Functional imaging provides a sensitive means of detecting brain abnormalities in parkinsonian syndromes, detecting focal changes in brain metabolism, cerebral blood flow (CBF), and presynaptic and postsynaptic dopaminergic abnormalities. The usefulness of functional imaging in regional detection, diagnosis, and disease progression in Parkinson's disease (PD) and dementia with Lewy bodies (DLB) using image modalities of positron emission tomography (PET), single photon emission computed tomography (SPECT), proton magnetic resonance spectroscopy (1H-MRS), and functional magnetic resonance imaging (fMRI) is reviewed.

FUNCTIONAL IMAGING METHODS

Both SPECT and PET involve the use of radioactive nuclides from either natural or synthetic sources. Their strength lies in the fact that they can be used in tracer studies, allowing various aspects of function (eg, CBF, neurotransmitter systems) to be investigated in vivo. The radioisotopes used in SPECT have relatively long half-lives (a few hours to a few days), making them easy to produce and relatively cheap. This represents the major advantage of SPECT as a brain-imaging technique because it is significantly cheaper than PET and is readily available to perform in most hospitals. However, SPECT is restricted by spatial (8-16 mm) and temporal resolution, and there are safety aspects concerning the administration of radioisotopes to the subject, especially for serial studies. Also, common SPECT radionuclides such as 99mTc and 123I have limited binding affinity with various neurochemicals compared with that of PET radionuclides (11C, 15O, or 18F). The PET technique has advantages over SPECT in terms of better spatial resolution (4-6 mm) and a wider choice of radiopharmaceuticals. However, positron emitters used in PET have short half-lives, of the order of 2 to 100 minutes. This means that the isotopes must usually be made at the site of the scanner, using an expensive cyclotron, and therefore are largely confined for research only. The short half-life means that dynamic studies of brain function can usually be carried out using the technique. The main drawbacks of PET are its use of radioisotopes and its very high cost.

Although structural MRI uses information from proton density and proton “relaxation” to build a structural image of the brain at high resolution, proton MRS detects very small differences in the frequencies of proton resonances from comparatively large volumes (1.0 mL or more) of brain tissue. The frequency of the resonance is affected by its local chemical environment (ie, the molecule in which the proton[s] reside), whereas the amplitude reflects its concentration. As such, MRS is able to provide a measurement of certain proton-containing chemical markers. Proton (1H) spectroscopy and MRS can measure changes in N-acetyl aspartate (NAA, a putative marker of mature neuronal integrity), choline-containing compounds (Cho),...
myo-inositol (thought to be a glial marker), and total creatine (Cr). Thus, a reduction of NAA detected by proton MRS indicates neuronal loss or dysfunction.

The fMRI technique measures changes in blood in response to altered demand consequent on neuronal activation by use of the blood oxygen level–dependent (BOLD) method, which relies on paramagnetic differences between oxygenated and deoxygenated hemoglobin to assess blood flow.

**IMAGING STUDIES**

Traditionally, region of interest (ROI) analysis has been used to perform semiquantitative analysis of regional tracer uptake in the brain in SPECT and PET studies. However, ROI methods tend to be subjective, time consuming, and prone to operator bias. An alternative means of analyzing the functional changes associated with PD and DLB is to use an automated voxel-based technique, such as statistical parametric mapping (SPM; Wellcome Department of Cognitive Neurology, London, United Kingdom). The SPM approach has the advantage that regional changes in function can be sensitively detected in brain areas that might not have been predicted. Its weakness possibly lies in the requirement of stereotactic transformation of image data, which reduces resolution and introduces error variance. The following discussion shall focus on previous studies using various functional imaging modalities in PD and DLB.

**Parkinson’s Disease**

In PD, 18F-2-fluoro-2-deoxyglucose (FDG) PET demonstrates increased glucose metabolism in the lentiform nucleus contralateral to affected limbs in hemiparkinsonian patients with early disease, suggesting that changes on imaging can be detected before the appearance of clinical symptoms. Another study reported a reduction in glucose uptake using FDG PET in several cortical areas (parietal, frontal, and temporal) and the caudate in advanced PD compared to controls, independent of whether the group members were “on” or “off” dopaminergic medication. Interestingly, an hour after receiving dopaminergic medication, glucose metabolism was more severely reduced, particularly in the orbital frontal cortex and thalamus. In addition, several tracers, 18F-fluoro-L-dopa, 11C-2-beta-carbomethoxy-3-beta-4-fluorophenyl-tropane (β-CIT:FE), 18F-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-N-tropane (FP-CIT), have been developed to assess various aspects of dopaminergic function. All have identified striatal abnormalities, particularly in the putamen, even in early-stage PD using both SPM and ROI methods of analysis.

Cerebral perfusion markers 99mTc-hexamethylpropylene amine oxime (HMPAO) and 99mTc-ethyl cysteinate dimer (ECD) have been used to identify regional CBF (rCBF) deficits in PD. Findings vary using ROI methods, with reductions in perfusion being reported in frontal, parietal, and temporal areas compared with age-matched controls. Using voxel-based analyses (SPM), bilateral occipitoparietal hypoperfusion has been reported, whereas others have demonstrated a reduction in parietal rCBF (Brodmann area 7) independent of brain atrophy in PD. Conversely, one study described hyperperfusion in both the putamen bilaterally and the right hippocampus in subjects with mild PD, extending to the left hippocampus and thalamus, right insula, and temporal regions in patients with more moderate and severe PD. Such increases may be a consequence of compensatory processes of the complicated functional architecture of thalamocortex-basal ganglion circuitry, although the influence of drug therapy cannot be excluded.

Tracers such as 123I-β-CIT and 123I-FP-CIT have been used to measure striatal dopamine transporter binding in PD. Studies using these SPECT ligands have generally used visual or semiquantitative methods to demonstrate significant reductions in striatal binding in PD compared with normal controls. Figure 1 illustrates the reduced striatal uptake in a typical patient with PD compared with the normal uptake associated with an age-matched control using the 123I-FP-CIT ligand. Notice uptake is almost exclusively confined to the caudate and anterior aspects of the putamen. Postsynaptic D2 receptor status has also been investigated using tracers such as 123I-iodobenzamide (IBZM) and 123I-iodobenzofuran, in which striatal binding appears to be preserved or even upregulated in PD. This suggests that in PD only presynaptic nerve fibers are likely to be affected.

A review of 15 studies on PD found a 5% decrease in NAA/Cr in the lentiform nucleus, which contrasted with a greater (15%) reduction in some other parkinsonian conditions such as progressive supranuclear palsy. Several cortical regions have also been investigated in PD, with studies reporting reductions in NAA/Cr concentrations in temporoparietal and posterior cingulate compared with that of normal controls. In Alzheimer’s Disease (AD), proton MRS consistently reveals reduced cortical NAA of similar magnitude in most regions examined (10%), with slightly greater loss in temporal lobes. In many studies, increases in myo-inositol are also seen.

Activation studies with fMRI represent a powerful tool in the study of functional anatomy in PD and offer the opportunity to study regional cerebral function under different conditions with the analysis of associated task-specific changes in BOLD signal. Compared with controls, cortical reductions in activation have been shown using various motor tasks in the sensorimotor and primary motor areas, whereas others have reported hyperactivation in supplementary motor areas accompanied by hyperactivation in both the primary and premotor cortices in PD. Cognitive function has also been assessed, with one study reporting significant intensity reductions dur-
ing a working-memory paradigm in striatofrontal sites in PD patients with cognitive impairment compared with those patients who were not cognitively impaired.34

Dementia With Lewy Bodies

The FDG PET studies in DLB have shown marked reductions in glucose metabolism, mainly in the parietal and occipital cortices. The loss in parietal uptake is more extensive in DLB than in AD, especially in Brodmann area 7; however, deficits in primary and secondary visual areas have been reported exclusively in DLB.35-38 Assessments of the various aspects of the dopaminergic system using PET in DLB have been few, with one ROI study demonstrating pronounced reductions in striatal uptake compared with AD39 and another using SPM to identify striatal deficits in a single case.6

Cerebral perfusion deficits are confined mainly to either parietal or occipital regions, or both, in DLB and are more pronounced than in AD.14,40-42 Frontal reductions have also been shown in DLB compared with controls40 and with AD.43 However, it has been suggested14 that such hypoperfusion may reflect loss of brain tissue in the frontal cortex. Figure 2 shows an example of occipital and parietal deficits in rCBF in DLB using the 99mTc-HMPAO marker. Studies of dopamine transporter binding in DLB have also demonstrated reductions in striatal uptake compared with patients with AD using 123I-β-CIT41 whereas others have reported similar reductions in striatal uptake from controls and patients with AD using 123I-FP-CIT.20,24

There have been very few MRS studies on DLB. Molina et al44 studied 12 DLB patients and 11 age-matched healthy controls, finding lower mean NAA/Cr, glutamate/Cr, and Cho/Cr ratios in the white matter but no differences in gray matter. Relatively normal cortical NAA contrasts with findings of gray matter loss on structural MRI16 and further studies are required. There is no literature at present describing the functional anatomy in DLB using fMRI.

DIFFERENTIAL DIAGNOSIS OF PD AND DLB

Accurate antemortem diagnosis in PD and DLB is particularly important in the early part of the disease for the treatment and management of the patient. Distinguishing PD from PD phenotypes, such as essential tremor (ET), and DLB from AD is a major goal of functional imaging. Only by increasing our understanding of the many aspects of brain function associated with PD and DLB are we capable of improving the sensitivity and specificity of diagnosis.

Essential tremor is a condition most commonly misdiagnosed with PD; in fact, up to 25% of cases are initially diagnosed as having PD.16 Dopamine transporter imaging has been successful in differentiating ET from PD using 123I-β-CIT46 and 123I-FP-CIT,16,47 with subjects with ET having levels of striatal uptake within normal limits. Such studies have found sensitivity and specificity for clinical diagnosis of distinguishing parkinsonism from ET to be 95% and 93%, respectively,16 whereas others reported sensitivity in diagnosing parkinsonism to be 98% with specificity of 83% for ET and healthy controls.47 More recently, there has been evidence that dopamine transporter imaging using SPECT may also have a role in distinguishing DLB from AD, with one study reporting sensitivity in detecting DLB to be 78% and specificity 85% using visual rating, whereas using ROI methods the specificity increased to 94%.20 In addition, others24 have found sensitivity and specificity in autopsy-confirmed cases of DLB to be 100% and 83%, respectively.

Interestingly, the FP-CIT SPECT studies observed similar patterns of striatal binding in DLB and PD, although there were subtle changes in rostro-caudal gradient, which was significantly lower in DLB compared to PD.20 This indicates relatively even loss in caudate and putamen in DLB, compared with the more marked putamen loss observed in PD.
ASSESSING DISEASE PROGRESSION AND TREATMENT RESPONSE IN PD AND DLB

The objective monitoring of disease progression with functional imaging in subjects with PD or DLB is important if we are to increase our awareness of the time course of the disease and to examine the efficacy of treatments on various aspects of brain function. At present, no serial studies of brain metabolism, rCBF, or the dopaminergic system have been reported on DLB.

Annual rates of decline of 5.9%, 8.3%, and 10.3% were measured in the caudate, anterior putamen, and posterior putamen, respectively, in PD using the tracer $^{123}$I-L-dopa, suggesting the disease process first affects the posterior putamen, followed by the anterior putamen, and then the caudate. Others have observed annual losses in uptake in the putamen of 12.5% in early-stage PD, exceeding that of an established PD group, which suggests that rates of decline are perhaps greater in the early stages of the disease. Another study assessed the postsynaptic dopaminergic D-2/D-3 receptor binding using the PET tracer $^{11}$C-FLB 457 and found annual rates of reduction of 6% to 11% in the left temporal and dorsolateral prefrontal cortex and bilateral thalamus in PD.

Several SPECT studies using the dopamine transporter tracer $^{123}$I-$\beta$-CIT showed annual rates of decline in striatal binding in subjects with early-stage PD of 11.2%, 7.1%, and 8.0%. In addition, a $^{123}$I-FP-CIT study reported an annual reduction of 8.0% in striatal binding in early-stage PD. Annual striatal loss in later stage PD seemed to be much less than in those with early-stage disease.

Treatment effects with ropinirole (a dopamine receptar agonist) or L-dopa in early-stage PD have also been assessed in numerous studies with $^{18}$F-L-dopa PET. One such study compared the rates of loss of uptake between subjects on ropinirole with those of patients on L-dopa, demonstrating significantly lower changes over 2 years in putamen binding with ropinirole (−13.4%) than with L-dopa (−20.3%). A similar study showed rates of −13.0% and −18.0% for ropinirole and L-dopa, respectively, highlighting the potential neuroprotective effects agonists have on dopaminergic function. A reduction in striatal D-1/D-2 receptor binding has also been found in dyskinetic and nondyskinetic PD subjects treated with L-dopa using $^{11}$C-raclopride PET. Response to treatment with L-dopa has also been studied with the presynaptic D2 ligand $^{123}$I-IBZM. Such studies have demonstrated the potential to differentiate between patients who respond to L-dopa from those who will not respond, with upregulation or preservation of the receptor associated with good clinical response. As such, imaging can provide a measure for predicting those who are likely to be responders/nonresponders to treatment in PD.

SUMMARY

In summary, neuroimaging findings in PD and DLB were reviewed in regard to cerebral glucose metabolism and perfusion, spectroscopy, and neurochemistry. Measurements of dopamine terminal function with PET and SPECT can sensitively discriminate PD from normal populations while playing an increasingly important role in objectively assessing disease progression and the effects of neuroprotective treatments. Occupitoparietal hypometabolism and perfusion as well as abnormal striatal uptake of the dopamine transporter provide potential markers in differentiating DLB from AD.

References


