38 patients with major depressive disorders and 16 controls, again using ^{133}Xe SPECT, Delvenne *et al.* (1990) also found that global right and left cerebral hemisphere blood flow did not differ between the two groups. However, when only cortical rCBF was considered, the cortical blood flow was significantly lower in the left hemisphere in right-handed bipolar patients compared with controls and unipolar patients. The same lateralization was also found in patients with the endogenous subtype of depression according to the Newcastle Scale.

In a study of rCBF, measured using ^{99m}Tc-HMPAO SPECT, in 18 elderly (age range 66-90 years) patients suffering from major depressive disorder, Upadhyaya *et al.* (1990) found a reduced blood flow in all cerebral regions compared with an elderly (age range 58-91 years) control group. The difference was found to be statistically significant for the total cerebral blood flow, and almost reached statistical significance ($\alpha = 0.05$) in the left temporal and right parietal regions.

A larger study of 41 patients with major depressive disorder found that rCBF, measured using ^{133}Xe inhalation SPECT, was reduced in selective frontal, central, superior temporal and anterior parietal regions, compared with a group of 40 matched normal controls (Sackeim *et al.*, 1990). The authors speculate this result may be caused by dysfunction in the parallel distributed cortical network involving frontal and temporo-parietal polymodal association areas.

Obsessive-compulsive disorder

A case report of a patient with a severe obsessive-compulsive disorder found a reduced rCBF, measured by ^{123}I-IMP SPECT, in the right basal ganglia and adjacent anterior right temporal lobe, which reverted to normal following major symptom reduction with pharmacotherapy (Hamlin *et al.*, 1989).

A series of 10 obsessive-compulsive patients was studied by Machlin *et al.* (1991). Compared with eight control subjects, the patients were found to have a significantly higher ratio of medial-frontal to whole cortex blood flow, which was unrelated to the severity of the obsessive-compulsive symptomatology, but was negatively correlated with anxiety symptoms. No orbital-frontal cerebral blood flow differences were found.

HIV infection and AIDS

CT and MRI are usually normal in early HIV encephalopathy (AIDS dementia complex), and therefore are not useful in differentiating it from psychogenic conditions. However, in a study of 32 patients with HIV encephalopathy, it was found that 30 of these patients had SPECT

changes which differed from the findings in 15 patients with non-HIV psychoses and in six controls (Masdeu *et al.*, 1991). The rCBF changes in HIV encephalopathy included multifocal cortical and subcortical areas of hypoperfusion. Furthermore, in four of the patients cognitive improvement took place following pharmocotherapy with zidovudine (AZT) which was mirrored by amelioration in the corresponding SPECT scintigraphic findings; CT scans remained unchanged, however. Another relatively large SPECT study of 26 patients with HIV encephalopathy also showed extensive cortical areas of hypoperfusion in all patients, particularly in the frontal and parietal lobes (Maini *et al.*, 1990). The extent of the hypoperfusion was highly significantly correlated with the severity of the dementia complex. Furthermore, in three of the patients CT scans were normal, while two patients had normal MRI signals. This again suggests that there is a high prevalence of cortical hypoperfusion in HIV encephalopathy and that SPECT is likely to be a better neuroimaging technique in the early diagnosis and follow-up of such patients, particularly when CT and MRI do not reveal any abnormalities. A similar conclusion was reached by Ajmani *et al.* (1991), who in a smaller study of five patients found that CT scans remained negative except in patients with the most severe dementia, whereas SPECT was very sensitive in showing brain perfusion defects.

Another study demonstrating that SPECT is likely to be a superior imaging technique to CT and MRI in patients with HIV infection and AIDS was carried out by Pigorini *et al.* (1991). In 11 patients with AIDS-related neurotoxoplasmosis it was shown that ^{99m}Tc-HMPAO SPECT may show focal hypoperfusing in patients with normal CT studies and/or non-focal MRI abnormalities. It was also found that the hypoperfusion may be more extensive than the corresponding MRI lesions and indeed may be present in regions with normal MRI signals.

LIGAND STUDIES

One of the potentially most exciting uses of SPECT is in the expanding field of neuroreceptor imaging. In a major advance on the studies of the last two decades or so using ^{3}H-labelled ligand receptor binding, new radiotracers are being developed which carry gamma radiation photon emitting radionuclides to neuroreceptors. The time-course of the regional concentration of such radiolabelled ligands can then be measured with SPECT and PET (Maziere and Maziere, 1990).

At the time of writing, radiotracers for use in SPECT central neuroreceptor imaging studies are available for dopamine receptors (D_1 and D_2), benzodiazepine receptors, and serotonin receptors (5-HT_1 and 5-HT_2). Two examples of recent research using such radiotracers are now outlined.

A recently introduced D_2 dopamine receptor ligand which can be used with SPECT is ^{123}I-IBZM (3-iodo-6-methoxybenzamide). Using this ligand a marked reduction was found in the density of D_2 dopamine receptors in the corpus striatum of 10 unmedicated patients with Huntington's disease compared with control subjects, thus demonstrating the clinical value of ^{123}I-IBZM SPECT in the diagnosis of Huntington's disease (Brucke *et al.*, 1991). By extension, it would be expected that using appropriate ligands SPECT would similarly be of diagnostic value in other neurodegenerative disorders. In the same study ^{123}I-IBZM was also administered to 12 patients receiving different neuroleptics. A curvilinear relationship was found between the total daily dose of neuroleptic and the reduction of the ratio of striatal to lateral frontal cortical counts per pixel. Under full neuroleptic treatment the estimated D_2 dopamine receptor blockade was 75-80%, and ^{123}I-IBZM binding decreased significantly with increasing age. The radiolabelled isomer used was S-(−)-IBZM. When a racemic mixture of IBZM was used there was a marked reduction in specific binding to D_2 dopamine receptors, while no specific binding occurred with the isomer R-(+)-IBZM, thus confirming the stereoselectivity of IBZM binding.

Similarly, using SPECT Innis *et al.* (1991) have demonstrated the use of ^{123}I-Iomazenil (^{123}I-Ro 16-0154), a central benzodiazepine receptor ligand, as an *in vivo* probe of this receptor in primate brains.

These results indicate the type of specific neuroreceptor studies that are possible with SPECT, and also point to the possibility of diagnostic uses and further direct clinical uses such as the monitoring of pharmacotherapy.

REFERENCES

Adams JH and Graham DI (1988) *An Introduction to Neuropathology*. Churchill Livingstone, Edinburgh.

Agniel A, Celsis P, Viallard G, Montastruc JL, Rascol O, Demonet JF, Marc-Vergnes JP and Rascol A (1991) Cognition and cerebral blood flow in lateralised parkinsonism: lack of functional lateral asymmetries. *Journal of Neurology, Neurosurgery and Psychiatry*, **54**, 783-786.

Ajmani A, Habte-Gabr E, Zarr M, Jayabalan V and Dandala S (1991) Cerebral blood flow SPECT with Tc-99m exametazine correlates in AIDS dementia complex stages. *Clinical Nuclear Medicine*, **16**, 656-659.

Benson DF, Kuhl DE, Hawkins RA, Phelps ME, Cummings JL and Tsai SY (1983) The fluoro-deoxyglucose ^{18}F scan in Alzheimer's disease and multi-infarct dementia. *Archives of Neurology*, **40**, 711-714.

Blass JP and Gibson GE (1991) The role of oxidative abnormalities in the pathophysiology of Alzheimer's disease. *Revue Neurologique*, **147**, 513-525.

Brucke T, Podreka I, Angelberger P, Wenger S, Topitz A, Kufferle B, Muller C and Deecke L (1991) Dopamine D_2 receptor

imaging with SPECT: studies in different neuropsychiatric disorders. *Journal of Cerebral Bood Flow and Metabolism*, **11**, 220-228.

Buchsbaum MS, Nuechterlein KH, Haier RJ, Wu J, Sicotte N, Hazlett E, Asarnow R, Hopkin S and Guich S (1990) Glucose metabolic rate in normals and schizophrenics during the continuous performance test assessed by positron emission tomography. *British Journal of Psychiatry*, **156**, 216-227.

Burns A, Philpot MP, Costa DC, Ell PJ and Levy R (1989) The investigation of Alzheimer's disease with single photon emission tomography. *Journal of Neurology, Neurosurgery and Psychiatry*, **52**, 248-253.

Bustany P, Hendry JF, Sargent T, Zarifian E, Cabanis E, Collard P and Comar D (1983) Local brain protein metabolism in dementia and schizophrenia: *in vitro* studies with ^{11}C methionine and positron emission tomography. In: *Positron Emission Tomography of the Brain* (Eds WD Heiss and M Phelps), pp. 208-211. Springer, Berlin.

Cleghorn JM, Kaplan RD, Nahmias C, Garnett ES, Szechtman H and Szechtman B (1989) Inferior parietal region implicated in neurocognitive impairment in schizophrenia. *Archives of General Psychiatry*, **46**, 758-759.

Cohen D, Krausz Y, Lossos A, Ben-David E and Atlan H (1989) Brain SPECT imaging with Tc-99m HM-PAO in Creutzfeld-Jakob disease. *Clinical Nuclear Medicine*, **14**, 808-810.

Costa DC, Ell PJ, Burns A, Philpot M and Levy R (1988) CBF tomograms with ^{99m}Tc-HM-PAO in patients with dementia (Alzheimer type and HIV) and Parkinson's disease: initial results. *Journal of Cerebral Blood Flow and Metabolism*, **8**, S109-S115.

Deisenhammer E, Reisecker F, Leblhuber F, Höll K, Markut H, Trenkler J and Schneider I (1989) Single-photon-emissions-computertomographie bei der differentialdiagnose der demenz. *Deutsche medizinische Wochenschrift*, **114**, 1639-1644.

DeLisi LE, Holcomb HH, Cohen RM, Pickar D, Carpenter W, Morihisa JM, King AC, Kessler R and Buchsbaum MS (1985) Positron emission tomography in schizophrenic patients with and without neuroleptic medication. *Journal of Cerebral Blood Flow and Metabolism*, **5**, 201-206.

DeLisi LE, Buchsbaum MS, Holcomb HH, Lanston KC, King AC, Kessler R, Pickar D, Carpenter W, Morihisa JM, Margolin R and Weinberger DR (1989) Increased temporal lobe glucose use in chronic schizophrenic patients. *Biological Psychiatry*, **25**, 835-851.

Delvenne V, Delecluse F, Hubain PhP, Schoutens A, De Maertelaer V and Mendlewicz J (1990) Regional cerebral blood flow in patients with affective disorders. *British Journal of Psychiatry*, **157**, 359-365.

Foster NL, Chase TN, Fedio P, Patronal NJ, Brooks RA and DiChiro G (1983) Alzheimer's disease: focal cortical changes shown by positron emission tomography. *Neurology*, **33**, 961-965.

Frackowiak RSJ, Pozzilli C, Legg NJ, Du Boulay GH, Marshall J, Lenzi GL and Jones T (1981) Regional cerebral oxygen supply and utilization in dementia: a clinical and physiological study with oxygen-15 and positron tomography. *Brain*, **104**, 753-778.

Geaney DP and Abou-Saleh MT (1990) The use and applications of single-photon emission computerised tomography in dementia. *British Journal of Psychiatry*, **157** (Suppl. 9), 66-75.

Gur RC, Gur RE, Obrist WD, Hungerbuhler JP, Younkin D, Rosen AD, Skolnick BE and Reivich M (1982) Sex and handedness differences in cerebral blood flow during rest and cognitive activity. *Science*, **213**, 659-661.

Gur RE, Skolnick BE, Gur RC, Caroff S, Rieger W, Obrist WD, Younkin D and Reivich M (1984) Brain function in psychiatric disorders. II. Regional cerebral blood flow in medicated unipolar depressiveness. *Archives of General Psychiatry*, **41**, 695-699.

Gustafson L, Risberg J and Silfverskiöld P (1981) Regional cerebral blood flow in organic dementia and affective disorders. In: *Advances in Biological Psychiatry*, Vol. 6, *Electroneurophysiology and Psychopathology* (Eds C Perris, D Kemali and L Vacca), pp. 109-116. Karger, Basel.

Habert MO, Spampinato U, Mas JL, Piketty ML, Bourdel MC, DeRecondo J, Rondot P and Askienazy S (1991) A comparative technetium 99m hexamethylpropylene amine oxime SPET study in different types of dementia. *European Journal of Nuclear Medicine*, **18**, 3-11.

Hamlin CL, Swayne LC and Liebowitz MR (1989) Striatal IMP-spect decrease in obsessive-compulsive disorder, normalized by pharmacotherapy. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*, **2**, 290-300.

Hawton K, Shepstone B, Soper N and Reznek L (1990) Single-photon emission computerised tomography (SPECT) in schizophrenia. *British Journal of Psychiatry*, **156**, 425-427.

Hayashi H, Odano I, Nishihara M, Higuchi S, Sakai K and Ishikawa A (1989) Clinical evaluation of Parkinson's disease using (123)I-IMP SPECT. *Kaku-Igaku*, **26**, 1405-1415.

Hoffman JM, Hanson MW, Earl NL and Coleman RE (1990) Beware the classic FDG-PET pattern of Alzheimer's disease. *Journal of Nuclear Medicine*, **31**, 740.

Holman BL, Johnson KA, Gerada B, Carvalho PA and Satlin A (1992) The scintigraphic appearance of Alzheimer's disease: a prospective study using technetium-99m-HMPAO SPECT. *Journal of Nuclear Medicine*, **33**, 181-185.

Hunter R, McLuskie R, Wyper D, Patterson J, Christie JE, Brooks DN, McCulloch J, Fink G and Goodwin GM (1989a) The pattern of function-related regional cerebral blood flow investigated by single photon emission tomography with ^{99m}Tc-HMPAO in patients with presenile Alzheimer's disease and Korsakoff's psychosis. *Psychological Medicine*, **19**, 847-855.

Hunter R, Gordon A, McLuskie R, Wyper D, Patterson J, Christie JE, Fink G and Goodwin GM (1989b) Gross regional cerebral hypofunction with normal CT scan in Creutzfeld-Jakob disease. *The Lancet*, **333**, 214-215.

Innis R, Zoghbi S, Johnson E, Woods S, al-Tikriti M, Baldwin R, Seibyl J, Malison R, Zubal G, Charney D, *et al.* (1991) SPECT imaging of the benzodiazepine receptor in non-human primate brain with [123I]Ro 16-0154. *European Journal of Pharmacology*, **193**, 249-252.

Kety S and Schmidt C (1948) The nitrous oxide method for quantitative determination of cerebral blood flow in man: theory, procedure, and normal values. *Journal of Clinical Investigation*, **27**, 475-483.

Kuhl DE, Barrio JR, Huang SC, Selin C, Ackermann RF, Lear JL, Wu JL, Lin TH and Phelps ME (1982) Quantifying local cerebral blood flow by *N*-isopropyl-*p*- ^{123}I iodoamphetamine (IMP) tomography. *Journal of Nuclear Medicine*, **23**, 196-203.

Lassen N and Ingvar D (1963) Regional cerebral blood flow measurement in man: a review. *Archives of Neurology*, **9**, 615-622.

Launes J, Sulkava R, Erkinjuntti T, Nikkinen P, Lindroth L, Liewendahl K and Iivanainen M (1991) ^{99m}Tc-HMPAO SPECT in

suspected dementia. *Nuclear Medicine Communications*, **12**, 757-765.

Lewis SW (1992) Brain imaging in psychiatry: another look. *British Journal of Hospital Medicine*, **47**, 175-183.

Lewis SW, Ford RA, Syed GM, Reveley AM and Toone BK (1992) A controlled study of 99mTc-HMPAO single-photon emission imaging in chronic schizophrenia. *Psychological Medicine*, **22**, 27-35.

Liddle PF (1987) Schizophrenic syndromes, cognitive performance and neurological dysfunction. *Psychological Medicine*, **17**, 49-57.

Liddle PF, Friston KJ, Frith CD, Hirsch SR, Jones T and Frackowiak RSJ (1992) Patterns of cerebral blood flow in schizophrenia. *British Journal of Psychiatry*, **160**, 179-186.

Machlin SR, Harris GJ, Pearlson GD, Hoehn-Saric R, Jeffery P and Camargo EE (1991) Elevated medial-frontal cerebral blood flow in obsessive-compulsive patients: a SPECT study. *American Journal of Psychiatry*, **148**, 1240-1242.

Maini CL, Pigorini F, Pau FM, Volpini V, Galgani S, Rosci MA and Narciso P (1990) Cortical cerebral blood flow in HIV-1-related dementia complex. *Nuclear Medicine Communications*, **11**, 639-648.

Masdeu JC, Yudd A, Van-Heertum RL, Grundman M, Hriso E, O'Connell RA, Luck D, Camli U and King LN (1991) Single-photon emission computed tomography in human immunodeficiency virus encephalopathy: a preliminary report. *Journal of Nuclear Medicine*, **32**, 1471-1475.

Mathew RJ, Meyer JS, Francis DJ, Semchuk KM, Mortel K and Claghorn J (1980) Cerebral blood flow in depression. *American Journal of Psychiatry*, **137**, 1449-1450.

Mathew RJ, Wilson WH, Hant SR, Robinson L and Prakash R (1988) Abnormal resting regional cerebral blood flow patterns and their correlates in schizophrenia. *Archives of General Psychiatry*, **45**, 542-549.

Matsuda H, Gyobu T, Masayasu 2d and Hisada K (1988) Increased accumulation of *n*-isopropyl (I123) *p*-iodo-amphetamine in the left auditory area in a schizophrenic patient with auditory hallucinations. *Clinics in Nuclear Medicine*, **13**, 53-55.

Maziere B and Maziere M (1990) Where have we got to with neuroreceptor mapping of the human brain? *European Journal of Nuclear Medicine*, **16**, 817-835.

Miller BL, Cummings JL, Villanueva-Meyer J, Boone K, Mehringer CM, Lesser IM and Mena I (1991) Frontal lobe degeneration: clinical, neuropsychological, and SPECT characteristics. *Neurology*, **41**, 1374-1382.

Momose T, Kosaka N, Nishikawa J, Ohtake T, Watanabe T, Yoshikawa K and Iio M (1988) *N*-isopropyl I-123 *p*-iodoamphetamine brain scintigraphy with SPECT in Creutzfeld-Jakob disease. *Kaku-Igaku*, **25**, 1137-1141.

Morimatsu M (1991) Diagnosis and treatment of Parkinson's disease in the elderly. *Nippon Ronen Igakkai Zasshi*, **28**, 123-128.

Mountz JM, Rogers WL, Wilson MW, Clinthorne NH, Gross MD, Speed NN and Schwartz JA (1991) Clinical SPRINT imaging: preliminary results compared to conventional SPECT brain scanning using Tc-99m HMPAO. *Clinical Nuclear Medicine*, **16**, 562-567.

Nagel JS, Ichise M and Holman BL (1991) The scintigraphic evaluation of Huntington's disease and other movement disorders using single photon emission computed tomography perfusion brain scans. *Seminars in Nuclear Medicine*, **21**, 11-23.

Nakayasu H, Araga S, Takahashi K, Otsuki K and Murata M (1991) Two cases of adult Down's syndrome presenting parietal low uptake in ^{123}I-IMP-SPECT. *Rinsho Shinkeigaku*, **31**, 557-560.

Neary D, Snowden JS, Shields RA, Burjan AW, Northen B, MacDermott N, Prescott MC and Testa HJ (1987) Single photon emission tomography using ^{99m}Tc-HM-PAO in the investigation of dementia. *Journal of Neurology, Neurosurgery and Psychiatry*, **50**, 1101-1109.

Neirinckx RD, Canning LR, Piper IM, Nowotnik DP, Pickett RD, Holmes RA, Volkert WA, Forster AM, Weisner PS, Marriott JA, *et al.* (1987) Technetium-99m *d*, *l*-HM-PAO: a new radiopharmaceutical for SPECT imaging of regional cerebral blood perfusion. *Journal of Nuclear Medicine*, **28**, 191-202.

Ono S, Fukunaga M, Otsuka N, Nagai K, Morita K, Muranaka A, Furukawa T, Yanagimoto S, Tomomitsu T, Kawai K, *et al.* (1989) A case of Creutzfeld-Jakob disease followed up by N-isopropyl *O*[^{123}I]-*p*-iodoamphetamine and ^{99m}Tc-hexamethyl propyleneamine oxime SPECT. *Kaku-Igaku*, **26**, 77-88.

Pigorini F, Maini CL, Pau FM, Galgani S, Volpini V, Leonetti C, Narciso P and Rosci MA (1991) Cerebral blood flow in AIDS-related neurotoxoplasmosis: a preliminary 99mTc-HMPAO SPECT study. *Nuklearmedizin*, **30**, 13-17.

Podreka I, Suess E, Goldenberg G, Steiner M, Brucke T, Muller C, Lang W, Neirinckx RD and Deecke L (1987) Initial experience with technetium-99m HM-PAO brain SPECT. *Journal of Nuclear Medicine*, **28**, 1657-1666.

Rae-Grant AD, Barbour PJ, Sirotta P and Gross P (1991) Alzheimer's disease in Down's syndrome with SPECT. *Clinical Nuclear Medicine*, **16**, 509-510.

Risberg J (1980) Regional cerebral blood flow measurements by (133)Xenon-inhalation: methodology and applications in neuropsychology and psychiatry. *Brain and Language*, **9**, 9-34.

Rubin P, Holm S, Friberg L, Videbech P, Andersen HS, Bendsen BB, Strømsø N, Larsen JK, Lassen NA and Hemmingsen R (1991) Altered modulation of prefrontal and subcortical brain activity in newly diagnosed schizophrenia and schizophreniform disorder: a regional cerebral blood flow study. *Archives of General Psychiatry*, **48**, 987-995.

Sackeim HA, Prohovnik I, Moeller JR, Brown RP, Apter S, Prudic J, Devanand DP and Mukherjee S (1990) Regional cerebral blood flow in mood disorders. I. Comparison of major depressives and normal controls at rest. *Archives of General Psychiatry*, **47**, 60-70.

Sakai F, Meyer JS, Yamaguchi F, Yamamoto M and Shaw T (1979) 133Xe inhalation method for measuring cerebral blood flow in conscious baboons. *Stroke*, **10**, 310-318.

Silfverskiöld P and Risberg J (1989) Regional cerebral blood flow in depression and mania. *Archives of General Psychiatry*, **46**, 253-259.

Smith FW, Besson JA, Gemmell HG and Sharp PF (1988) The use of technetium-99m-HMPAO in the assessment of patients with dementia and other neuropsychiatric conditions. *Journal of Cerebral Blood Flow and Metabolism*, **8**, S116-S122.

Spampinato U, Habert MO, Mas JL, Bourdel MC, Ziegler M, de Recondo J, Askienazy S and Rondot P (1991) ^{99m}Tc-HM-PAO SPECT and cognitive impairment in Parkinson's disease: a comparison with dementia of the Alzheimer type. *Journal of Neurology, Neurosurgery and Psychiatry*, **54**, 787-792.

Szechtman H, Nahmias C, Garrett ES, Firnau G, Brown GM, Kaplan RD and Cleghorn JM (1988) Effect of neuroleptics on altered glucose metabolism in schizophrenia. *Archives of General Psychiatry*, **45**, 523-533.

Tohgi H, Chiba K, Sasaki K, Hiroi S and Ishibashi Y (1991) Cer-

ebral perfusion patterns in vascular dementia of Binswanger type compared with senile dementia of Alzheimer type: a SPECT study. *Journal of Neurology*, **238**, 365-370.

Upadhyaya AK, Abou-Saleh MT, Wilson K, Grime SJ and Critchley M (1990) A study of depression in old age using single-photon emission computerised tomography. *British Journal of Psychiatry*, **157** (Suppl. 9), 76-81.

Uytdenhoef P, Portelange P, Jacquy J, Charles G, Linkowski P and Mendlewicz J (1983) Regional cerebral blood flow and lateralized hemispheric dysfunction in depression. *British Journal of Psychiatry*, **143**, 128-132.

Weinberger R, Berman KF and Zec RF (1986) Physiological function of dorsal lateral pre frontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. *Archives of General Psychiatry*, **43**, 114-125.

Weinstein HC, Haan J, van Royen EO, Derix MM, Lanser JB, van der Zant F, Dunnewold RJ, van Kroonenburgh MJ, Pauwels EK, van der Velde EA, *et al.* (1991) SPECT in the diagnosis of Alzheimer's disease and multi-infarct dementia. *Clinical Neurology and Neurosurgery*, **93**, 39-43.