Movement Disorders
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CHAPTER 12

Imaging

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12.1. Introduction

Brain imaging plays an important role in the evaluation of patients with movement disorders. Anatomic imaging is essential for ruling out structural lesions in subcortical nuclei and cortex, and for identifying regional atrophic changes. Imaging of brain metabolism and neurotransmitter function is an important adjunct to the clinical examination in patients with atypical akinetic-rigid syndromes that might not be secondary to idiopathic Parkinson's disease. Functional activation studies provide unique insight into normal motor control as well as the pathophysiologic basis of abnormal motor control. These imaging methods encompass techniques based on conventional x-rays, magnetic resonance and radionuclide tomography. In this chapter these techniques are reviewed and related to clinical applications, basic research and assessment of pharmacological and surgical therapy for movement disorders.

12.2. Structural imaging

Although conventional x-rays of the skull are no longer used diagnostically in movement disorders, they are important historically for lesion localization and premorbid clinical-radiological correlation. In a classic 1917 study of injured soldiers, Holmes used conventional x-rays to relate the location of bullets lodged in the cerebellar hemispheres to cardinal signs of cerebellar damage including unilateral ataxia, hypotonia and dysiadochokinesia (Holmes, 1917). With the development of computer assisted tomographic imaging (CT) in the 1970s it became possible to identify supratentorial structural lesions that could cause secondary movement disorders. This early imaging work revealed that the most common structural lesion leading to parkinsonian symptoms was a large cortical or glial tumor with deformation of the basal ganglia. It is extremely rare for tumors located directly within the basal ganglia to cause parkinsonism (Waters, 1993). Other lesions, occasionally associated with parkinsonism are listed in Table 1. The advent of CT also brought attention to the incidental finding of basal ganglia calcification, i.e. Fahr's disease. The incidence of basal ganglia calcification in a general adult population is approximately 0.7%. Of these persons, less than 7% have any motor symptoms (Murphy, 1979; Brannan et al., 1980). However, if the patient presents with hypoparathyroidism there is a 70% chance of basal ganglia calcification. This increases to almost 100% for patients with pseudohypoparathyroidism. The likelihood of motor symptoms also increases (Muenter and Whisnant, 1968; Sachs et al., 1982; Illum and Dupont, 1985). With CT it also became possible to identify white matter changes consistent with sub-

Table 1

Structural lesions associated with an akinesis or rigidity

Cortical tumors
Glioma
Meningioma
Other
Subdural hematoma
Striatal abscess
Midbrain tuberculoma
Ventriculomegally
Posterior fossa cyst
Normal pressure hyodrocephalus
Vascular parkinsonism

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cortical infarction and associated arteriosclerotic parkinsonism (Critchley, 1929), i.e. subcortical arteriosclerotic encephalopathy (Binswanger's disease) (Thompson and Marsden, 1987; Bennett et al., 1990). CT was the first method to generate reliable volumetric measurements of brain anatomy in vivo. Striatal atrophy in advanced Huntington's disease was readily measured and it became possible to correlate clinical severity with tissue loss in the head of the caudate nucleus (Grafton et al., 1992).

With the introduction of magnetic resonance imaging in the early 1980s, image resolution and tissue contrast improved dramatically. The primary use of anatomic MR imaging in movement disorders is to exclude vascular disease or neoplasm causing symptoms that could mimic a neurodegenerative disease (Waters, 1993). Infratentorial lesions such as cerebellar atrophy in the hereditary ataxias can also be screened reliably. MRI changes in the basal ganglia can be seen in a variety of systemic diseases, as listed in Table 2. Most of these can be readily diagnosed clinically. Structural imaging with MRI allows for unprecedented accuracy in volumetric measurements of complete nuclei, such as the putamen or caudate. Large databases of normal and pathologic brain anatomy are currently being generated for probabilistic assessment of structure form and volume (Mazziotta et al., 2001; Toga and Thompson, 2001). These measures can be correlated with clinical progression in Huntington's disease and possibly used to detect presymptomatic gene-positive persons at risk for the disease (Aylward et al., 2000). Using special acquisition parameters, it may be possible to identify subtle changes in other neurodegenerative disorders including Parkinson's disease (Hu et al., 2001).

Table 2

Diseases with MRI signal changes in basal ganglia

Hypointensity
Wilson's diease
Leigh's disease
CO intoxication
Anoxia
Hallervorden-Spatz diease
Cyanide poisoning
Methanol intoxication
GM2-gangliosidosis
Hemolytic uremic disease
Hyperintensity
Wilson's disease
Creutzfeldt-Jakob disease
Manganese toxicity
Hepatic encephalopathy
AIDS
Normal aging
Calcified basal ganglia
Hypo- and pseudohypoparathyroidism
Fahrs syndrome
CO intoxication
Birth anoxia
Tuberous sclerosis
Mitochondrial encephalopathies
Radiation and methotrexate therapy
AIDS
Congenital folate deficiency, dihydropteridine reductase deficiency
Japanese B encephalitis, herpes simplex encephalitis
Down syndrome
Cockayne's syndrome

MRI, magnetic resonance imaging; CO, carbon monoxide; AIDS, acquired immune deficiency syndrome.

12.3. Functional imaging

12.3.1. Radionuclide imaging

The advent of single photon emission tomographic (SPECT) imaging provided early measurements of brain cerebral blood flow. With this method patients are injected with a radioactive agent that binds to cerebral tissue in proportion to local cerebral blood flow, a receptor or some other biologic marker (Podreka et al., 1987). Injections and images are acquired with the subject at rest. Gamma-ray energy is detected with a set of collimated detectors rotating slowly around the head. Images are of low resolution (>1.5 cm) and non-uniform. Deep brain structures such as basal ganglia are of low image intensity due to attenuation of the radioactive emitter by overlying tissue. SPECT studies using blood flow tracers provided early evidence for changes in basal ganglia with Huntington's disease and temporo-parietal hypoperfusion in Alzheimer's disease. More recently, the cocaine analog 2 beta-carbomethoxy-3 beta-4-iodophenyltropane (beta-CIT) labeled with ^{123}I and related compounds have played an essential role in the assessment of the presynaptic striatal dopamine transporter uptake site (Brucke et al., 1993).

Development of positron emission tomography (PET) imaging in the early 1980s resolved many of the technical limitations of SPECT (better resolution, no attenuation artifacts) (Phelps et al., 1975). The range of biologic radiotracers that could be created with cyclotron produced radioisotopes was greatly expanded. Dominating these new compounds was ^{18}F-fluorodeoxyglucose (FDG) (Reivich et al., 1979). The tracer is trapped within cells in proportion to glucose transport and utilization. Imaging of regional radioactivity within the brain provided a direct, simple assessment of relative glucose metabolism. Glucose metabolism is strongly correlated with local neuronal activity (Jueptner and Weiller, 1995). In particular, lesions and physiologic studies in rodents and non-human primates have established that regional metabolism reflects both excitatory and inhibitory neuronal activity and this activity is predominantly a reflection of pre-synaptic function (Nudo and Masterton, 1986). Under pathologic conditions glucose metabolism is altered when there is a change of neuronal density. Importantly, this measure was observed to be highly sensitive to underlying pathologic conditions and more reliable than other imaging methods such as blood flow imaging with SPECT or PET agents. Early clinical studies identified marked metabolic changes in temporoparietal cortex in both early and advanced Alzheimer's disease and mesial temporal hypometabolism in complex partial epilepsies. Thus, one might hope to identify subtle alterations of function circuits in movement disorders using metabolic rather than structural imaging. However, glucose metabolism also shows large changes in association with normal neuronal activation (Sokoloff, 1977). Thus, the behavioral state of the human or animal during the 20–30 minute uptake period of FDG after intravenous injection will have a strong impact on the regional metabolism measured by PET imaging. In disorders with involuntary movement neural systems associated with movement production could have increased metabolic activity (Colebatch et al., 1990; Brooks et al., 1992b). This can potentially blur the distinction between metabolic abnormalities due to a disease (trait) with those due to a symptom (state).

12.3.1.1. Hypokinetic movement disorders

A variety of cortical and subcortical metabolic changes are observed in the hypokinetic movement disorders, i.e. disorders where there is a reduction of volitional movement. In Parkinson's disease the characteristic finding on PET imaging is elevated glucose metabolism in the striatum and mild to moderate reductions of cortical metabolism (Kuhl et al., 1984; Eidelberg et al., 1994). The hyperactivity in striatum is consistent with autoradiographic studies of non-human primates with parkinsonian symptoms secondary to the neurotoxin *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Crossman et al., 1985). Using this pattern of striatal hypermetabolism of PD as a benchmark, it was apparent that atypical parkinsonian syndromes, including multiple systems atrophy, striatonigral degeneration and olivopontocerebellar atrophy had different metabolic signatures as listed in Table 3 (Rosenthal et al., 1988; De Volder et al., 1989; Fulham et al., 1991; Otsuka et al., 1991; Eidelberg et al., 1993; Gilman et al., 1994; Otsuka et al., 1994). An important generality is that all of the atypical syndromes are likely demonstrate striatal hypometabolism with variable involvement of cortical or cerebellar hypometabolism. Large clinical series have not yet been performed to establish the sensitivity and specificity of PET imaging. Nevertheless, the available evidence from smaller studies supports the utility of PET glucose metabolic imaging as an adjunct for diagnosing patients with clinically atypical akinetic-rigid movement disorders. Approximately 15% of PD patients will develop a significant dementia. With dementia there is a reduction of temporal-parietal cortical metabolism in the same areas as seen in Alzheimer's disease (Kuhl et al., 1985). Whether this dementia and metabolic finding represents PD+AD, a special form of PD, or diffuse Lewy body disease with dementia is unknown.

The neuropharmacology of movement disorders can be evaluated with PET radioisotopes that reflect presynaptic dopaminergic function (^{18}F-Dopa), postsynaptic D1/D2 dopamine receptor binding (Spiperone, Raclopride) and non-specific opiod receptor binding (Garnett et al., 1983). In Parkinson's disease there is an approximately 30% loss of FDOPA uptake in striatum compared to normal subjects at symptom onset, progressing to a 60% reduction with advanced disease (Garnett et al., 1984; Leenders et al., 1984; Leenders et al., 1986; Martin et al., 1987). There is a greater loss of F-DOPA in the putamen than the caudate, whereas in

Table 3

Imaging in hypokinetic movement disorders

	PD	PD-Dementia	Atypical PD	PSP	CBGD
Metabolism	Inc striatum	Inc striatum	Dec striatum	Dec Frontal	Dec thalamus, parietal, temporal
	Mild dec frontal	Mild dec frontal	Dec frontal	Dec striatum, cerebellum, thalamus	Asymmetric!
		Dec temperoparietal	Dec cerebellar (ataxic)		
Presynaptic Dopamine	Dec putamen	Dec putamen	Dec putament	Dec putamen	Dec putamen
	Mild dec caudate	Mild dec caudate	Dec caudate	Dec caudate	Dec caudate
Postsynaptic D2	Nl-mild inc striatum (untreated) Nl-mild dec striatum (treated)		Dec striatum	Dec striatum	Dec striatum
Opiod Receptors	Normal		Dec striatum	Dec striatum	
PMRS	Normal Striatum?	Normal Striatum?	Dec NAA/creatine	Dec NAA/creatine	Dec NAA/creatine

PD: Parkinson's disease
PSP: Progressive supranuclear palsy
CBGD: Corticobasalganglionic degeneration
Atypical PD includes striatonigral degeneration, olivopontocerebellar degeneration, and multiple systems atrophy
PMRS: Proton magnetic resonance spectroscopy

the atypical parkinsonian syndromes both caudate and putamen are typically involved (Table 3) (Brooks et al., 1990a, b; Laihinen et al., 1995; Brucke et al., 1997). The reliability of using these findings for radiologic diagnosis in an individual patient depends on the experience of the imaging center performing FDOPA imaging. Individual subject diagnosis requires the study of a large normative population with low measurement variability that patient data can be compared to. Post-synaptic dopamine receptors are normal or mildly increased in untreated early Parkinson's disease, suggestive for receptor upregulation (Rinne et al., 1990a, b). With long standing treatment with l-Dopa the postsynaptic binding is normal or reduced, consistent with mild receptor down regulation (Brooks et al., 1992a; Turjanski et al., 1997).

12.3.1.2. Hyperkinetic movement disorders

The prototypic hyperkinetic movement disorder is Huntington's disease (HD), in which the loss of medium aspiny neurons in the striatum is accompanied by profound hypometabolism and reductions of dopaminergic, opiod and GABA associated benzodiazepine binding. All of these changes can be observed in vivo with PET imaging (Myers et al., 1988; Kuwert et al., 1990). Reductions of metabolism likely precede clinical onset and then parallel disease progression (Mazziotta et al., 1985b; Young et al., 1986; Mazziotta et al., 1987; Young et al., 1987; Grafton et al., 1990; Grafton et al., 1992). The development of a direct genetic test for Huntington's disease obviates the use of functional brain imaging as a diagnostic aid for this disease (Gusella et al., 1983, 1993). It is interesting to note that different causes of chorea can have opposing changes of striatal metabolism as listed in Table 4. There is a common pattern of striatal hypometabolism in HD, benign familial chorea and neuroacanthocytosis (Suchowersky et al., 1986; Hosokawa et al., 1987; Dubinsky et al., 1989). Hypermetabolism is observed in Sydenham's chorea, lupus and tardive

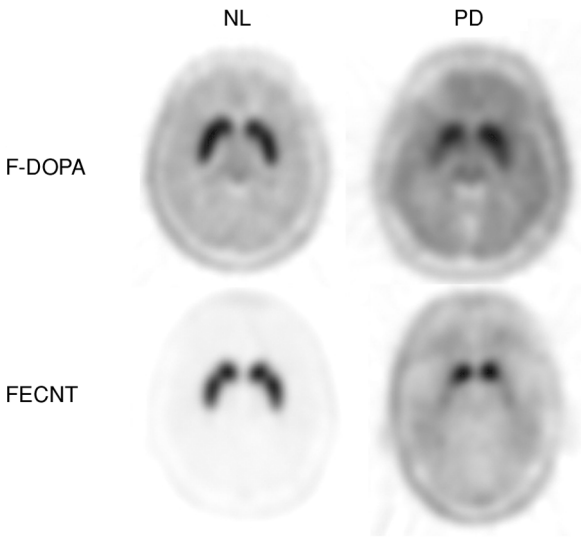

Fig. 1. Functional neurochemistry of the basal ganglia. Integrity of pre-synaptic dopamine synthesis can be assessed with fluoro-dopa (F-DOPA). In Parkinson's disease (PD) there is a marked reduction of uptake and decarboxylation of this compound compared to normal controls (NL), particularly in the putamen. Integrity of presynaptic dopamine terminals can also be assessed by labeling the dopamine transporter protein with compounds such as 2β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-(^{18}F)fluoroethyl)nortropane (FECNT). This protein is normally involved in reuptake of synaptic dopamine and is a marker of dopamine terminal density. Note the marked reduction in Parkinson's disease. Images provided by Mark Goodman and Margaret Davis of Emory University, Atlanta GA.

dyskinesia (Guttman et al., 1987; Weindl et al., 1993; Pahl et al., 1995). No changes in post-synaptic dopamine receptor function have been observed in TD, suggesting the clinical symptoms may be a result of GABA related disinhibition of motor circuits rather than upregulation of the dopaminergic pathways (Blin et al., 1989; Andersson et al., 1990).

The other important set of hyperkinetic movement disorders are the dystonias. The etiology of focal, segmental, hemi- or generalized dystonia, irrespective of the distribution of symptoms is remarkably diverse. MRI has been useful in identifying focal lesions within the spine, brainstem, striatum, thalamus and white matter resulting in acquired dystonia (Grafton et al., 1988; Gille et al., 1996; Kostic et al., 1996; Lehericy et al., 1996; Karsidag et al., 1998; Kurita et al., 1998). This diversity of lesion location makes it difficult to generate a unifying pathophysiologic model that predicts the occurrence of dystonic movements. Functional imaging is an important alternative approach for characterizing the pathophysiology of dystonia. By definition, there is forceful and prolonged simultaneous co-contraction of agonist and antagonist muscles which distort the affected extremities into stereotypic postures (Oppenheim, 1911). Thus, imaging studies examining neural substrates of the dystonias can potentially be complicated by movement related activation. Using fluorodeoxyglucose (FDG), brain glucose metabolism has been measured in both focal and generalized dystonia (Stoessl et al., 1986; Martin et al., 1988; Karbe et al., 1992; Hirato et al., 1993; Eidelberg et al., 1995; Galardi et al., 1996; Dethy et al., 1998; Mazziotta et al., 1998). Experimental strategies to avoid movement-related activation include scanning subjects in their sleep or scanning presymptomatic subjects who test positive for the dystonia gene DYT1 (Eidelberg et al., 1998; Mazziotta et al., 1998). The main finding in DYT1 patients was an increased covariance of metabolism within the lentiform nucleus, cerebellum and supplementary motor area, suggesting disregulated control between cortical and subcortical motor areas.

12.3.2. Proton magnetic resonance spectroscopy

Given appropriate technical modifications, conventional MRI scanners can be used to perform proton magnetic resonance spectroscopy (PMRS) of brain metabolites. The most commonly detected signals are related to *N*-acetylaspartate (NAA) a relative marker of neuronal density, choline-containing compounds (Cho) and creatine-phosphocreatine (Cr). Absolute quantification is difficult and most studies investigate altered ratios of these metabolites with each other. Comparative studies of PD, MSA, PSP and CBGD have been performed (Federico et al., 1999; Abe et al., 2000). Single volume assays, localized to the lentiform nucleus as well as frontal cortex assays, usually demonstrate reductions of the NAA/Cho and NAA/Cr peak ratio in all of the atypical parkinsonian syndrome patients compared to controls. Reductions of NAA/Cho or NAA/Cr are less dramatic and inconsistently observed in the frontal lobe or striatum of PD, in part due to measurement error secondary to inorganic paramagnetic substances within the basal ganglia (Clarke and Lowry, 2000). When a reduction is observed it

Table 4

Imaging in hyperkinetic movement disorders

	Huntington's disease	Neuroacantho-cystosis	Benign Familial Chorea	DRPLA	SLE	Sydenham's Chorea	Tardive Dyskinesia
Metabolism	Dec dorsal striatum Dec frontal (advanced)	Dec dorsal striatum	Dec dorsal striatum	Dec dorsal striatum	Inc striatum	Inc striatum	Inc striatum
Postsynaptic D2	Dec striatum	Dec striatum			Normal		Normal
Opiod Receptors	Dec striatum						
Central Benzodiazepine	Dec striatum						

DRPLA: Dentatorubropallidoluysian atrophy
SLE: Systemic lupus erythematosis
PMRS: Proton magnetic resonance spectroscopy

can correlate with disease severity (Abe et al., 2000). Recent studies show reductions of NAA/Cr ratios in both motor cortex and temporo-parietal cortex compared to healthy controls, suggesting alterations of thalamocortical projection areas in PD (Lucetti et al., 2001). Animal models of Parkinson's disease reveal an increase of striatal glutamate activity. However, several proton magnetic resonance spectroscopy studies of striatal glutamate+glutamine relative to Cr have been normal in PD patients who are dyskinetic, non-dyskinetic and there has been no change with acute dopaminergic treatment by apomorphine (Clarke et al., 1997; Taylor-Robinson et al., 1999). This suggests the changes observed in animal models are currently too subtle to be detected by PMRS.

12.3.3. Functional brain mapping

Over a century ago Sherrington and Roy noticed the relationship of brain blood flow and regional activity (Roy and Sherrington, 1890). It is a remarkable fact that increases of neuronal activity, down to the columnar level of spatial resolution will lead to corresponding changes of local blood flow across a slightly larger volume of tissue and with a delay of approximately 4 s (Malonek and Grinvald, 1996; Logothetis et al., 2001). This change of blood flow can be measured with radionuclide techniques such as PET as well as magnetic resonance imaging (Mazziotta et al., 1985a; Belliveau et al., 1991).

12.3.3.1. PET CBF

The PET blood flow method requires injections of radioactive water or inhalation of radioactive CO_2 (which is converted to water in the lungs by carbonic anhydrase). The amount of radioactivity appearing in the brain is proportional to local blood flow. The temporal resolution is limited to the time it takes to acquire sufficient radioactive counts, typically on the order of 45–90 s. Spatial resolution is nominally 5 mm and more realistically 10–15 mm after image processing. Only 10–15 scans are acquired per subject due to limits on human exposure to radioactivity. Subject motion leads to image blurring, rather than signal dropout, thus the technique can be useful in patients with abnormal movements.

12.3.3.2. FMRI BOLD imaging

The most commonly used functional magnetic resonance imaging technique is the blood oxygen level dependent method (BOLD) (Ogawa et al., 1990). The method detects change in the contrast of T2* weighted images by varying levels of oxygen saturation. As blood flow to an area increases, so does the delivery of oxygenated blood. The method is enhanced with MRI gradients that are capable of

rapid acquisition using echo planar imaging (EPI) techniques (Cohen and Weisskoff, 1991). A typical commercial 1.5 Tesla scanner is capable of acquiring 10–12 slices per second with EPI imaging. Signal detection is improved with surface coils, stronger magnetic fields and acquisition at lower sampling densities (64×64 matrix). The method is very sensitive to head movement (signal dropout rather than signal blurring), artifacts from motion in the magnetic field (from eye or limb movements) and susceptibility artifacts maximal at air tissue interfaces such as near the sinuses. Run to run and across session variance in fMRI can be significant and create challenges for across session experimental designs (Aguirre et al., 1998; Glover, 1999; Waldvogel et al., 2000). The tight confines of an MRI scanner have also set limits on the types of movements and behavior that can be examined in this restrictive environment. Nevertheless, fMRI has replaced PET as the most commonly used method for investigating functional anatomy in normal subjects.

12.3.3.3. Functional imaging of normal motor control

Nearly two decades of experiments have mapped the functional anatomy of normal human motor behavior while subjects performed a broad range of motor tasks during brain imaging. The scope of this work is beyond the capacity of this chapter. Core observations include: (1) the delineation of the somatotopic organization of motor cortex, SMA and premotor areas (Colebatch et al., 1991; Grafton et al., 1991; Walter et al., 1992; Grafton et al., 1993; Sanes et al., 1995); (2) the identification of premotor and parietal areas for movement selection, preparation, and on-line control (Deiber et al., 1991, 1996; Honda et al., 1998b; Desmurget et al., 1999); (3) the involvement of cerebellum in movement timing and coordinated motor control (Jueptner et al., 1996; Jueptner and Weiller, 1998; Wolpert et al., 1998; Miall et al., 2001); (4) the involvement of motor cortex and SMA in procedural and sequential learning (Jenkins et al., 1994; Grafton et al., 1995a; Karni et al., 1995; Sadato et al., 1996; Doyon et al., 1997; Hazeltine et al., 1997; Boecker et al., 1998; Honda et al., 1998a; Toni et al., 1998; Grafton et al., 2001); (5) modulation of activity in motor cortex and cerebellum as a function of force and velocity (Dettmers et al., 1995, 1996a, b; Turner et al., 1998). These experiments form a critical background for interpreting changes of functional circuits in patients with movement disorders.

12.3.3.4. Functional brain mapping of movement disorders

Functional brain imaging has been used most intensively to understanding the pathophysiologic basis of Parkinson's disease. This work forms an essential benchmark for interpreting future investigations of the functional topography of other movement disorders. The goal in PD imaging research has been to determine how altered basal ganglia (BG) information processing due to dopamine deficiency leads to altered control of movements at both the cortical and subcortical levels. A key advance was developing reliable methods that could detect movement-related activity throughout cortical and subcortical circuits. For example, PET and fMRI studies of simple movement can detect activation in almost all of the nuclei of the cortico-subcortical motor circuit (Bucher et al., 1995; Winstein et al., 1997; Turner et al., 1998). A related goal asks if patterns of activity observed by imaging studies correspond to specific parkinsonian signs such as bradykinesia or akinesia.

Most published imaging studies of PD have focused on the hypothesis that SMA underactivity is a cause of akinesia. In this model BG dysfunction culminates in an inadequate recruitment of SMA neurons resulting in impaired movement initiation. In principal, this is a reasonable approach as the SMA is one of the main cortical receiving areas of the BG motor circuit (Schell and Strick, 1984) and the SMA has been linked to a variety of motor behaviors that are impaired in PD, including, most notably, the selection and generation of internally-guided movements. Thus, tasks that require repeated internal selection and initiation of discrete movements should provide a good substrate for testing the association between parkinsonian akinesia and SMA activity. As predicted, PD patients show a smaller-than-normal increase in CBF in the SMA during movement tasks that require selection and execution of unidirectional ballistic joystick movements (Playford et al., 1992). In a critical follow-up experiment, a more carefully designed movement task was used to compare internally- and externally-generated movements in normal subjects and PD patients (Jahanshahi et al., 1995). Subjects were trained to

make simple index finger extensions every 3 s by self initiation or external triggering, yoked to the same rate. The tasks required minimal working memory or other cognitive demands. PD patients had a smaller-than-normal activation of SMA for self-initiated movements. It is noteworthy that no differences in brain activity between normal subjects and PD patients were found in this study when they performed similar movements under an externally triggered condition. When PD patients performing the internal generation task are treated with dopamine agonists (apomorphine) there is a "normalization" of the movement-related activation of SMA accompanied by a reduction in reaction times (Jahanshahi et al., 1995). A similar effect of dopamine replacement therapy was observed by Rascol et al. in PD patients performing a sequential movement task which requires frequent initiation of self-generated discrete finger-to-thumb movements (Rascol et al., 1992). They showed with single photon emission tomography (SPECT), that the SMA is under-activated in PD patients during this task (i.e. that that SMA had a smaller-than-normal task-related increase in CBF) and that the SMA defect normalized with apomorphine therapy. These results provide additional evidence that SMA activation is modulated by the BG motor circuit and that dopamine replacement therapy can ameliorate the inadequate thalamocortical facilitation of the SMA. Dopamine replacement therapy, by releasing thalamocortical facilitation, restores normal SMA activation patterns and movement initiation improves.

Alternative models are emerging from imaging experiments to understand the symptoms of PD. One of these models is task specific compensation. Imaging studies have detected patterns of CBF in PD patients that may reflect adaptive changes, some of which may be closely linked to the particular motor task being performed. Using SPECT, (Rascol et al., 1997) found that untreated PD patients demonstrated an abnormally high activation of the cerebellum ipsilateral to the moving arm when they performed sequential finger-to-thumb movements. Coincident with the cerebellar overactivation was a smaller-than-normal activation of the SMA, as predicted by the akinesia model. The increased activity in cerebellum was not seen in a separate group of PD subjects who were studied when on their normal dopamine replacement therapy. Cerebellar overactivation in untreated PD patients may be part of a compensatory recruitment of alternate motor circuits in the parkinsonian brain (including the visually-driven cortico-ponto-cerebellar loop (Glickstein and Stein, 1991)) in an attempt to overcome impaired function of the mesial frontal cortical circuits.

Other studies also provide evidence of abnormal increased cerebral activity (CBF) in PD patients and indicate, additionally, that the specific patterns of under- and over-activation hinge on what behavioral task is used. Using PET, Samuel et al. found a bilateral task-related increase in CBF in dorsolateral premotor and inferior parietal cortices in untreated PD subjects performing a sequential finger tapping task (Samuel et al., 1997a). These areas were not activated in normal subjects performing the same task. Samuel et al. also found a task-related under-activation of mesial frontal and prefrontal areas in the PD subjects. These observations have been confirmed and extended recently by Catalan et al. (Catalan et al., 1999) in a PET study of PD and normal subjects performing either sequential finger movements of increasing complexity or an internal generation task (similar to the internal generation task first used by Playford et al. (1992). During sequential finger movements, they found a relative overactivation (i.e. a greater task-related increase in CBF than observed in normals) of bilateral parietal cortices, lateral premotor areas, and precuneus. Interestingly, Catalan et al. observed that mesial frontal areas (anterior SMA/cingulate cortex) were activated during motor sequence performance in both PD and normal subjects, but that CBF increased progressively with more complex sequences only in the PD subjects. In contrast, when the same PD subjects performed the internal generation task, no parietal or premotor overactivations were observed and the mesial frontal areas, including SMA, were under-active, as previous studies predicted. Although some of the results described thus far can be interpreted within the model for parkinsonian akinesia, other results call for a revised or expanded model. The contrasting results for sequential movement and internal generation tasks in the Catalan et al. study, for instance, indicate that the specific differences in brain activity between PD and normal subjects depend critically on the nature of the behavioral task being performed. The use of tasks that accentuate different facets of parkinsonian motor impairment may expand our understanding of

the functional substrates of parkinsonian symptoms other than akinesia.

12.4. Imaging therapy in movement disorders

12.4.1. Ablative surgical therapy

The current model of PD pathophysiology provides a clear rationale for surgical treatment of PD by stereotaxic ablation of the posteroventral GPi (pallidotomy). Both in PD patients and in primate models of PD, pallidotomy can reduce significantly the cardinal symptoms of PD while producing no overt side-effects (Laitinen et al., 1992; Dogali et al., 1995; Baron et al., 1996). The presumed mechanism of action for pallidotomy is an elimination of excessive pallidothalamic inhibition and a subsequent recovery of function in the previously under-excited frontal cortical areas. The efficacy of pallidotomy as a treatment for PD points clearly to the conclusion that most of the symptoms of PD arise from the impaired function of cortical motor areas secondary to excessive inhibitory outflow from the pallidum and not, as might be assumed, from impaired BG function per se (Wichmann and DeLong, 1996).

Functional imaging studies of pallidotomy have provided results consistent with the akinesia model of PD pathophysiology (Ceballos-Baumann et al., 1994; Grafton et al., 1994, 1995b; Samuel et al., 1997b). A consistent finding across studies has been that following pallidotomy, there is a movement related increase of activity in the SMA compared to rest conditions.

12.4.2. Deep brain stimulation

A relative drawback of surgical pallidotomy is the potential morbidity (acute and chronic) resulting from a permanent brain lesion. The introduction of high frequency deep brain stimulation (DBS) is an important alternative to ablation because the electrode can be introduced without producing significant brain damage and, by adjusting stimulation sites and parameters, the optimal response can be obtained. Reports of clinical response to DBS are promising (Siegfried and Lippitz, 1994; Limousin et al., 1997; Krack et al., 1998; DBS study group, 2001). The stimulating electrode can be positioned at several nodes of the subcortical motor circuit, including the GPi, subthalamic nucleus (STN) and the motor thalamus. Evidence to date in unblinded, non-randomized trials suggest similar maximal benefit for placement in the STN and pallidum, although patients with STN stimulators may require lower amounts of supplemental L-DOPA therapy (DBS study group, 2001). The mechanism by which DBS achieves therapeutic results remains speculative. PET has been used to examine the effects of therapeutic DBS on CBF. In the first report, Limousin et al. explored the effects on cerebral blood flow of DBS in GPi and STN (Limousin et al., 1997). Clinically effective levels of stimulation in STN led to a greater task-related increase in CBF in

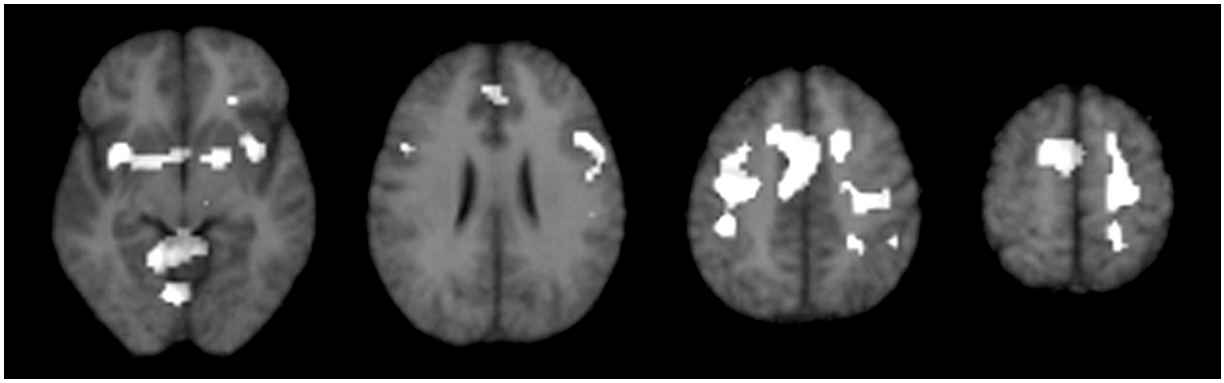

Fig. 2. Functional adaptation in Parkinson's disease. PET blood flow imaging was used to assess motor system activity during visually guided tracking at different velocities. Areas in white represent sites where PD patients show a greater increase of activity as movements become faster relative to controls. These sites include bilateral premotor cortex, motor cortex, globus pallidus and cerebellum. In PD these areas are recruited to a greater degree than normal subjects to achieve the same level of performance. Images provided by Robert Turner, UC San Francisco, California.

the SMA and dorsolateral prefrontal cortex compared to ineffective stimulation. Of concern, however, clinically-effective stimulation of the GPi produced no significant changes in CBF. In a second study, Davis et. al., examined the effect of GPi DBS on brain activity during a "rest" condition (Davis et al., 1997). Clinically beneficial stimulation in the GPi was associated with a CBF increase in mesial frontal cortex anterior to the SMA. This result suggests that DBS altered the inhibitory GPi output in a manner analogous to ablation and thereby disinhibited the frontal thalamocortical circuit. The authors proposed that the increased CBF in the mesial cortical areas, although observed under a "resting" condition, could be responsible for a reduction of akinesia. In a more recent study, patients were examined while they performed simple paced sequential reaching movements. Concurrent regional cerebral blood flow recordings revealed a significant enhancement of motor activation responses in the left sensorimotor cortex and bilateral supplementary motor area. Significant correlations were evident between the improvement in motor performance and the regional cerebral blood flow changes mediated by stimulation (Fukuda et al., 2001). The combined results of these different imaging studies can be taken as further evidence that surgical therapeutic interventions for PD lead to increased cerebral activity in areas that are targets from pallido-thalamic connections.

12.4.3. Fetal transplantation

Functional imaging of dopaminergic function is extremely useful for assessing the in vivo viability and growth of transplants of fetal substantia nigra tissue in patients with advanced Parkinson's disease (Lindvall et al., 1989; Lindvall et al., 1994). Fluorodopa imaging can be used as an independent measure of tissue viability (Freed et al., 1990; Lindvall et al., 1990). In a recent large randomized trial there was significant evidence for increased fluorodopa uptake in the patients treated by transplantation therapy suggesting dopamine producing fiber outgrowth of transplanted tissue (Freed et al., 2001). An interesting observation emerging from the randomized clinical trials of PD using fetal transplantation has been a potent placebo effect in the patients receiving sham surgery. A functional imaging study helps to explain this puzzling response. PD patients who were told they were to get a new medical therapy for their disease were scanned and the availability of post-synaptic dopamine receptors was assessed with PET (de la Fuente-Fernandez et al., 2001). Patients given a placebo showed reduced receptor availability, suggesting they were releasing endogenous dopamine in the setting of increased reward expectancy (a new therapy). This measurable increase of endogenous dopamine could also improve parkinsonian symptoms. This finding is consistent with recent studies in non-human primates establishing the importance of the BG for facilitating reward expectancy and learning (Schultz, 2001).

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