Movement Disorders
Vol. 18, Suppl. 6, 2003, pp. S88–S95

Use of Functional Imaging in Parkinsonism and Dementia

David J. Burn, MD, FRCP,[1,2]* and John T. O'Brien, DM, MRCPsych[2]

[1]*Department of Neurology, Regional Neurosciences Centre, Newcastle General Hospital, United Kingdom*
[2]*Institute for Ageing and Health, Wolfson Research Centre, Newcastle General Hospital, United Kingdom*

Abstract: Neuropsychiatric symptoms, including dementia, frequently coexist with parkinsonian disorders and may cause diagnostic confusion as well as management problems. Functional imaging studies include single photon emission computerised tomography (SPECT), positron emission tomography (PET), proton magnetic resonance spectroscopy, diffusion tensor imaging, and functional magnetic resonance imaging. This review addresses the utility of these techniques, from the clinician's perspective, focusing on the most common causes of parkinsonism and cognitive impairment, Parkinson's disease with dementia, dementia with Lewy bodies, and Alzheimer's disease. The potential and limitations of these techniques for accurate and early diagnosis, monitoring disease progression, and establishing the pathophysiological basis underlying key clinical features are considered. The development of new probes for SPECT and PET cameras capable of labeling protein aggregates (e.g., β-amyloid) will offer exciting new insights into the spatial and temporal pattern of pathophysiological processes. Longitudinal studies with clinicopathological correlation represent the "gold standard" for fully evaluating functional imaging techniques. © 2003 Movement Disorder Society

Key words: SPECT; PET; PMRS; diffusion tensor imaging; parkinsonism; dementia; functional imaging

Dementia not uncommonly complicates several akinetic–rigid disorders (Table 1). Many of these conditions may be readily diagnosed by the clinician, supplemented where necessary by blood tests. Some forms of functional imaging are not widely available, and the studies may also be costly and time-consuming. Consequently, the question may be asked: What is the role of functional imaging in the study of parkinsonism and dementia? This review addresses this question from the clinician's perspective, focusing on the utility of functional imaging techniques in the most common causes of parkinsonism and cognitive impairment, Parkinson's disease with dementia (PDD), dementia with Lewy bodies (DLB), and Alzheimer's disease (AD). The potential of these techniques for accurate and early diagnosis, monitoring disease progression, and assisting our understanding of the pathophysiological basis for several clinical features will be highlighted.

*Correspondence to: Dr. David J. Burn, Regional Neurosciences Centre, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, United Kingdom. E-mail: d.j.burn@ncl.ac.uk
Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10568

FUNCTIONAL IMAGING TECHNIQUES

Functional imaging studies include single photon emission computerised tomography (SPECT), positron emission tomography (PET), proton magnetic resonance spectroscopy (^{1}H-MRS), diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI). PET measurements are performed by administering intravenously or by inhalation a tracer tagged with a short-lived positron-emitting isotope, prepared using a cyclotron. Examples include ^{18}F ($t^1/_2$, 110 minutes; tagged as ^{18}F-6-fluorodopa [^{18}F-dopa] and as ^{18}F-2-fluoro-2-deoxyglucose [^{18}FDG]), and $^{15}O_2$ ($t^1/_2$, 2.03 minutes). Access to PET is restricted because of the high costs involved in establishing and running PET scanners and cyclotrons and, at least for PD, is largely confined to research purposes. SPECT lacks spatial resolution in comparison with PET, although, as it can be undertaken on standard gamma cameras already present in most hospitals, it is much more widely available. Furthermore, the range of tracers for the study of dementia and parkinsonism is also increasing. An example is FP-CIT ([^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane, also known as DaTSCAN) that binds to the presynaptic dopamine transporter with good signal-to-noise

TABLE 1. *Conditions causing parkinsonism and dementia*

Parkinson's disease plus dementia
Dementia with Lewy bodies
Alzheimer's disease
Cerebrovascular disease
Progressive supranuclear palsy
Corticobasal degeneration
Hydrocephalus
Frontotemporal dementia–parkinsonism, linked to chromosome 17
Parkinsonism–dementia complex of Guam
Cerebral anoxia & carbon monoxide poisoning
Creutzfeldt-Jakob disease
Huntington's disease
Neuroacanthocytosis
Wilson's disease
Iron storage diseases
Encephalitis lethargica
Repeated head trauma ("punch-drunk" syndrome)

characteristics. Unlike previous cocaine analogues, the patient has only to wait a relatively short time (3 to 6 hours) after FP-CIT injection before scanning can occur, making day-case studies possible.

^{1}H-MRS can detect chemical changes of certain molecules containing protons within selected brain areas. The N-acetyl aspartate (NAA) peak, usually expressed as a ratio against a creatine "standard" (NAA:Cr), is believed to reflect neuronal integrity, whereas myoinositol (mI) is often regarded as a marker of glial cells. Other compounds, such as choline (a membrane constituent), can be detected at standard (1.5 Tesla, T) field strengths, whilst at higher field strengths (3.0 T), transmitters such as γ-aminobutyric acid (GABA) and glutamate can also be measured. DTI measures differences in proton anisotropy (direction of movement) and can examine the integrity of white matter fibre tracts. fMRI offers noninvasive functional assessment, usually of blood flow changes using the blood oxygen level dependent technique, with excellent temporal and spatial resolution. The role of DTI and fMRI in the investigation of parkinsonism and dementia is limited at present, and these modalities will not be discussed further in this review.

CAN FUNCTIONAL IMAGING ASSIST IN THE DIFFERENTIAL DIAGNOSIS?

Accurate diagnosis of neurodegenerative parkinsonian and dementia syndromes, particularly early in their disease course, may be problematic. Reduced diagnostic sensitivity and specificity are commonly caused by phenotypic overlap, delayed appearance of characteristic clinical features or the presence of atypical signs. For example, while there is considerable debate as to their pathophysiological basis and frequency, extrapyramidal signs are well documented in AD. In PSP, a supranuclear gaze paresis may be delayed or may not appear at all, whereas frontosubcortical dementia and akinetic–rigid features can lead to an erroneous diagnosis of PD with dementia or DLB.[1] Conversely, falls are common in DLB and vertical supranuclear gaze palsy has been reported in several cases, making a misdiagnosis of PSP likely. Sensitive and specific functional imaging tests would be of tremendous benefit in these situations.

Parkinsonism (Table 2)

^{18}F-dopa PET can robustly show loss of nigrostriatal dopaminergic projections in patients with parkinsonism, as evidenced by reduced striatal tracer uptake.[2] Although

TABLE 2. *Functional imaging abnormalities in parkinsonian syndromes (modified from Brooks, 2002[2])*

Condition	Site	Functional imaging characteristics
Parkinson's disease	Striatum	Asymmetric low F-dopa, FP-CIT uptake (putamen < caudate)
		Normal putamen FDG & raclopride (dopamine D_2)
		Normal ^{1}H-MRS NAA:Cr ratio
Multiple system atrophy	Striatum	Asymmetric low F-dopa, FP-CIT uptake (putamen < caudate)
		Asymmetric low putamen FDG & raclopride
		Low ^{1}H-MRS NAA:Cr ratio
	Cerebellum	Low FDG
Progressive supranuclear palsy	Striatum	Symmetric low F-dopa, FP-CIT uptake (putamen = caudate)
		Symmetric low putamen & caudate FDG & raclopride
		Low ^{1}H-MRS NAA:Cr ratio
	Frontal	Low FGD (posterior < inferior)
Corticobasal degeneration	Striatum	Asymmetric low F-dopa, FP-CIT uptake (putamen = caudate)
		Low putamen & caudate FDG & raclopride
		Low ^{1}H-MRS NAA:Cr ratio
	Thalamic	Asymmetric low FDG
	Cortical	Asymmetric low FDG inferior parietal & posterior frontal

FDG, fluorodeoxyglucose; ^{1}H-MRS NAA:Cr, proton magnetic resonance spectroscopy, N-acetyl aspartate to creatine peak ratio; FP-CIT, [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane.

the pattern of nigral pathological features varies between the different neurodegenerative akinetic–rigid syndromes (e.g., relatively selective ventrolateral nigral cell loss in PD compared with more widespread and severe cell loss in PSP),[3] ^{18}F-dopa PET is unable to reliably differentiate between individual cases of PD, PSP, and multiple system atrophy (MSA).[4] FP-CIT SPECT can differentiate tremors resulting from damage to the nigrostriatal dopaminergic terminals from those due to essential tremor,[5] drug-induced, or psychogenic causes, but it *cannot* differentiate between typical and atypical parkinsonism.[6]

Striatal metabolism (assessed using FDG PET) and dopamine D_2 receptor binding (assessed using [^{11}C]raclopride and PET, or [^{123}I]IBZM and SPECT) are generally normal in PD, whereas striatal glucose metabolism is reduced in 80 to 100% of probable atypical parkinsonism patients.[2] FDG PET is not able, however, to discriminate MSA from PSP and corticobasal degeneration (CBD), limiting the sensitivity of this investigation in the differential diagnosis of parkinsonism and dementia.

Using ^{1}H-MRS, decreases in NAA concentration have been reported in PD patients in the lentiform nucleus and temporoparietal cortex. PSP patients show greater decreases in NAA in frontal cortex and lentiform nucleus than PD, although the numbers studied have been generally small.[7] The ^{1}H-MRS findings for MSA have been ambiguous to date, with no consistent difference detectable in the lentiform NAA:Cr ratio, in comparison with PD.[8]

Dementia

Significant reductions in striatal binding of β-carbomethoxy-iodophenyl-tropane (a ligand for the dopamine transporter) using PET have been demonstrated in DLB but not AD, a difference that would be predicted from the nigrostriatal dopaminergic pathological state associated with DLB.[9] FP-CIT SPECT has also recently been reported to differentiate DLB from AD.[10] In this study of 27 patients with DLB, 17 with AD, 19 drug-naïve PD patients and age-matched controls, semiquantitative analysis of the SPECT data revealed clear separation of the AD and DLB groups, with no overlap of the 95% confidence intervals. Not unexpectedly, striatal ratios for the PD and DLB groups showed significant overlap.

Reduced D2 receptor density in basal ganglia using IBZM has also been reported in DLB,[11] although, somewhat inexplicably, significant differences for striatal ratios between DLB and AD groups were only observed for the left but not the right side. Until the significance of this finding is confirmed by other studies, the use of IBZM SPECT for separating AD from DLB cannot be recommended.

FDG PET and SPECT investigations in DLB using blood flow markers such as ^{99m}Tc-HMPAO have demonstrated many similarities to the patterns seen in AD.[9,12–15] Pronounced biparietal hypoperfusion is observed, together with variable and usually symmetric deficits in frontal and temporal lobes. Biparietal hypoperfusion in DLB is even more extensive than in AD cases matched for age and dementia severity, particularly in Brodmann area 7, an area mediating important aspects of visuospatial function.[16]

Occipital hypometabolism on PET and hypoperfusion on PET and SPECT have been robustly associated with DLB in several studies and appear to affect primary visual cortex as well as visual association areas (Brodmann areas 17–19). In contrast, temporal lobe perfusion is relatively preserved, paralleling the findings from structural imaging studies. Minoshima and colleagues reported a sensitivity of 90% and specificity of 80% for occipital hypometabolism in separating DLB from AD, although only 11 DLB cases were studied.[14] In a larger SPECT study, Lobotesis and coworkers showed that, although occipital hypoperfusion had reasonable specificity (86%) for distinguishing DLB from AD and controls, sensitivity was lower (64%).[15]

Scintigraphy with [^{123}I]metaiodobenzyl guanidine (MIBG) enables quantification of postganglionic sympathetic cardiac innervation. This technique may be useful in distinguishing PD (where the signal is reduced) from other akinetic–rigid syndromes, notably MSA.[17,18] Recently, however, studies have suggested that cardiac MIBG scanning may also be able to differentiate DLB (where the signal is reduced) from AD (where the signal is similar to control values).[19,20]

Using ^{1}H-MRS, there is a decrease in NAA concentration in the temporal lobe of AD patients of approximately 20%, while in the rest of the brain, there is global decrease of 10%. It is not known whether these decreases relate to reduced neuronal density, metabolism, or both.[7] mI levels are elevated by around 15% in AD, but choline levels are unchanged. NAA is reduced in the hippocampus of AD cases relative to vascular dementia, whereas NAA may be lower in the white matter and frontal region of vascular dementia patients.[7] Further studies are necessary to clarify whether robust metabolic differences exist, detectable by ^{1}H-MRS, that may usefully contribute to the differential diagnosis of AD, DLB, and other dementias.

IS FUNCTIONAL IMAGING ABLE TO DETECT DISEASE IN "AT-RISK" GROUPS

At present, drug treatment for parkinsonism and dementia is symptomatic. However, several putative disease-modifying treatments are under development. When these agents become available the presymptomatic detection of disease, or ability to anticipate the onset of complications such as dementia in PD, will assume even greater importance.

A discussion of the ability of functional imaging techniques to detect abnormalities in individuals considered to be at "high risk" of developing PD is beyond the scope of this review. Suffice it to say, in the clinically unaffected co-twins of a twin with PD,[21] in asymptomatic family members of which two or more other family members are affected by PD,[22] and in patients with drug-induced parkinsonism and persisting extrapyramidal signs,[23] ^{18}F-dopa PET is capable of demonstrating subclinical nigrostriatal dopaminergic abnormalities. Furthermore, both ^{18}F-dopa PET and also FP-CIT SPECT can detect significant abnormalities in hemiparkinsonian PD patients in the ipsilateral striatum.[24]

In asymptomatic individuals at risk of familial AD with an identifiable genetic mutation, FDG PET can detect biparietal bitemporal hypometabolism.[25] The changes are quantitatively less severe than those found in affected individuals.[26] Furthermore, in cognitively normal individuals homozygous for the ϵ4 allele of apolipoprotein E (at high risk of developing AD), FDG PET demonstrates reduced rates of glucose metabolism in the same posterior cingulate, temporoparietal, and prefrontal regions as in previously studied cases of probable AD.[27] In addition, using ^{1}H-MRS, high mI levels have been detected in occipital and parietal regions of the predementia phase of AD associated with Down's syndrome.[28]

In community-based studies, approximately 20 to 30% of patients with PD are demented. Several clinical risk factors have been identified for incident dementia, including increased age, visual hallucinations, and excessive daytime somnolence. Depression as a risk factor for cognitive impairment is more contentious.[29] The use of an objective "surrogate marker" for incident dementia in PD would allow cognition-enhancing drugs and disease-modifying therapies to be targeted more effectively.

In a recent ^{18}F-dopa PET study in patients with PD, reduced tracer uptake in the caudate nucleus and frontal cortex correlated with impairment in neuropsychological tests measuring verbal fluency, working memory, and attentional functioning.[30] The 28 patients studied spanned a wide range of cognitive impairments, with 6 fulfilling DSM-III criteria for dementia. This finding indicates that ascending dopaminergic projections play an important role in mediating cognitive dysfunction in PD and that abnormalities detected by functional imaging may be correlated with some neuropsychological measures. Frankly demented PD patients show a pattern of reduced FDG similar to that found in AD and DLB.[31]

Temporoparietal cortical hypometabolism, assessed using FDG-PET, may also be found in nondemented PD patients, perhaps identifying individuals at risk of incident dementia.[32] Using ^{1}H-MRS, NAA levels are significantly reduced in the occipital cortex of demented versus nondemented PD patients and correlate with some measures of neuropsychological performance (backward digit span and block design tests).[33] Notably, ^{1}H-MRS can also detect reductions in NAA:Cr ratios in the temporoparietal cortex of nondemented PD patients.[34] Furthermore, a significant correlation has been found between reduction in NAA:Cr ratio and measures of global cognitive decline, independent of motor impairment. Follow-up of these cohorts will be of great interest to assess the predictive value of the PET and spectroscopic data.

CAN FUNCTIONAL IMAGING MONITOR DISEASE PROGRESSION?

An objective measure of progression in extrapyramidal and cognitive functions is highly desirable for several reasons. First, clinical rating scales of motor impairments are influenced by the time of testing in relation to medication. The drug regimen may also influence outcomes on neuropsychological testing. Second, most rating scales are nonlinear and are a composite of clinical signs, while different features, such as tremor, bradykinesia, and rigidity, may progress at different rates.

Parkinsonism

^{18}F-dopa PET and CIT analogues have been used to objectively monitor loss of nigrostriatal dopaminergic function in PD. Both PET and SPECT techniques have estimated broadly similar rates of disease progression, with a mean 9% annual decline of whole putamen[35] and 10% posterior putamen[36] ^{18}F-dopa uptake, compared with mean 7%[37] and 11% annual losses of striatal [^{123}I]β-CIT uptake.[38] In all of these studies, the mean disease duration was relatively short. When the disease duration is longer, the annual loss is reduced, as evidenced by both PET[35] and SPECT[37] studies.

A recent study using [^{123}I]β-CIT and SPECT showed that the annual reduction of tracer binding in 10 patients with "atypical parkinsonian syndromes" (probable MSA, PSP, or CBD) was over twice that of 24 PD patients

matched for disease duration. The mean interscan interval was 25.5 months.[37] No correlations were demonstrated between individual changes in clinical parameters (e.g., motor Unified Parkinson's Disease Rating Scale [UPDRS] scores) in the PD patients and changes in striatal [^{123}I]β-CIT binding. Equivalent data were not reported for the atypical parkinsonism group.

More recently, functional imaging techniques have been used to assess rate of disease progression in PD patients exposed to different initial drug treatments. In the REAL-PET study, 186 de novo PD patients were randomly assigned to receive either ropinirole or levodopa.[39] As measured by ^{18}F-dopa PET, at 2-year follow-up, putaminal tracer uptake had declined by 13% in the agonist-treated patients compared with 20% in those allocated levodopa treatment, a significant difference ($P = 0.022$). The CALM-PD study used [^{123}I]β-CIT SPECT to monitor rate of dopaminergic cell loss longitudinally in 82 PD patients. Of the 82 patients, 42 initially received levodopa, whereas the other 42 were treated with pramipexole.[40] At 46 months, the mean percentage loss of uptake in the two groups compared with baseline was 16% in the pramipexole group and 25.5% in the levodopa groups ($P = 0.01$). The interpretation of these data remains open to debate and, in particular, whether the SPECT results may have occurred from a differential effect of the agonist and levodopa upon the regulation of the dopamine transporter, rather than directly reflecting nigral cell death.[41] A confounding effect of the agonist upon the dopamine transporter would be supported by a recent study performed by Guttman and colleagues using [^{11}C]RTI-32 and PET.[42] In this study, a 16% reduction in posterior putamen dopamine-transporter binding was found in PD patients treated with levodopa at 6 weeks compared with only a 7% reduction on patients treated with pramipexole. The short rescanning interval made the observed changes unlikely to be due to disease progression. Further studies are required to determine unequivocally that dopamine agonists may be neuroprotective (or, alternatively, that levodopa is neurotoxic) and the clinical correlate of observed changes on functional imaging of the dopaminergic system.

Dementia

Whilst [^{123}I]β-CIT SPECT imaging shows significant promise in differentiating DLB from AD, no serial studies of the dopaminergic system have yet been reported for DLB (or AD). With regard to cerebral blood flow, using ^{99m}Tc-HMPAO SPECT to study both AD and DLB in a cross-sectional design, a positive correlation was found between cognitive test score and temporoparietal blood flow.[16] A 2-year longitudinal study showed that cognitive decline in AD was associated with reduction in frontal blood flow.[43] However, in a later study, the reduction in cerebral perfusion in 10 AD patients over 2 years, again assessed by ^{99m}Tc-HMPAO SPECT, did not correlate significantly with the decline in various indices of neuropsychological function, either globally, or for specific brain regions.[11] Furthermore, no single perfusion index was a significant predictor of clinical progression of dementia.

From a pathological perspective, it has been proposed that there is a progression of neurofibrillary burden, such that entorhinal, limbic, and neocortical stages of AD may be distinguished; this proposal forms the basis of Braak staging.[44] In an elegant study using this staging method, single template ^{99m}Tc-HMPAO SPECT scans, derived from antemortem studies, were produced corresponding to each pathological stage.[45] A progression in reduced regional cerebral perfusion was demonstrated, correlating with Braak stage. The earliest regions showing perfusion deficits are the anterior medial temporal lobes, subcallosal region, and the posterior cingulate region. Then, large posterior temporoparietal defects develop, and finally frontal lobe defects, sparing the motor and somatosensory cortices. This course is consistent with other evidence from PET studies, suggesting that the posterior cingulate and hippocampus/entorhinal cortex are metabolically abnormal in patients with mild cognitive impairment who subsequently go on to develop AD.[46,47]

Functional imaging has also been used to assess regional cerebral blood flow changes in AD patients treated with acetylcholinesterase inhibitor (AChEI) therapy. In the short-term, several studies have shown AChEIs increase cortical and subcortical blood flow.[48,49] With long-term treatment, AD patients whose cognitive function had stabilised on this treatment showed no significant difference between baseline and repeat SPECT studies. This finding contrasted with those patients whose cognition had worsened despite AChEI treatment, where significant perfusion reductions were detected in several cortical regions.[49]

^{1}H-MRS may also be useful in early AD in predicting cognitive decline. In a study of 12 patients clinically diagnosed with probable AD, baseline NAA:Cr ratios were positively correlated with Mini-Mental State Examination (MMSE) scores at follow-up and inversely correlated with the change from baseline in score at 12 months.[50] In a more recent study of 21 subjects with AD, absolute brain concentrations of NAA, but not mI or total creatine, were positively correlated with MMSE score.[51]

DOES FUNCTIONAL IMAGING SHED LIGHT ON THE PATHOPHYSIOLOGICAL PROCESS?

Using ^{18}F-dopa PET, the degree of dysfunction of the nigrostriatal dopaminergic projections observed in PD correlates with bradykinesia and rigidity, as scored using the motor subsection of the UPDRS.[52] This finding supports current models of basal ganglia function and, in particular, the critical role for putaminal dopamine deficiency in mediating akinetic–rigid features. Tremor severity, on the other hand, does not correlate with reduced striatal ^{18}F-dopa uptake. A recent PET study using ^{11}C-WAY 100635 (a ligand for the $5HT_{1A}$ receptor) has suggested that tremor may be mediated by means of dysfunction of ascending serotonergic projections, as a significant correlation was shown between tracer binding in the midbrain raphé nuclei and individual tremor rating scores.[53]

In both PD and AD, an inflammatory response has been postulated to play a role in the aetiopathogenesis. PK11195 is an isoquinoline ligand capable of binding to activated microglia, thus providing a marker of the inflammatory process. Using ^{11}C-PK11195 and PET, areas of increased signal have been detected in both AD (entorhinal, temporoparietal, and cingulate cortex,[54]) and PD (substantia nigra and globus pallidus,[55]). These data suggest that topographically specific microglial activation occurs in PD and AD and at early stages of the disease,[54] although they cannot, of course, differentiate between whether the activation represents a primary or secondary ("reactive") pathogenic process.

In DLB, pronounced hypoperfusion in Brodmann area 7 may underpin the characteristic visuospatial impairments, although further studies correlating imaging changes with detailed neuropsychology are needed. Whether occipital hypoperfusion is related to the occurrence of visual hallucinations remains unclear.[14,15]

The pathological substrate underpinning dementia in PD is variable, with involvement of both cortical and subcortical processes. As discussed above, nigrostriatal and mesocortical dopaminergic deficiency, particularly involving the caudate nucleus and frontal lobes, is an example of one subcortical process contributing to cognitive impairment. The ascending cholinergic system is also involved, as evidenced by greater neuronal loss in the nucleus basalis of Meynert in demented versus nondemented PD cases.[56] Using a marker of vesicular acetylcholine transporter, [^{123}I]iodobenzovasamicol (IBVM), and SPECT, significant differences between AD subjects and controls as well as between Parkinson's disease subjects with and without dementia have been demonstrated.[57] In PD patients without dementia, IBVM binding is confined to the parietal and occipital cortex, whereas demented PD cases have extensive cortical binding decreases similar to early-onset AD.

The cholinergic system is also affected in DLB and to a greater extent than in AD. In addition to lower cortical choline acetyltransferase in the cortex measured at autopsy, [^{11}C]*N*-methyl-4-piperidyl acetate (a cholinesterase inhibitor) and PET detect significantly greater cholinergic loss in DLB compared with AD.[58] Cortical choline acetyltransferase reductions in DLB correlate with cognitive impairment and visual hallucinations.

Newly developed ligands suitable for PET and SPECT studies mean that it is also possible to study individual acetylcholine receptor subtypes. Thus, agents targeting both muscarinic (quinuclidinyl-4-iodobenzilate) and nicotinic (epibatidine and A-85380) receptors are now available.[59,60] The potential utility of these ligands is illustrated in DLB postmortem neurochemistry studies, where nicotinic receptor density is lower in hallucinating compared with nonhallucinating patients,[61] while muscarinic M1 receptor binding is more elevated in DLB cases with delusions than those without.[62] Disturbances in consciousness in DLB are associated with abnormalities in the nicotinic receptor subtype binding agonists with high affinity ($\alpha4\beta2$). It will be of interest, thus, to correlate these data in vivo using SPECT and/or PET and to use these imaging techniques to determine the temporal and spatial evolution of the disease process.

Cortical pathological findings in PD dementia may be minimal, predominantly plaque and tangle (i.e., AD-like), predominantly Lewy body (i.e., DLB-like), or mixed. Probes capable of labeling β-amyloid plaques in the brain are under development. These agents include styrylbenzene and thioflavin derivatives.[63,64] They could offer an unparalleled opportunity to monitor disease progression and effects of therapeutic intervention in AD, to study the pathophysiological process of dementia in PD, and to assist in the differential diagnosis of DLB from AD.

CONCLUSION

This review has addressed the potential uses of functional imaging in the context of parkinsonism and dementia. Although not available in every centre dealing with such patients, both SPECT and MRS facilities, in particular, are becoming more accessible. In the clinical arena, like every investigation, the use of functional imaging needs to be targeted to a specific question. The clinician should understand the limitations of the technique and/or ligand and, thus, whether it is capable of answering the question posed. If this essential step is not followed, then the results obtained will either be uninterpretable or frankly misleading. It is our view that,

from the research perspective, longitudinal functional imaging studies should be pursued, with clinicopathological correlation whenever possible. It is only through these studies that the techniques will be fully validated and their appropriate use established.

REFERENCES

1. Burn DJ, Lees AJ. Progressive supranuclear palsy: where are we now? Lancet Neurology 2002;1:359–369.
2. Brooks DJ. Diagnosis and management of atypical parkinsonian syndromes. J Neurol Neurosurg Psychiatry 2002;72:i10–i16.
3. Fearnley JM, Lees AJ. Striatonigral degeneration: a clinicopathological study. Brain 1990;113:1823–1842.
4. Burn DJ, Sawle GV, Brooks DJ. Differential diagnosis of Parkinson's disease, multiple system atrophy, and Steele-Richardson-Olszewski syndrome: discriminant analysis of striatal 18F-dopa PET data. J Neurol Neurosurg Psychiatry 1994;57:278–284.
5. Benamer HTS, Patterson J, Grosset DG, et al. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [^{123}I]-FP-CIT SPECT imaging: the [^{123}I]-FP-CIT study group. Mov Disord 2000;15:503–510.
6. Varrone A, Marek KL, Jennings D, Innis RB, Seibyl JP. [^{123}I]β-CIT SPECT imaging demonstrates reduced density of striatal dopamine transporters in Parkinson's disease and multiple system atrophy. Mov Disord 2001;16:1023–1032.
7. Firbank MJ, Harrison RM, O'Brien JT. A comprehensive review of proton magnetic resonance spectroscopy studies in dementia and Parkinson's disease. Dement Geriatr Cogn Disord 2002;14:64–76.
8. Clarke CE, Lowry M. Systematic review of proton magnetic resonance spectroscopy of the striatum in parkinsonian syndromes. Eur J Neurol 2001;8:573–577.
9. Donnemiller E, Heilmann J, Wenning GK, et al. Brain perfusion scintigraphy with ^{99m}Tc-HMPAO or ^{99m}Tc-ECD and ^{123}I-beta-CIT single-photon emission tomography in dementia of the Alzheimer-type and diffuse Lewy body disease. Eur J Nucl Med 1997;24:320–325.
10. Walker Z, Costa DC, Walker RWH, et al. Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. J Neurol Neurosurg Psychiatry 2002;73:134–140.
11. Sachdev P, Gaur R, Brodaty H, et al. Longitudinal study of cerebral blood flow in Alzheimer's disease using single photon emission tomography. Psychiatry Res 1997;68:133–141.
12. Ishii K, Yamaji S, Kitagaki H, Imamura T, Hirono N, Mori E. Regional cerebral blood flow difference between dementia with Lewy bodies and AD. Neurology 1999;53:413–416.
13. Defebvre LJ, Leduc V, Duhamel A, et al. Technetium HMPAO SPECT study in dementia with Lewy bodies. J Nucl Med 1999; 40:956–962.
14. Minoshima S, Foster NL, Sima AA, Frey KA, Albin RL, Kuhl DE. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolism distinction with autopsy confirmation. Ann Neurol 2001;50:358–365.
15. Lobotesis K, Fenwick J, Phipps A, et al. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. Neurology 2001;56:643–649.
16. Colloby SJ, Fenwick JD, Williams ED, et al. A comparison of (99m)Tc-HMPAO SPET changes in dementia with Lewy bodies and Alzheimer's disease using statistical parametric mapping. Eur J Nucl Med Mol Imaging 2002;29:615–622.
17. Braune S, Reinhardt M, Schnitzer R, Riedel A, Lucking CH. Cardiac uptake of [123I]MIBG separates Parkinson's disease from multiple system atrophy. Neurology 1999;53:1020–1025.
18. Druschky A, Hilz MJ, Platsch G, et al. Differentiation of Parkinson's disease and multiple system atrophy in early disease stages by means of I-123-MIBG-SPECT. J Neurol Sci 2000;175:3–12.
19. Yoshita M, Taki J, Yamada M. A clinical role for [^{123}I]MIBG myocardial scintigraphy in the distinction between dementia of the Alzheimer's-type and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2001;71:583–588.
20. Watanabe H, Ieda T, Katayama T, et al. Cardiac ^{123}I-meta-iodobenzylguanidine (MIBG) uptake in dementia with Lewy bodies: comparison with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001;70:781–783.
21. Piccini P, Burn DJ, Ceravolo R, Maraganore DM, Brooks DJ. The role of inheritance in sporadic Parkinson's disease: evidence from a longitudinal study of dopaminergic function in twins. Ann Neurol 1999;45:577–582.
22. Piccini P, Morrish PK, Turjanski N, et al. Dopaminergic function in familial Parkinson's disease: a clinical and ^{18}F-dopa positron emission tomography study. Ann Neurol 1997;41:222–229.
23. Burn DJ, Brooks DJ. Nigral dysfunction in drug-induced parkinsonism: an ^{18}F-dopa PET study. Neurology 1993;43:552–556.
24. Marek KL, Seibyl JP, Zoghbi SS, et al. ^{123}I β-CIT/SPECT imaging demonstrates bilateral loss of dopamine transporters in hemi-Parkinson's disease. Neurology 1996;46:231–237.
25. Rossor MN, Kennedy AM, Frackowiak RS. Clinical and neuroimaging features of familial Alzheimer's disease. Ann N Y Acad Sci 1996;777:49–56.
26. Kennedy AM, Frackowiak RS, Newman SK, et al. Deficits in cerebral glucose metabolism demonstrated by positron emission tomography in individuals at risk of familial Alzheimer's disease. Neurosci Lett 1995;186:17–20.
27. Reiman EM, Caselli RJ, Yun LS, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the ϵ4 allele for apolipoprotein E. N Engl J Med 1996;334:752–758.
28. Huang W, Alexander GE, Daly EM, et al. High brain myo-inositol levels in the pre-dementia phase of Alzheimer's disease in adults with Down's syndrome. Am J Psychiatry 1999;156:195–202.
29. Burn DJ. Beyond the iron mask: towards better recognition and treatment of depression associated with Parkinson's disease. Mov Disord 2002;17:445–454.
30. Rinne JO, Portin R, Ruottinen H, et al. Cognitive impairment and the brain dopaminergic system in Parkinson's disease: [^{18}F]fluorodopa positron emission tomographic study. Arch Neurol 2000;57: 470–475.
31. Peppard RF, Martin WR, Carr GD, et al. Cerebral glucose metabolism in Parkinson's disease with and without dementia. Arch Neurol 1992;49:1262–1268.
32. Hu MTM, Taylor-Robinson SD, Ray Chaudhuri K, et al. Cortical dysfunction in non-demented Parkinson's disease patients: a combined ^{31}P-MRS and ^{18}FDG-PET study. Brain 2000;123:340–352.
33. Summerfield C, Gómez-Ansón B, Tolosa E, et al. Dementia in Parkinson's disease: a proton magnetic resonance spectroscopic study. Arch Neurol 2002;59:1415–1420.
34. Hu MTM, Taylor-Robinson SD, Ray Chaudhuri K, et al. Evidence for cortical dysfunction in clinically non-demented patients with Parkinson's disease: a proton MR spectroscopy study. J Neurol Neurosurg Psychiatry 1999;67:20–26.
35. Morrish PK, Sawle GV, Brooks DJ. An [18F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. Brain 1996;119:585–591.
36. Nurmi E, Ruottinen HM, Bergman J, et al. Rate of progression in Parkinson's disease: a 6-[^{18}F]fluoro-L-dopa PET study. Mov Disord 2001;16:608–615.
37. Pirker W, Djamshidian S, Asenbaum S, et al. Progression of dopaminergic degeneration in Parkinson's disease and atypical parkinsonism: a longitudinal beta-CIT SPECT study. Mov Disord 2002;17:45–53.
38. Marek KL, Innis RB, van Dyck C, et al. [123I]beta-CIT SPECT imaging assessment of the rate of Parkinson's disease progression. Neurology 2001;57:2089–2094.
39. Whone AL, Remy P, Davis MR, et al. The REAL-PET study: slower progression in early Parkinson's disease treated with ropinirole compared with L-dopa. Neurology 2002;58:A82–A83.

40. Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole versus levodopa on Parkinson disease progression. JAMA 2002;287:1653–1661.
41. Clarke CE, Guttman M. Dopamine agonist monotherapy in Parkinson's disease. Lancet 2002;360:1767–1769.
42. Guttman M, Stewart D, Hussey D, Wilson A, Houle S, Kish S. Influence of L-dopa and pramipexole on striatal dopamine transporter in early PD. Neurology 2001;56:1559–1564.
43. Brown DR, Hunter R, Wyper DJ, et al. Longitudinal changes in cognitive function and regional cerebral function in Alzheimer's disease: a SPECT blood flow study. J Psychiatr Res 1996;30:109–126.
44. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl) 1991;82:239–259.
45. Bradley KM, O'Sullivan VT, Soper ND, et al. Cerebral perfusion SPET correlated with Braak pathological stage in Alzheimer's disease. Brain 2002;125:1772–1781.
46. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. Ann Neurol 1997;42:85–94.
47. de Leon MJ, Convit A, Wolf OT, et al. Prediction of cognitive decline in normal elderly subjects with 2-[(18)F]fluoro-2-deoxy-D-glucose positron emission tomography. Proc Natl Acad Sci U S A 2001;98:10966–10971.
48. Freo U, Pizzolato G, Dam M, Ori C, Battistin L. A short review of cognitive and functional neuroimaging studies of cholinergic drugs: implications for therapeutic potentials. J Neural Transm 2002;109:857–870.
49. Nobili F, Koulibaly M, Vitali P, et al. Brain perfusion follow-up in Alzheimer's patients during treatment with acetylcholinesterase inhibitors. J Nucl Med 2002;43:983–990.
50. Doraiswamy PM, Charles HC, Krishnan KRR. Prediction of cognitive decline in early Alzheimer's disease. Lancet 1998;352:1678.
51. Huang W, Alexander GE, Chang L, et al. Brain metabolite concentration and dementia severity in Alzheimer's disease: a (1)H MRS study. Neurology 2001;57:626–632.
52. Vingerhoets FJ, Schulzer M, Calne DB, Snow BJ. Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? Ann Neurol 1997;41:58–64.
53. Doder M, Rabiner EI, Turjanski N, Lees AJ, Brooks DJ. Functional imaging of tremor in Parkinson's disease with [11C]-WAY 100635 PET. Neurology 2001;56:A271–A272.
54. Cagnin A, Brooks DJ, Kennedy AM, et al. In-vivo measurement of activated microglia in dementia. Lancet 2001;358:461–467.
55. Gerhard A, Banati RB, Cagnin A, Brooks DJ. In vivo imaging of activated microglia with [11C]PK11195 positron emission tomography (PET) in idiopathic and atypical Parkinson's disease. Neurology 2001;56:A270.
56. Jellinger KA, Bancher CH. Structural basis of mental impairment in Parkinson's disease. Neuropsychiatrie 1995;9:9–14.
57. Kuhl DE, Minoshima S, Fessler JA, et al. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. Ann Neurol 1996;40:399–410.
58. Shinotoh H, Aotsuka A, Ota T, et al. Brain cholinergic function in dementia with Lewy bodies and Alzheimer's disease measured by PET. Abstracts, Proceeding of the 5th International Conference on Progress in PD and AD 2001:74. April 1–5, 2001, Kyoto, Japan.
59. Sunderland T, Esposito G, Molchan SE, et al. Differential cholinergic regulation in Alzheimer's patients compared to controls following chronic blockade with scopolamine: a SPECT study. Psychopharmacology 1995;121:231–241.
60. Sihver W, Langstrom B, Nordberg A. Ligands for in vivo imaging of nicotinic receptor subtypes in Alzheimer brain. Acta Neurol Scand 2000;176:27–33.
61. Court JA, Ballard CG, Piggott MA, et al. Visual hallucinations are associated with lower α-bungarotoxin binding in dementia with Lewy bodies. Pharmacol Biochem Behav 2001;70:571–579.
62. Ballard C, Piggott M, Johnson M, et al. Delusions associated with elevated muscarinic binding in dementia with Lewy bodies. Ann Neurol 2000;48:868–876.
63. Zhuang ZP, Kung MP, Hou C, et al. IBOX (2-(4′-dimethylaminophenyl)-6-iodobenzoxazole): a ligand for imaging amyloid plaques in the brain. Nucl Med Biol 2001;28:887–894.
64. Kung MP, Hou C, Zhuang ZP, et al. Radioiodinated styrylbenzene derivatives as potential SPEC imaging agents for amyloid plaque detection in Alzheimer's disease. J Mol Neurosci 2002;19:7–10.