Movement disorders 1

The expanding universe of disorders of the basal ganglia

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The basal ganglia were originally thought to be associated purely with motor control. However, dysfunction and pathology of different regions and circuits are now known to give rise to many clinical manifestations beyond the association of basal ganglia dysfunction with movement disorders. Moreover, disorders that were thought to be caused by dysfunction of the basal ganglia only, such as Parkinson's disease and Huntington's disease, have diverse abnormalities distributed not only in the brain but also in the peripheral and autonomic nervous systems; this knowledge poses new questions and challenges. We discuss advances and the unanswered questions, and ways in which progress might be made.

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Introduction

In modern clinical practice, the basal ganglia refers mainly to the striatum, the internal and external globus pallidus, the subthalamic nucleus, and the substantia nigra pars compacta and pars reticulata because of their close anatomical connectivity and pathophysiological implications (figure 1). The basal ganglia were implicated in the origin of movement disorders by Wilson's observations 100 years ago that lesions of the lenticular nucleus were associated with dystonia and parkinsonism[1] and that focal lesions of the subthalamic nucleus and substantia nigra pars compacta caused hemichorea-ballism[2] and parkinsonism,[3] respectively. In his seminal Croonian lecture in 1925,[4] Wilson stated: "I have found no reason to modify in any important respect…that the main features of disease of the corpus striatum consist of disorders of muscle tone regulation and the appearance of involuntary movements". The recognition that Parkinson's disease arises as a consequence of degeneration of the substantia nigra pars compacta and loss of striatal dopamine[5] reinforced this idea. Marsden[6] subsequently concluded that "on the basis of the motor deficits observed in patients with Parkinson's disease, the basal ganglia normally are responsible for the automatic execution of learned motor plans". In the mid-1980s, the emergence of a basal ganglia model[7–10](figure 2), which focused on the pathophysiology of parkinsonism and dyskinesias, further strengthened the association between the basal ganglia and abnormal movements. During the past two decades, robust evidence has accumulated that the basal ganglia are intimately connected with the cortex through several segregated but parallel loops (figure 1), which have been subdivided into motor, associative (cognitive), and limbic (emotional) domains.[11] They deal, respectively, with the control of movement, behaviour and cognition, and reward and emotions. These features have also been documented for the striatum and subthalamic nucleus by MRI in people.[12,13] Accordingly, dysfunction in any one of these circuits can give rise to movement disorders, behavioural and cognitive abnormalities, and mood changes.

Search strategy and selection criteria

We reviewed only articles published in English. We identified references through searching PubMed using the terms "movement disorders", "Parkinson´s disease", "Huntington's disease", "dystonia", "executive dysfunctions", "cognitive impairment-Parkinson's disease", "psychiatric complications", "genetics", and "levodopa and dopamine agonists" as main keywords between January, 1970, and October, 2013. The reference list shows the main work published in the specialty according with our understanding of relevance for the different domains included in this Series paper.

Movement disorders

Two fundamental disorders of muscle activation in the absence of paralysis or weakness are linked to disorders of the basal ganglia (videos 1–3). First, the parkinsonian syndrome is characterised by poverty and slowness of movement (akinesia or bradykinesia) and typically associated with increased muscle tone (rigidity), giving rise to the akinetic-rigid or parkinsonian syndrome, which can also be accompanied by tremor at rest. Second, dyskinesias and hyperkinesias are movements characterised by excessive involuntary muscular activity that perturb voluntary motor commands, interfering with normal intended actions. These movements have two main forms: dystonia, in which long (100–500 ms) muscle spasms with co-contraction of antagonist muscles twist and distort the body into abnormal posturing, while retaining the capacity to achieve the desired movement; and chorea, which consists of fragments of movements, often mimicking normal voluntary movements, but irregularly flowing from one body segment to another, causing a dance-like appearance. Ballism is typically associated with larger amplitude and more proximal movements but is qualitatively similar to chorea. Levodopa-induced dyskinesias (chorea, dystonia) in patients with Parkinson's disease are the most common clinical cause of dyskinesias.

The akinetic-rigid syndrome, best represented by Parkinson's disease, is primarily related to cell loss in

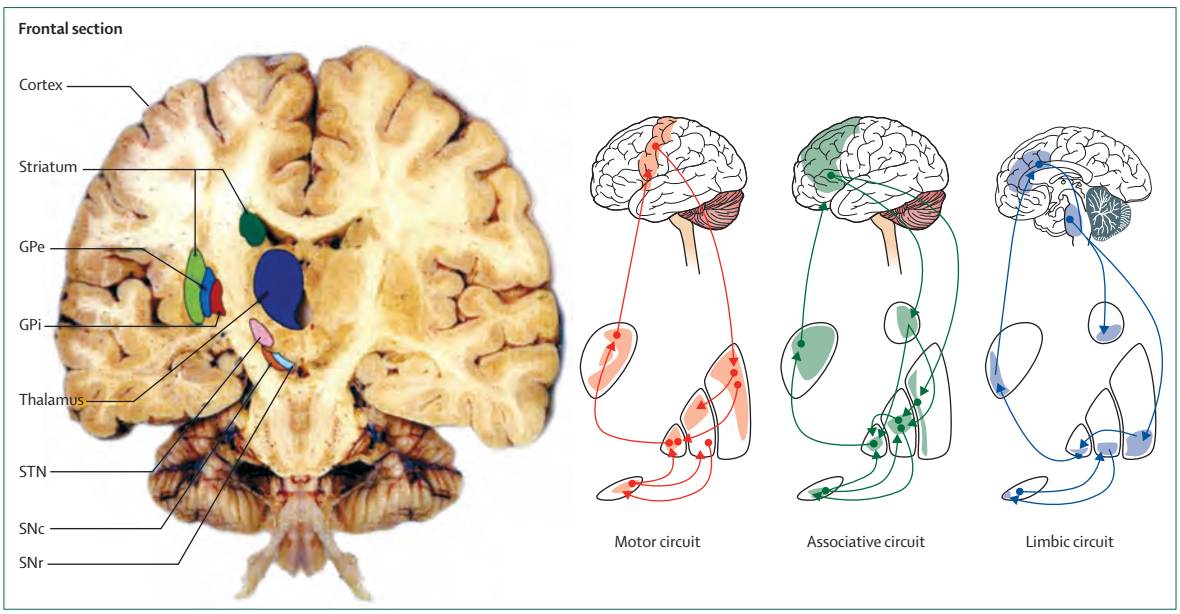

Figure 1: **A coronal view of a human brain angled to show the main basal ganglia nuclei and related structures and a schematic diagram of the main loops between cortex and basal ganglia**

The loops comprise the motor, associative, and limbic domains, which respectively transit through the posterior, anterior, and ventral striatum, thus segregated functionally and anatomically. GPe=globus pallidus externa. GPi=globus pallidus interna. STN=subthalamic nucleus. SNc=substantia nigra pars compacta. SNr=substantia nigra pars reticulata.

the substantia nigra pars compacta and dopaminergic striatal depletion. The neurodegenerative process in Parkinson's disease initially targets and predominantly affects the ventrolateral tier of the substantia nigra pars compacta, which projects to the caudal (posterior) putamen, where dopamine deficit begins and is most severe (figure 3). This part of the brain corresponds to the sensorimotor striatal subregion within the motor circuit (figure 1), which explains the early impairment of automatic movements (eg, blinking, arm swinging, writing, walking) in Parkinson's disease.[6] When the dopaminergic striatal deficit reaches a threshold, estimated at about 60–70%, the balance of striatopallidal activity shifts towards the indirect circuit (figure 2B), leading to excessive activity of the subthalamic nucleus, which overstimulates the globus pallidus pars interna and substantia nigra pars reticulata.[10] Increased output from this region overinhibits the thalamocortical projection, reducing cortical neuronal activation associated with the initiation and execution of both automatic and more voluntary movements. However, patients retain the capacity to improve movement speed and amplitude by increasing attention and effort. This feature is classic in patients with short-stepping gait leading to gait arrest (freezing), which can be overcome by use of external cues such as stepping on papers on the floor or following a rhythm.

Tremor in Parkinson's disease is typically rhythmical at 4–6 Hz, seen at rest, with distal limb predominance, and is also secondary to the lesion in the substantia nigra pars compacta. However, the link between dopaminergic depletion and the mechanisms leading to synchronous neuronal activity in the basal ganglia and cerebellothalamocortical circuits is unknown. Thus, nearly 200 years after James Parkinson's recognition and careful clinical descriptions, the origin of tremor in the disease remains a mystery.

Dyskinesias, such as chorea-ballism, can be regarded as being at the opposite end of the parkinsonian state, whereby excessive movements contaminate motor control.[14] They arise from abnormal striatopallidal activity, leading to reduced output in the globus pallidus interna and disinhibition of the thalamocortical projection.[7] Lesions and neurodegenerative diseases associated with chorea and ballism are typically recognised in the striatum and subthalamic nucleus. Ablation or blockade of basal ganglia output nuclei eliminates dyskinesias without impairing voluntary movements, which suggests that surgery eliminates abnormal (noisy) activity interfering with routine motor control mechanisms.[14,15]

Behavioural disorders

Anatamo-functional basis

Just as parkinsonism and dyskinesia represent opposite ends of the movement disorder spectrum and dysfunction of the motor circuit, impairments in the associative/limbic cortico-basal ganglia loop (figure 1) can give rise to reduced or excessive appetite and impulses (apathy and impulsivity). Whether a particular action is pertinent is controlled by the prefrontal cortex and the anterior striatum, which are typically engaged in executive functions such as sequential learning, decision making, and task switching.[16–18]

Functional MRI studies have identified an inhibitory network that prevents the execution of an already initiated order.[19] Successful inhibition was linked to activation of cortical (inferior frontal gyrus), presupplementary motor area and subcortical areas (caudate nucleus, thalamus, subthalamic region) for the right hemisphere.[19] The subthalamic nucleus was particularly highlighted as an essential node within this inhibitory network, as shown by imaging studies and by neuronal recording in patients with Parkinson's disease[20] and by the effect of subthalamotomy both in rats[21] and in patients.[22]

We concentrate here on discussing behavioural manifestations in two important examples—the pathological impulsivity and disorganised behaviour in some Parkinson's disease patients treated with dopaminergic drugs and in Tourette's syndrome.

Abnormal impulsivity in Parkinson's disease

Perhaps owing to the increasing use of non-ergot dopamine agonists, disarray behaviours and excessive and uncontrolled self-medication have become a major source of disability among patients with Parkinson's disease. The prevalence of all impulse control disorders is estimated at about 15% of treated patients with Parkinson's disease,[23] but it could be much higher in patients treated with dopaminergic agonists.[24] By contrast, in untreated patients the prevalence of impulse control disorders is similar to that of controls.[25] Frequent manifestations of impulse control disorders in patients with Parkinson's disease are hypersexuality, gambling, overeating, and excessive shopping, but also exaggerated activities such as obsessive working, long hours on the internet, extreme house-cleaning, and prolific writing. Although the former are intimately related to reward and pleasure, the latter are less so, which suggests involvement of different neural circuits in their origin. Levodopa and dopaminergic agonists are also associated with punding (repetitive handling, examining, sorting and rearranging objects, hoarding, and so on) and also with excessive consumption of levodopa (dopamine dysregulation syndrome), which also represent abnormal behaviours triggered by unphysiological dopaminergic stimulation.[26]

The dopamine reuptake transporter, measured in vivo by single photon emission CT (SPECT), is more reduced in the ventral striatum in patients with Parkinson's disease who have impulsivity than in those who do not; by contrast, in the dorsal striatum the dopamine reuptake transporter reduction was similar in those with and without impulse control disorders.[27] PET with carbon-11-labelled raclopride (a dopaminergic type-2 receptor ligand) showed that patients with Parkinson's disease with pathological gambling had increased dopamine concentrations in the ventral striatum while undertaking a gambling task.[28] Results of an H_2[15]0-PET study showed that patients with Parkinson's disease with increased gambling behaviour

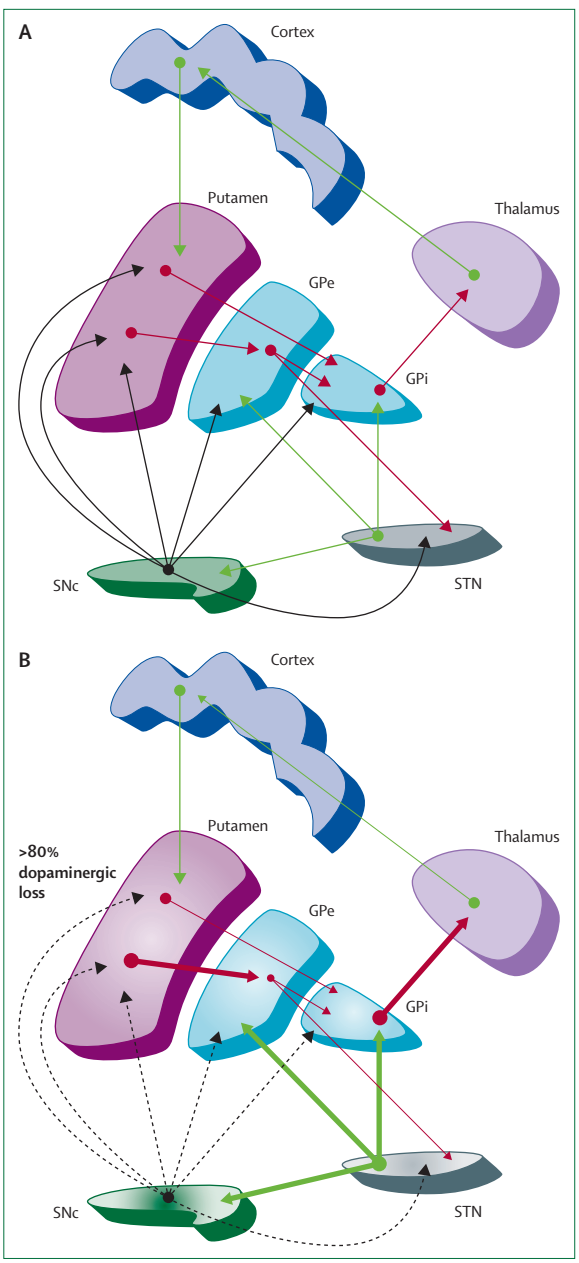

Figure 2: **Schematic of the classic model of the motor circuit**
Red arrows indicate inhibitory GABA-ergic projections, green arrows represent excitatory glutamatergic projections, and black arrows indicate dopaminergic innervation. In the normal state (A), the striatum receives cortical excitatory input and projects to output neurons in the GPi through a direct pathway, and by a polysynaptic indirect pathway via the GPe and the STN. Dopamine is thought to inhibit neuronal activity in the indirect pathway and to excite neurons in the direct pathway. In the parkinsonian state (B), when neuronal degeneration in the SNc and dopamine striatal depletion fall below 50% and 80%, respectively, striatal physiology is disrupted. Dopamine D1 receptor-expressing striatal neurons in the direct pathway become hypoactive, whereas dopamine D2 receptor-bearing striatal neurons in the indirect pathway are hyperactive. The latter response leads to increased inhibition of the GPe, and disinhibition of the STN. Overactivity in STN neurons and reduced inhibition in the direct pathway provokes excessive excitation of neurons in the GPi and overinhibition of thalamocortical and brainstem motor centres, resulting in parkinsonism. The thickness of the arrows indicates the degree of activation of each projection. GPe=globus pallidus externa. GPi=globus pallidus interna. STN=subthalamic nucleus. SNc=substantia nigra pars compacta.

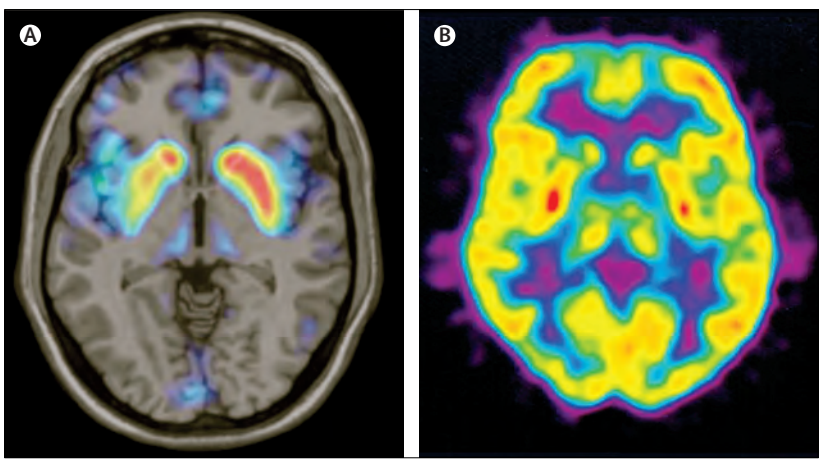

Figure 3: **MRI and PET of the brain from a patient with Parkinson's disease confined to the right arm at the time of diagnosis**
PET with fluorine-18-labelled dopamine as marker of striatal dopaminergic activity (A) to show pronounced (74% below normal) dopaminergic deficit in the posterior putamen of the left hemisphere and mild (33% below normal) reduction on the right side. PET with 2-fluorodeoxyglucose as indicator of metabolic activity of the same patient (B). A characteristic increase in the posterior putamen of the most denervated (left) side is apparent, whereas a slight increment in glucose uptake is present in the least (right) denervated side.

had substantial dopamine-agonist-induced reductions in regional blood flow in the orbitofrontal cortex, anterior cingulate, and amygdala compared with non-gambling patients.[29] These findings suggest that impulse control disorders in Parkinson's disease are related to abnormal dopaminergic activity in the ventral striatum in a subset of patients.

This notion is further supported by experience from Parkinson's disease patients treated with deep-brain stimulation in the subthalamic nucleus. Stimulation through the contacts of the electrode located in the ventral (limbic) portion of the nucleus triggered abnormal impulsive behaviours similar to those induced by dopaminergic drugs.[30] Furthermore, recordings of neuronal oscillatory activity showed a specific peak (6·5 Hz) in patients with Parkinson's disease with impulse control disorders in the ventral portion of the subthalamic nucleus and the anterior frontal cortex, in contrast to patients with levodopa-induced dyskinesias (LIDs), who have similar activity but in the dorsal motor region and primary motor cortex.[31]

Taken together, these data indicate that the combination of nigrostriatal denervation and dopaminergic drugs is likely to induce behavioural disorders in Parkinson's disease via abnormal activation of the associative (limbic) loops between the basal ganglia and the cortex and reduced inhibitory activity in the connections between the frontal cortex and the subthalamic nucleus. Such abnormalities in Parkinson's disease can be understood as the behavioural counterpart of dyskinesias,[26] whereby the former is the manifestation of dysfunction in the associative (limbic) circuits and the latter in the motor circuit (figure 1). In keeping with this idea, deep-brain stimulation of the subthalamic nucleus can improve impulse control disorders in Parkinson's disease,[32] whereas reduction of dopaminergic drug intake after the successful treatment of motor complications by deep-brain stimulation of the subthalamic nucleus can result in severe apathy.[33]

Tourette's syndrome

The clinical manifestations of Tourette's syndrome best represent the range of disorders associated with a basal ganglia lesion (video 4). Several motor and one or more vocal or phonic tics can combine with stereotypies, echopraxia, and coprolalia, and, in a substantial proportion of patients, with obsessive-compulsive manifestations.[34] Many patients feel the need to complete the tic or to repeat it several times to relieve the tension or feeling of discomfort, but a distinctive feature of Tourette's syndrome is that the tics and impulsivity can be controlled by conscious effort for a short time. Also, tics are commonly preceded by a sensation or urge, which stops only once the tic has occurred.

Comorbid neuropsychiatric disorders occur in about 90% of patients. The most common features are attention deficit hyperactivity disorder (60–80%) and obsessive-compulsive disorder (11–80%). There is also a lifetime risk of 10% for affective disorder.[34] However, since no definitive genetic marker for Tourette's syndrome is available, the clinical heterogeneity of this disorder is difficult to ascertain.

Several lines of evidence indicate that tics are mediated by abnormal activity in corticobasal ganglia connections comprising sensorimotor, premotor, and perhaps supplementary motor area cortices and the striatopallidothalamic projection to the motor areas.[35] Results of neurophysiological studies have shown that cortical activity coupled with tics differs from voluntary movements and that faulty GABAergic synaptic inhibitory mechanisms in the cortex and striatum are present in Tourette's syndrome.[35] Thus, the main manifestations are probably associated with abnormal neuronal activity in both the motor and associative loops, producing involuntary movements and behaviours that are inappropriately released according to circumstances. Additionally, the manifestations of Tourette's syndrome are extremely sensitive to emotions, which suggests an important involvement of the limbic system and the amygdala, in particular.[35] Blockage of or interference with such abnormal neuronal patterns by deep brain stimulation of the globus pallidus interna or other brain regions could lead to clinical improvement according to preliminary results.[36]

Cognitive and emotional manifestations

The role of dopamine

The basal ganglia and the dopaminergic projections (mesostriatal, mesolimbic, mesocortical) are involved in several cognitive functions, such as decision making, task switching, and dual tasking, which are typically

associated with the frontal lobe but also with time estimation mechanisms and speech, and which engage large neuronal networks. The role of dopamine and the ventral striatum in the control of mood, pleasure, reward, and motivation in people is now well documented. A reasonable assumption, therefore, is that reduced or excessive dopamine activity or lesions of specific subregions of the basal ganglia can lead to neuropsychiatric symptoms that can be isolated[37] but more commonly occur with behavioural and movement disorders.

Here, we concentrate on cognitive and mood disorders of Parkinson's disease and other neurodegenerative disorders with prominent involvement of the basal ganglia.

Parkinson's disease

Dopaminergic activity deficit and dysfunction in the associative striatofrontal loop are probably the cause of the typical dysexecutive syndrome of Parkinson's disease, which is now recognised in untreated patients soon after diagnosis.[38] Thus, patients with Parkinson's disease have difficulties in shifting attention, planning and problem solving, suppression of habitual responses, and dividing attention in the concurrent performance of two tasks. As with motor execution, these tasks are more impaired when patients have to rely on internal attention control than when external cues are available. They also show impaired implicit learning on both cognitive and motor tasks. Some of these dysexecutive features can improve with dopaminergic therapy, whereas some worsen.

Apathy, anxiety, and depression are common psychiatric manifestations in untreated Parkinson's disease. Depression and anxiety can precede the onset of motor features by several years.[39] Clinically significant depressive symptoms occur in around a third of people with Parkinson's disease[40] and anxiety in 20–49%.[41] Generalised anxiety disorder and panic disorder are particularly common, with the latter more frequent in patients who are young at onset and in those with motor fluctuations.[42] The presence and severity of depression and anxiety are unrelated to or only modestly associated with the overall severity of the motor signs and typically have no linear association with disease duration. The pathophysiological basis of these mood disorders in Parkinson's disease is not clear. Depressed patients with Parkinson's disease might have greater neuronal loss and gliosis in catecholaminergic areas of the brain (specifically, the locus coeruleus, dorsal vagus nerve, and substantia nigra pars compacta) than those without depression; in-vivo imaging studies have suggested possible associations with serotonergic, noradrenergic, and cholinergic systems, and white-matter abnormalities.[43–45]

Other akinetic-rigid syndromes

Cognitive and neuropsychiatric symptoms are commonly major features in other akinetic-rigid syndromes that have prominent basal ganglia pathology, although the neurodegenerative process is frequently more widespread. These syndromes include another synucleinopathy, multiple system atrophy, and the four-repeat tauopathies, progressive supranuclear palsy, and corticobasal degeneration. Functional cortical deafferentation, via basal ganglia dysfunction, loss of ascending projections from subcortical structures, and intrinsic cortical pathology probably have key pathophysiological roles, leading to dementia and neuropsychiatric disturbance in these conditions. Progressive supranuclear palsy has thus long been held as the prototypical subcortical dementia. Young patients are more likely to present with personality change or cognitive dysfunction (notably reduced mental speed, attention deficits, and executive dysfunction).[46] Results of functional imaging studies have drawn attention to theory of mind deficits in progressive supranuclear palsy, with atrophy in the anterior rostral medial frontal cortex; such deficits can contribute to difficulty in integration of socially relevant stimuli and interpretation of their social meaning.[47]

Dyskinetic/hyperkinetic disorders

We discuss here only selected hyperkinetic disorders that exemplify how movement disorders, primarily mediated by basal ganglia pathology, have a much broader clinical phenotype.

Huntington's disease is mainly associated with striatal pathology (medium spiny GABA neurons) and specific neuronal loss in layers V and VI of the cerebral cortex, which disrupt neuronal network activity in several corticobasal ganglia loops. Accordingly, patients have dyskinetic movement, behavioural disorders, and cognitive defects. In premanifest carriers of the gene mutation for Huntington's disease, impairments in visuomotor performance and working memory in subjects have been found close to their predicted time of clinical disease onset.[48] Altered emotion recognition and processing for anger, disgust, and happiness have also been shown in premanifest disease.[49] Estimates of lifetime prevalence of psychiatric disorders in Huntington's disease vary widely; they include mood disturbance (anxiety 34–61%; depression 33–69%), irritability (38–73%), apathy (34–76%), obsessive-compulsive disorder (10–52%), and psychosis (3–11%).[50]

In Wilson's disease, in which there is excessive striatal copper deposition, about 70% of stable, long-term treated patients experience psychiatric symptoms such as anxiety, depression, irritability, disinhibition, and apathy.[51] As for Huntington's disease, these patients can also show impaired recognition of disgust. When present, cognitive impairment can manifest as impaired social judgment, apathy, decreased attention, poor planning and decision making, and emotional lability.

Myoclonic dystonia (DYT-11) is a genetically heterogeneous disorder of probable basal ganglia origin, with mutations in the maternally imprinted epsilon-

sarcoglycan gene (*SGCE*) in 30–50% of cases. Clinically, patients show a combination of dystonic spasms of the proximal and axial musculature and brief myoclonic jerking of distal distribution (video 5). Both movement disorders can be largely improved by drinking of standard alcoholic beverages. *SGCE* mutations seem to predispose to anxiety, obsessive-compulsive disorder, and executive impairments, compared with patients with myoclonus-dystonia without an *SGCE* mutation.[52] By contrast, depression is common in myoclonus-dystonia, independently of genotype. The mechanism linking the movement disorder to the neuropsychiatric features is unclear, but one suggestion is dysfunction of the limbic frontostriatal circuitry, including anterior cingulate and orbitofrontal cortex to ventral striatal areas, ventral pallidum, and medial thalamus.[53] Neuropsychiatric features similar to those described for DYT-11 also occur in other primary dystonias, particularly adult-onset craniocervical dystonia, including genetic forms such as DYT-1 and DYT-6.[54]

Effect of genetically defined conditions

Initial discoveries

The development and expansion of the study of movement disorders has been mainly driven by and based on the recognition of clinical patterns (phenomenology of movement disorders, associated neuropsychiatric conditions) and pathophysiological mechanisms. However, as in all disciplines of medicine, genetics is now having an extraordinary effect in revealing new perspectives on old clinical conditions and in providing a better understanding of aetiopathogenesis and pathophysiology. Genetic studies enable an accurate diagnosis in disorders previously diagnosed entirely as clinical phenotypes and give previously unsuspected insight into molecular pathways underpinning movement disorders.[55,56]

The first major discovery was the gene for Huntington's disease,[56] but the most important discovery was the finding of α-synuclein gene mutations underlying a familial form of Parkinson's disease.[57] Whereas a few other genes have been linked to typical Parkinson's disease presentations and can be found more frequently, the α-synuclein gene attracted great attention because the gene encodes a protein that is a fundamental constituent of Lewy bodies, the histopathological hallmark of the disease. This gene discovery led to many animal models of Parkinson's disease and exploration of prion-like mechanisms for progression of the disease.

One gene expanding the phenotype but also many different phenotypes

A gene is traditionally linked to the recognition of a characteristic phenotype, but once a genetic defect is identified, the phenotypic characterisation broadens. The characterisation might include the recognition not only of different movement disorders,[58–60] but also of other neurological, systemic, or psychiatric features,[61,62] providing clues for wider underlying pathophysiological processes but also challenging the classic concepts of the role of basal ganglia. For example, in genetic parkinsonism, patients with Parkin mutations can have prominent anxiety and depression (even preceding parkinsonism) but can also have peripheral neuropathy and are prone to unusual dyskinesias.[63,64] For the primary dystonias, non-motor features with abnormalities in sensory and perceptual functions (temporal discrimination) and neuropsychiatric, cognitive, and sleep domains can occur,[54] and some of these features could be endophenotypes.[65]

However, completely different phenotypes can be caused by mutations of the same gene and sometimes the same mutation. For example, mutations in *ATP1A3*, which typically cause rapid-onset dystonia-parkinsonism, can also cause alternating hemiplegia of childhood.[66,67] Similarly, genes such as *PGRN*[68,69] and *C9ORF72*,[70] which are known to cause amyotrophic lateral sclerosis frontotemporal dementia, can also cause parkinsonism manifesting as progressive supranuclear palsy or a corticobasal syndrome.[71–73] Likewise, in dystonia, mutations in *PRRT2* that cause paroxysmal kinesigenic dyskinesia[74] also cause several other paroxysmal disorders, such as infantile convulsions with choreoathetosis, benign familial infantile seizures, and episodic ataxia, hemiplegic migraine, and benign paroxysmal torticollis of infancy.[75–77] Furthermore, the same condition can present predominantly with chorea in some family members or with aggressive and severe parkinsonism in others, as is the case in Huntington's disease-like 2 due to junctophilin-3 gene mutations.[78,79] Another interesting feature is the low penetrance of certain genes, which suggests that other genetic or non-genetic (environmental) factors are needed to cause the clinical phenotype. DYT-1-gene-related dystonia is an example—the gene manifests itself causing generalised dystonia at a young age in only 30% of mutation carriers. However, within the same family, some gene mutation carriers have very mild dystonia or none at all.

Future effect of genetics

Common underlying or converging pathways resulting from quite disparate genetic mutations could well be deciphered by molecular genetic studies. Already, in Parkinson's disease, several cell signalling pathways and cell death mechanisms are known to be involved and interact.[80–82] Insight into the pathophysiology gained from molecular genetics will aid the discovery of novel, tractable therapeutic targets.[83]

Findings from genome-wide association studies providing genetic risk loci for disease development could also provide targets for therapeutic intervention by, for example, modulating expression of these genes. Moreover, the identification and study of individuals at high risk of disease will allow the identification of biomarkers, which will be crucial for better assessment

of neuroprotective treatments. This vast potential has not yet been realised in any effective therapeutic development. The most striking example is Huntington's disease, in which the gene defect and toxic protein have been known for some 20 years but no clinically relevant treatment has been established. This absence of progress relates to the complexity and size of the problem.

Challenges for basal ganglia disorders

Beyond movement disorders

Dysfunction and pathology of different regions and circuits are now known to give rise to many clinical manifestations that contradict the classic concept equating dysfunction of the basal ganglia with movement disorders. Additionally, typical diseases associated with the basal ganglia have diverse pathologies distributed not only in the brain but also in the peripheral and autonomic nervous systems. This knowledge has substantially expanded investigation and also posed new challenges. Although some features of movement disorders remain incomprehensible, some limitations could be resolved by new, and as yet unimagined, approaches.

Cause

A definite association between cause and disease is essential. To that end, the recognition of biomarkers and neuroimaging methods to establish and monitor disease onset and evolution will be a major asset.

Aetiopathogenesis

A prevailing feature of basal ganglia disorders is the common occurrence of lesions and neurodegeneration in neuronal populations showing selective vulnerability. This feature is clear in metabolic disorders where the striatum (in mitochondrial defects with lactic acidosis, homocysteinuria, methylmalonic aciduria) and the globus pallidus interna (ferritinopathies, cyanide intoxication, carbon monoxide poisoning, Wilson's disease) are predominantly targeted. Moreover, the ventral tier of the substantia nigra pars compacta, which is the predominant site for neuronal loss in Parkinson's disease, seems to be selectively vulnerable to genetic defects (*LRRK-2*, or Parkin mutations), viruses (eg, Epstein-Barr, influenza), and even toxins such as methyl-phenyltetrahydropyridine or 6-hydroxydopamine. When the molecular deficits underlying the selective vulnerability associated with these conditions and the association between the anatomical and functional organisation and the different insults can be deciphered, some of the mysteries of basal ganglia disorders could be elucidated. However, several conditions, such as torsion dystonia, tics, and Tourette's syndrome, have no established pathological basis; they probably represent abnormal coding or dysregulation of neuronal activity through the basal ganglia.

Pathophysiology

A better definition of the basal ganglia and brain circuits specifically engaged in the clinical manifestations is needed. Even for the resting tremor of Parkinson's disease the link between dopaminergic deficit and basal ganglia abnormalities and the rhythmic neuronal activity in the cerebellothalamomotor cortex connections is largely unknown.

Phenotypic variability

Why there is such a varied expression of motor and non-motor features in a given disorder is still unclear. This feature can pose both diagnostic and management challenges for clinicians. Epigenetic modification might explain this variability, but knowledge about it in the context of movement disorders is minimum.

Therapy

In the coming decades major advances are expected in how to delay or even halt the neurodegenerative process of diseases such as Parkinson's and Huntington's diseases, and to understand basic molecular abnormalities leading to dysfunction of specific basal ganglia circuits (focal dystonias, depression, and apathy) or more generalised network dysfunction (Tourette's syndrome, attention deficit hyperactivity disorder).

In conclusion, while the universe of basal ganglia disorders continues to expand, we need more powerful and discriminative means to decipher the remaining mysteries.

Contributors

JAO conceived the Series paper and took part in writing and critical revision. MCR-O and MS took part in writing and critical revision. KPB and DJB took part in writing of the Series paper.

Declaration of interests

JAO has received honoraria for lecturing at meetings organised by GlaxoSmithKline, Lundbeck, and UCB in Spain, and is a consultant to AbbVie Spain, and Boehringer Ingelheim Mexico. MCR-O has served on a scientific advisory board for UCB and Abbvie, received honorarium for lectures, travel, and accommodation to attend scientific meetings from UCB, Lundbeck, and Medtronic, and received research support from national and regional government bodies in Spain and Europe (S-PE12BN01 , GV-2011111074, EC11-380, PI11/02109, DFG 11/0190 and PIM2010, ERN-00733). MS has received speakers' and travel honoraria from Novartis, Ipsen, and the Movement Disorders Society. KPB has received funding for travel from GlaxoSmithKline, Orion Corporation, Ipsen, and Merz Pharmaceuticals, LLC; speakers' honoraria from GlaxoSmithKline, Ipsen, Merz Pharmaceuticals, LLC, and Sun Pharmaceutical Industries Ltd; personal compensation for scientific advisory board for GlaxoSmithKline and Boehringer Ingelheim. KPB serves on the editorial boards of Movement Disorders and Therapeutic Advances in Neurological Disorders, and receives royalties from the publication of Oxford Specialist Handbook of Parkinson's Disease and Other Movement Disorders (Oxford University Press, 2008), and has received research support from Ipsen and from the Halley Stewart Trust through Dystonia Society UK, and the Wellcome Trust MRC strategic neurodegenerative disease initiative award (Ref. number WT089698), a grant from the Dystonia Coalition, and a grant from Parkinson's UK (Ref. number G-1009). DJB has received grant support from Parkinson's UK, Wellcome Trust, the Michael J Fox Foundation, the Newcastle upon Tyne NIHR Biomedical Research Unit for Lewy Body Dementia, and GSK. He has received honoraria from Teva-Lundbeck, Genus Pharmaceuticals, and UCB for speaking at meetings.

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References

1 Wilson S. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. *Brain* 1912; **34:** 295–509.
2 Purdon Martin J. Hemichorea resulting from a location lesion of the brain (the syndrome of the body of Luys). *Brain* 1927; **50:** 637–51.
3 Parent M, Parent A. Substantia nigra and Parkinson's disease: a brief history of their long and intimate relationship. *Can J Neurol Sci* 2010; **37:** 313–19.
4 Wilson S. Disorders of motility and tone. *Lancet* 1925; **1:** 1–103.
5 Ehringer H, Hornykiewicz O. [Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system]. *Klin Wochenschr* 1960; **38:** 1236–39.
6 Marsden CD. The mysterious motor function of the basal ganglia: the Robert Wartenberg Lecture. *Neurology* 1982; **32:** 514–39.
7 Crossman AR. Primate models of dyskinesia: the experimental approach to the study of basal ganglia-related involuntary movement disorders. *Neuroscience* 1987; **21:** 1–40.
8 Mitchell IJ, Clarke CE, Boyce S, et al. Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Neuroscience* 1989; **32:** 213–26.
9 Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci* 1989; **12:** 366–75.
10 DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 1990; **13:** 281–85.
11 Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986; **9:** 357–81.
12 Lehéricy S, Bardinet E, Tremblay L, et al. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. *Cereb Cortex* 2006; **16:** 149–61.
13 Lambert C, Zrinzo L, Nagy Z, et al. Confirmation of functional zones within the human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion weighted imaging. *Neuroimage* 2012; **60:** 83–94.
14 Obeso JA, Rodriguez-Oroz MC, Rodriguez M, DeLong MR, Olanow CW. Pathophysiology of levodopa-induced dyskinesias in Parkinson's disease: problems with the current model. *Ann Neurol* 2000; **47** (suppl 1)**:** S22–32, discussion S32–34.
15 Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain* 1994; **117:** 877–97.
16 Wilkinson L, Jahanshahi M. The striatum and probabilistic implicit sequence learning. *Brain Res* 2007; **1137:** 117–30.
17 Hikosaka O, Isoda M. Switching from automatic to controlled behavior: cortico-basal ganglia mechanisms. *Trends Cogn Sci* 2010; **14:** 154–61.
18 Doyon J, Bellec P, Amsel R, et al. Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behav Brain Res* 2009; **199:** 61–75.
19 Aron AR, Poldrack RA. Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. *J Neurosci* 2006; **26:** 2424–33.
20 Alegre M, Lopez-Azcarate J, Obeso I, et al. The subthalamic nucleus is involved in successful inhibition in the stop-signal task: a local field potential study in Parkinson's disease. *Exp Neurol* 2013; **239:** 1–12.
21 Baunez C, Robbins TW. Effects of transient inactivation of the subthalamic nucleus by local muscimol and APV infusions on performance on the five-choice serial reaction time task in rats. *Psychopharmacology (Berl)* 1999; **141:** 57–65.
22 Obeso I, Wilkinson E, Casanova E, et al. Involvement of the subthalamic nucleus in inhibitory control and adjusting response thresholds. Evidence from unilateral subthalamotomy in Parkinson's disease. *Brain* (in press).
23 Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* 2010; **67:** 589–95.
24 Bastiaens J, Dorfman BJ, Christos PJ, Nirenberg MJ. Prospective cohort study of impulse control disorders in Parkinson's disease. *Mov Disord* 2013; **28:** 327–33.
25 Weintraub D, Papay K, Siderowf A, and the Parkinson's Progression Markers Initiative. Screening for impulse control symptoms in patients with de novo Parkinson disease: a case-control study. *Neurology* 2013; **80:** 176–80.
26 Voon V, Fernagut PO, Wickens J, et al. Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. *Lancet Neurol* 2009; **8:** 1140–49.
27 Cilia R, Ko JH, Cho SS, et al. Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. *Neurobiol Dis* 2010; **39:** 98–104.
28 Steeves TD, Miyasaki J, Zurowski M, et al. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. *Brain* 2009; **132:** 1376–85.
29 van Eimeren T, Pellecchia G, Cilia R, et al. Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD. *Neurology* 2010; **75:** 1711–16.
30 Mallet L, Schüpbach M, N'Diaye K, et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. *Proc Natl Acad Sci USA* 2007; **104:** 10661–66.
31 Rodriguez-Oroz MC, López-Azcárate J, Garcia-Garcia D, et al. Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. *Brain* 2011; **134:** 36–49.
32 Okun M, Weintraub D. Should impulse control disorders and dopamine dysregulation syndrome be indications for deep brain stimulation and intestinal levodopa? *Mov Disord* 2013; **28:** 1915–19.
33 Lhommée E, Klinger H, Thobois S, et al. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. *Brain* 2012; **135:** 1463–77.
34 Cavanna AE, Servo S, Monaco F, Robertson MM. The behavioral spectrum of Gilles de la Tourette syndrome. *J Neuropsychiatry Clin Neurosci* 2009; **21:** 13–23.
35 Ganos C, Roessner V, Münchau A. The functional anatomy of Gilles de la Tourette syndrome. *Neurosci Biobehav Rev* 2013; **37:** 1050–62.
36 Hariz M, Blomstedt P, Zrinzo L. Future of brain stimulation: New targets, new indications, new technology. *Mov Disord* 2013; **28:** 1784–92.
37 Park HK, Kim HJ, Kim SJ, Kim JS, Shin HW, Kim JS. From Jekyll to Hyde after limbic subthalamic nucleus infarction. *Neurology* 2011; **77:** 82–84.
38 Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain* 2004; **127:** 550–60.
39 Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology* 2005; **65:** 1239–45.
40 Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord* 2008; **23:** 183–89, quiz 313.
41 Gallagher DA, Schrag A. Psychosis, apathy, depression and anxiety in Parkinson's disease. *Neurobiol Dis* 2012; **46:** 581–89.
42 Burn DJ, Landau S, Hindle JV, et al, and the PROMS-PD Study Group. Parkinson's disease motor subtypes and mood. *Mov Disord* 2012; **27:** 379–86.
43 Frisina PG, Haroutunian V, Libow LS. The neuropathological basis for depression in Parkinson's disease. *Parkinsonism Relat Disord* 2009; **15:** 144–48.
44 Bohnen NI, Kaufer DI, Hendrickson R, Constantine GM, Mathis CA, Moore RY. Cortical cholinergic denervation is associated with depressive symptoms in Parkinson's disease and parkinsonian dementia. *J Neurol Neurosurg Psychiatry* 2007; **78:** 641–43.
45 Duncan GW, Firbank MJ, O'Brien JT, Burn DJ. Magnetic resonance imaging: a biomarker for cognitive impairment in Parkinson's disease? *Mov Disord* 2013; **28:** 425–38.

46 Donker Kaat L, Boon AJ, Kamphorst W, Ravid R, Duivenvoorden HJ, van Swieten JC. Frontal presentation in progressive supranuclear palsy. *Neurology* 2007; **69:** 723–29.

47 Ghosh BC, Calder AJ, Peers PV, et al. Social cognitive deficits and their neural correlates in progressive supranuclear palsy. *Brain* 2012; **135:** 2089–102.

48 Papp KV, Kaplan RF, Snyder PJ. Biological markers of cognition in prodromal Huntington's disease: a review. *Brain Cogn* 2011; **77:** 280–91.

49 Novak MJ, Warren JD, Henley SM, Draganski B, Frackowiak RS, Tabrizi SJ. Altered brain mechanisms of emotion processing in pre-manifest Huntington's disease. *Brain* 2012; **135:** 1165–79.

50 van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. *J Neuropsychiatry Clin Neurosci* 2007; **19:** 441–48.

51 Svetel M, Potrebić A, Pekmezović T, et al. Neuropsychiatric aspects of treated Wilson's disease. *Parkinsonism Relat Disord* 2009; **15:** 772–75.

52 Peall KJ, Waite AJ, Blake DJ, Owen MJ, Morris HR. Psychiatric disorders, myoclonus dystonia, and the epsilon-sarcoglycan gene: a systematic review. *Mov Disord* 2011; **26:** 1939–42.

53 van Tricht MJ, Dreissen YE, Cath D, et al. Cognition and psychopathology in myoclonus-dystonia. *J Neurol Neurosurg Psychiatry* 2012; **83:** 814–20.

54 Stamelou M, Edwards MJ, Hallett M, Bhatia KP. The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. *Brain* 2012; **135:** 1668–81.

55 Lohmann K, Klein C. Genetics of dystonia: what's known? What's new? What's next? *Mov Disord* 2013; **28:** 899–905.

56 The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993; **72:** 971–83.

57 Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 1997; **276:** 2045–47.

58 Stamelou M, Mencacci NE, Cordivari C, et al. Myoclonus-dystonia syndrome due to tyrosine hydroxylase deficiency. *Neurology* 2012; **79:** 435–41.

59 Djarmati A, Schneider SA, Lohmann K, et al. Mutations in THAP1 (DYT6) and generalised dystonia with prominent spasmodic dysphonia: a genetic screening study. *Lancet Neurol* 2009; **8:** 447–52.

60 Houlden H, Schneider SA, Paudel R, et al. THAP1 mutations (DYT6) are an additional cause of early-onset dystonia. *Neurology* 2010; **74:** 846–50.

61 Ohshima S, Tsuboi Y, Yamamoto A, et al. Autonomic failures in Perry syndrome with DCTN1 mutation. *Parkinsonism Relat Disord* 2010; **16:** 612–14.

62 Apartis E, Blancher A, Meissner WG, et al. FXTAS: new insights and the need for revised diagnostic criteria. *Neurology* 2012; **79:** 1898–907.

63 Khan NL, Graham E, Critchley P, et al. Parkin disease: a phenotypic study of a large case series. *Brain* 2003; **126:** 1279–92.

64 Kägi G, Klein C, Wood NW, et al. Nonmotor symptoms in Parkin gene-related parkinsonism. *Mov Disord* 2010; **25:** 1279–84.

65 Hutchinson M, Kimmich O, Molloy A, et al. The endophenotype and the phenotype: Temporal discrimination and adult-onset dystonia. *Mov Disord* 2013; **28:** 1766–74.

66 Heinzen EL, Swoboda KJ, Hitomi Y, et al, and the European Alternating Hemiplegia of Childhood (AHC) Genetics Consortium, and the Biobanca e Registro Clinico per l'Emiplegia Alternante (I.B.AHC) Consortium, and the European Network for Research on Alternating Hemiplegia (ENRAH) for Small and Medium-sized Enterpriese (SMEs) Consortium. De novo mutations in ATP1A3 cause alternating hemiplegia of childhood. *Nat Genet* 2012; **44:** 1030–34.

67 Rosewich H, Thiele H, Ohlenbusch A, et al. Heterozygous de-novo mutations in ATP1A3 in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification study. *Lancet Neurol* 2012; **11:** 764–73.

68 Chen-Plotkin AS, Martinez-Lage M, Sleiman PM, et al. Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. *Arch Neurol* 2011; **68:** 488–97.

69 Le Ber I, Camuzat A, Hannequin D, et al, and the French research network on FTD/FTD-MND. Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. *Brain* 2008; **131:** 732–46.

70 Cooper-Knock J, Hewitt C, Highley JR, et al. Clinico-pathological features in amyotrophic lateral sclerosis with expansions in C9ORF72. *Brain* 2012; **135:** 751–64.

71 Lesage S, Le Ber I, Condroyer C, et al, and the French Parkinson's Disease Genetics Study Group. C9orf72 repeat expansions are a rare genetic cause of parkinsonism. *Brain* 2013; **136:** 385–91.

72 O'Dowd S, Curtin D, Waite AJ, et al. C9ORF72 expansion in amyotrophic lateral sclerosis/frontotemporal dementia also causes parkinsonism. *Mov Disord* 2012; **27:** 1072–74.

73 Stamelou M, Quinn N, Bhatia K. "Atypical" atypical parkinsonism: new genetic conditions presenting with features of progressive supranuclear palsy, corticobasal degeneration, or multiple system atrophy-a diagnostic guide. *Mov Disord* 2013; **28:** 1184–99.

74 Chen WJ, Lin Y, Xiong ZQ, et al. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. *Nat Genet* 2011; **43:** 1252–55.

75 Lee HY, Huang Y, Bruneau N, et al. Mutations in the gene PRRT2 cause paroxysmal kinesigenic dyskinesia with infantile convulsions. *Cell Rep* 2012; **1:** 2–12.

76 Gardiner AR, Bhatia KP, Stamelou M, et al. PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine. *Neurology* 2012; **79:** 2115–21.

77 Dale RC, Gardiner A, Antony J, Houlden H. Familial PRRT2 mutation with heterogeneous paroxysmal disorders including paroxysmal torticollis and hemiplegic migraine. *Dev Med Child Neurol* 2012; **54:** 958–60.

78 Schneider SA, Marshall KE, Xiao J, LeDoux MS. JPH3 repeat expansions cause a progressive akinetic-rigid syndrome with severe dementia and putaminal rim in a five-generation African-American family. *Neurogenetics* 2012; **13:** 133–40.

79 Stevanin G, Fujigasaki H, Lebre AS, et al. Huntington's disease-like phenotype due to trinucleotide repeat expansions in the TBP and JPH3 genes. *Brain* 2003; **126:** 1599–603.

80 Martin I, Dawson VL, Dawson TM. Recent advances in the genetics of Parkinson's disease. *Annu Rev Genomics Hum Genet* 2011; **12:** 301–25.

81 Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. *Lancet Neurol* 2012; **11:** 986–98.

82 Tofaris GK. Lysosome-dependent pathways as a unifying theme in Parkinson's disease. *Mov Disord* 2012; **27:** 1364–69.

83 Singleton AB, Farrer MJ, Bonifati V. The genetics of Parkinson's disease: progress and therapeutic implications. *Mov Disord* 2013; **28:** 14–23.