Functional Imaging of Movement Disorders

The spectrum of movement disorders runs from simple tics to more complex multisystem degenerations such as progressive supranuclear palsy, and the vast majority remain clinical diagnoses with no diagnostic tests. In the past the importance of functional brain imaging has lain mainly in characterising the brain networks involved in the disorders and the changes effected by treatment. However in the future, the importance of such imaging paradigms may lie with progression studies as the most practicable objective method of evaluating the effects of potential neuroprotective agents and restorative interventions.

Functional imaging allows us to interrogate both resting brain function and task-related cerebral activation patterns in vivo in health and disease. For example, "F-fluoro-2-deoxy-D-glucose positron emission tomography ("F-FDG PET) provides a measure of resting regional glucose metabolism whereas "O-labelled water (H₂"O) PET allows detection of changes in regional blood flow elicited by performing a task. Functional imaging also enables quantification of pre-synaptic properties, post-synaptic receptor availability, enzyme activity and neuroinflammatory changes. Indeed, the cellular sites which can be examined are limited only by the difficulties of developing practical radiotracers with sufficient specificity and kinetic characteristics to allow quantitative analysis. In this review we will consider the application of functional imaging, especially PET, to akinetic-rigid syndromes and involuntary movement disorders in turn. All involve alterations in the outputs from basal ganglia circuits to cortex (Figure 1).

Akinetic-rigid syndromes

Parkinson’s disease Diagnosis

The defining abnormality in Parkinson’s disease (PD) is the progressive loss of dopaminergic neurons in the nigrostriatal pathway which can be imaged by PET most clearly at its termination in the striatum using markers for pre-synaptic properties. "F-fluorodopa PET reflects pre-synaptic dopa uptake, decarboxylation to dopamine and storage; "F-dopa uptake rate constants have been shown to correlate with the number of functional dopaminergic neurons.

"I-F-F-CIT single photon emission computed tomography (SPECT) visualises the pre-synaptic dopamine transporter with a sensitivity of detecting striatal dysfunction of 97% and a specificity of 100%. It is now commercially available as DaTSCAN™ and may prove useful in cases of diagnostic difficulty.

Aetiology

Other functional imaging studies have given insights into the aetiology and brain circuitry of PD and have provided a means of evaluating therapeutic interventions. The cause of PD is likely to be an integration of genetic susceptibility and various environmental factors, all varying in their relative contributions in the individual patient. An insight into the genetic contribution in sporadic PD has been given by "P-dopa PET studies of twin pairs, one of whom was affected by PD at the beginning of the study. At baseline the concordance for nigrostriatal dopaminergic dysfunction was significantly higher in monozygotic than in dizygotic pairs and it became even higher after 7 years of follow-up, with 4 of the 18 monozygotic and none of the 16 dizygotic co-twins developing clinical PD. These results suggest either a substantial direct role of inheritance in sporadic PD or an associated increase in susceptibility to causative environmental agents.

Pathophysiology and treatment effects

In recent years fluorodopa PET scanning has yielded relevant information about the pattern of dopaminergic depletion, involving predominantly the dorsal putamen in early disease; rates of disease progression and possible compensatory changes in early disease in other dopaminergic pathways: the nigropallidal, mesolimbic and mesocortical. C"O and H₂"O PET both quantify regional cerebral blood flow (rCBF) and have been used to demonstrate that underfunctioning of the supplementary motor area (SMA) occurs in PD and is associated with akinesia and bradykinesia and that activation of the dorsal prefrontal cortex in normal and PD subjects occurs only when making self-paced and not cued movements.

The lateral parietal and premotor areas, regions targeted by cerebellar projections, show increased activation in PD patients performing sequential finger movements. It is mooted that, in PD, there is a partial switch in operation from dysfunctional basal ganglia circuits to other motor circuitry. The connections from globus pallidus interna via pedunculopontine nucleus to the cerebellum could mediate such a switch.

"C-raclopride PET enables estimation of dopamine release by measuring relative differences in D₂ receptor occupancy before and after a dopamine releasing challenge. Using repetitive transcranial magnetic stimulation and "C-raclopride PET, Straffella and colleagues have demonstrated that prefrontal cortical projections to the striatum can modulate dopamine release.

The surgical interventions of medial pallidotomy and deep brain stimulation of the medial pallidum (globus pallidus interna: Gpi) or subthalamic nucleus in PD are all intended to affect the overactivity of these nuclei in the Figure 1: Coronal section through the brain illustrating the indirect and direct pathways running from cortex via basal ganglia back to cortex: the cortico-pallido-thalamo-cortical loops. The substantia nigra pars reticularis is also involved in parallel to the Gpi (path not shown). The balance of activity in the pathways is altered in many movement disorders, eg. reduced input from the direct and increased input from the indirect pathways to the Gpi in Parkinson's disease. Red = excitatory (glutamate), Blue = inhibitory (GABA) Hi = hippocampus, sn = substantia nigra.
disease. All have been shown to increase SMA resting rCBF or activation during arm or finger movements with reduced bradykinesia. In addition restoration of activation of SMA and prefrontal cortex during a motor task has been shown in PD patients after bilateral striatal transplantation of human foetal mesencephalic cells. Indeed this transplantation of foetal nigral tissue into the putamen of PD subjects results in sustained motor improvement with restored dopamine storage and release, evaluated by 18F-dopa PET and 11C-raclopride respectively, in one case at ten years after transplantation. The same group has presented data indicating that severe off-dyskinesias occasionally observed in PD after foetal dopaminergic cell transplantation are not directly related to increases in striatal dopamine storage after grafting as measured by 18F-dopa PET.

Gial cell line-derived neurotrophic factor (GDNF) has neurorestorative properties in animal models of PD and has now been used in man as part of phase I safety trials, delivered chronically by infusion to the putamen. PET studies in the 5 subjects involved revealed a 28% increase in putaminal 18F-dopa uptake 18 months after catheter implantation, supporting a restorative effect on dopaminergic function.

The REAL-PET study was an international double-blind study which evaluated the 2 year decline in putaminal 18F-dopa uptake in 186 PD subjects taking either L-dopa or ropinirole, a D2/D3 agonist. The finding of a significant difference in the fall from baseline of the ropinirole group compared to the L-dopa group supports either a protective role for ropinirole or a deleterious role for L-dopa on progression.

**Atypical Parkinsonism and differential diagnosis**

Evaluation of pre-synaptic function with 18F-dopa PET or 11C-FP-CIT SPECT shows reductions in striatal uptake in the presence of nigrostriatal degeneration. They therefore display normal striatal uptake in drug-induced parkinsonism, dopa-responsive dystonia and essential tremor and reduced uptake in PD, multiple system atrophy (MSA), Lewy body dementia, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Further discrimination between the diagnoses of parkinsonism using other functional imaging studies is made difficult by imaging findings often overlapping between conditions. However, using 18F-FDG PET in a case of chronic parkinsonism, only in PD is there lentiform (putamen + globus pallidus) and thalamic relative hypermetabolism contralateral to the clinically more affected limbs. In MSA, PSP and CBD there is usually lentiform and thalamic relative hypometabolism, the latter reflecting loss of different activity from the degenerating globus pallidus. A greater than 5% side-to-side asymmetry of parietal glucose uptake would support a diagnosis of CBD and cerebellar hypometabolism: PSP or MSA. To discriminate PSP from MSA with functional imaging is more difficult as both share more uniform loss of caudate and a more specific measure of survival and growth of graft tissue. However, in one published study using FDG PET, it was demonstrated that there were local striatal increases in transplanted patients and restoration of distant (cortical) metabolism away from the site of surgery where local glucose metabolism may be difficult to interpret.

Clinical studies evaluating potential neuroprotective agents in HD have required large numbers of patients, for example 347 patients with established HD over 30 months after surgery in dystonia that sensory processing is altered with increased size and overlapping of receptive fields, so that, for example, reducing sensory inputs from the affected limb with local anaesthetic can ease writer’s cramp. However, imaging studies have revealed underlying abnormalities in both sensory and motor networks affecting structures from the lentiform nucleus to the cortex with PET. A unifying feature of both primary and secondary (for example, in the presence of a striatopallidal or thalamic lesion) dystonias appears to be inappropriate overactivity of basal ganglia projections to accessory motor areas.

**Huntington’s disease**

Huntington’s disease (HD) is an autosomal dominantly inherited CAG trinucleotide repeat disorder in which the pathology initially targets the GABAergic medium spiny neurons of the striatum and subsequently progresses to involve multiple brain areas. As these neurons bear both D1 and D2 receptors, binding of both 11C-SCH23390 (D1 receptor ligand) and 11C-raclopride (D2) are progressively reduced in HD patients at a rate of about 5% per annum. Reduced D1 binding has also been demonstrated in temporal and frontal cortex of HD patients (Figure 2).

Characteristically in HD there is glucose hypometabolism on 18F-FDG PET of the caudate and putamen and this appears to precede atrophy of these structures, in addition, there are relative mediotemporal and occipital metabolic reductions and increases respectively. This covariance pattern allows discrimination between controls and pre-symptomatic gene carriers and between the latter and early-stage HD patients.

Activation studies whilst moving a joystick revealed underactivation of striatum and frontal projection areas including the SMA which could explain the background bradykinesia invariably present in choreic HD patients.

Grafting of human foetal striatal cells into the striatum of HD patients is currently under evaluation and PET measures of D1 and D2 binding would be expected to provide a more specific measure of survival and growth of graft tissue. However, in one published study using FDG PET, it was demonstrated that there were local striatal increases in transplanted patients and restoration of distant (cortical) metabolism away from the site of surgery where local glucose metabolism may be difficult to interpret.

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to assess coenzyme Q10. Coenzyme Q10 300mg b.d. showed a trend in the slowing of functional decline. PET measures of striatal D1 or D2 dopamine binding could be used in the future to interrogate the rate of progression associated with different dosages of coenzyme Q10 and other neuroprotective agents. Indeed functional imaging could aid in the practical assessment of emerging disease modifying treatments for this condition, and this could include the asymptomatic HD mutation carriers as whilst they have been shown to be actively progressing on PET (=50% of subjects), they have no clinical signs with which to monitor progression.

References