ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol. Exp. 1998, 58: 79-93

Motor deficiency in Parkinson's disease

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Abstract. The basal ganglia comprise a group of gray matter structures beneath the cerebral cortex, that surrounds the thalamus and hypothalamus. The basal ganglia play an important role in controlling movement. The motor circuits within the striato-pallidal complex are thought to facilitate desired movement and inhibit unwanted movement through their influence, via the thalamus, mainly on cortical precentral motor regions. Localized damage to parts of the basal ganglia occurs in certain diseases such as Parkinson's disease. Parkinsonism is a common neurological disorder that affects about one person in every 1,000 of the general population and about 2% in the elderly. The diagnosis of Parkinson's disease is based on the presence of two or more of the major symptoms: tremor, rigidity, postural instability, and bradykinesia. The pathological process behind the motor disabilities of Parkinsonism is a progressive degeneration of dopaminergic neurons of the substantia nigra, that results in dopamine depletion in the striatum. Brain dopamine deficiency is sufficient to explain all of the major symptoms of Parkinson's disease.

Review

Key words: Parkinson's disease, basal ganglia, motor control, tremor,

PATHONEUROPHYSIOLOGY OF MOTOR DEFICIT IN PARKINSON'S DISEASE

The basal ganglia comprise a group of gray matter structures beneath the cerebral cortex, that surrounds the thalamus and hypothalamus. Details of their anatomy and physiology have been well documented (Carpenter 1981, DeLong and Georgopoulos 1981, Horynkiewicz 1981, Graybiel 1984, Young and Penney 1984, 1988, Lange et al. 1997). It is generally accepted that the basal ganglia are responsible for modulating and facilitating various motor and cognitive programs, although mechanisms of these processes are still unknown (Young and Penney 1988).

Localized damage to parts of the basal ganglia occurs in certain diseases such as Parkinson's disease (PD), Wilson's disease, and Huntington's chorea. The extent of the damage varies from patient to patient, so that each shows his own pattern of symptoms. In his "Essay on Shaking Palsy" James Parkinson (1817) focused on postural and gait deficits: ... the patient is found to be less strict than usual in preserving an upright posture... and "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellect being uninjured" (Barbeau 1986).

Parkinsonism is a common neurological disorder; it affects about one person in every 1,000 of the general population and about 2% in the elderly (Peterson et al. 1988). The diagnosis of Parkinson's disease is based on the presence of two or more of the major symptoms: tremor, rigidity, postural instability, and bradykinesia. Other signs and symptoms of PD include seborrhoea, intolerance of heat, edema, cyanosis, increased salivation, decreased rate of swallowing. These will not be discussed in this paper.

The pathological process behind the motor disabilities of PD is a progressive degeneration of dopaminergic neurons of the substantia nigra, that results in dopamine depletion in the striatum. Brain dopamine deficiency is sufficient to explain all of the major symptoms of PD (Marsden 1982, 1984, for review see Narabayashi 1995). In early stages of parkinsonism, there appears to be a compensatory increase in the number of dopamine receptors to accommodate the initial loss of dopamine neurons (Ebadi et al. 1996). As the disease progresses, the number of dopamine receptors decreases, apparently due to the concomitant degeneration of dopamine target sites on striatal neurons.

The basal ganglia play an important role in controlling movement. The motor circuits within the striato-pallidal complex are thought to facilitate desired movement and inhibit unwanted movement through their influence, *via* the thalamus, mainly on cortical precentral motor regions (Marsden and Obeso 1994). In patients with Parkinson's disease stereotaxic lesions directed at the motor thalamus improve rigidity and tremor and do not worsen parkinsonian hypokinesia and bradykinesia. The motor circuits of the basal ganglia are part of a distributed motor system which can operate, albeit imperfectly, in the absence of striato-pallido-thalamo-cortical feed--back. It seems most likely that a pause in firing of medial pallidal and substantia nigra reticulata neurons permits movements generated by cortical motor areas. An increase in firing of medial pallidal neurons, which so far has been the major focus of attention, may be more concerned with inhibition of unwanted movement.

A change in firing of medial pallidal neurons appears to occur too late to initiate a new movement. However, the motor circuit within the striato-pallidal system routinely receives a continuous delayed read-out of cortical motor activity and issues an output directed *via* the thalamus mainly to premotor cortical regions. This may permit the routine automatic execution of sequences of movements generated in cortical motor areas. There is evidence that other regions of the striatum respond to significant external or internal cues as dictated by their cortical inputs, the significance being determined by memory, novelty, emotional and other contexts. Such events capture the attention of the non-motor striatum, which then interrupts the routine operation of the motor circuit, perhaps at the level of the medial pallidum and substantia nigra pars reticulata, to permit new cortical motor action.

The function of the basal ganglia has also been examined in terms of changes in behavior caused by pathology, as in PD (Marsden 1985, Roos et al. 1996). The observations of poorer concept formation (Bowen et al. 1975, Flowers and Robertson 1985), impairment in learning (Frith et al. 1986, Verschueren et al. 1997), poorer attentional processes (Lee and Smith 1983, Cools et al. 1984), as well as depression (Dakof and Mendelsohn 1986, Gotham et al. 1986, Taylor et al. 1986) in PD patients suggest that the basal ganglia are also involved in higher cognitive functions. Impairments in these cognitive factors may also affect movement performance (Jordan et al. 1992b).

TREATMENT STRATEGIES

The major motor disturbances in Parkinson's disease are thought to be caused by overactivity of the internal segment of the globus pallidus, in large part due to excessive drive from the subthalamic nucleus. The excessive inhibitory activity of the globus pallidus is thought to inhibit the motor thalamus and the cortical motor system thus producing the slowness, rigidity, and poverty of movement characteristic of parkinsonian states. Pallidotomy and thalamotomy are the stereotactic procedures most commonly performed in PD patients who fail to obtain satisfactory relief of their symptoms with drug therapy. Small lesions disrupt the abnormal activity of basal ganglia circuitry (Nakamura et al. 1979, Jankovic et al. 1995, Lozano et al. 1995, Baron et al. 1996, Kraus and Jankovic 1996). Therefore, pallidotomy enhances motor performance, reduces akinesia, improves gait, and almost completely eliminates levodopa--induced dyskinesias (Lozano et al. 1995).

Fetal nigral transplantation, which is still an experimental procedure, has the potential for restoring the lost nigrostriatal pathway (Krauss and Jankowic 1996). Also a new experimental procedure, external application of picoTesla range magnetic fields has been reported recently to be efficacious in the treatment of Parkinson's disease (Sandyk and Derpapas 1993). Improvement with magnetic therapy was noted not only in the motor control (gait, postural instability) but also in nonmotor aspects of the disease including mood, anxiety, autonomic and cognitive functions.

MOTOR DEFICITS IN PARKINSONISM

The impairment of motor functions observed in PD patients may be considered to consist of a primary deficit - so called negative symptoms including poverty of movement and impairment of postural reflexes, and secondary defects - positive symptoms such as rigidity and tremor (Knutson and Martensson 1986). When executing a repetitive motor task, parkinsonians have difficulties in maintaining an unchanged speed and amplitude of the individual movements. In walking, for instance, there is a tendency for individual steps to become shorter and eventually come to a complete stop (Morris et al. 1994). The gait may become arrested by even the smallest obstacle (Stern et al. 1980, 1983a). Generally, any sensory stimuli may markedly affect motor performance (Knutson and Martensson 1986, Morris et al. 1994). If walking is stopped by a sensory stimulus and stress and anxiety is added, the patient may not be able to start locomotion again for a long period. In some patients the problem of gait may be overcome by various external cues. Speech defects are common in advanced PD and include disturbances in respiration, phonation and articulation. These problems have also attracted the attention of some motor control researchers (Stewart et al. 1995).

TREMOR

Tremor at rest is a cardinal sign of Parkinson's disease. Some patients have only a resting tremor for at least 5 years without developing other parkinsonian signs or symptoms. Recent findings suggest the existence of a separate subtype of the disease, namely, tremulous Parkinson's disease in which there is a resting tremor alone (Chang et al. 1995). Tremor can also be a manifestation of Wilson's disease, lesions of the cerebellum and midbrain, peripheral neuropathy, trauma, alcohol, and conversion disorders (Anouti and Koller 1995).

The origin of the PD tremor is still uncertain. Patients with PD are reported to have tremor predominantly in their hands, feet, and chin (Jankovic and Frost 1981). Electromyographic recordings show rhythmic activity alternating in antagonistic muscles at a frequency range between 3.5 and 7 Hz (Hagbarth et al. 1975, Shahani and Young 1976, Findley et al. 1981, Delwaide and Gonce 1988, Marsden 1992, Koller et al. 1994, Anouti and Koller 1995, Palmer and Hutton 1995, Volkman et al. 1996). The tremor frequency can differ between the upper and lower limbs, and even between the two upper limbs (Delwaide and Gonce 1988).

Rhythmically alternating contractions of a given muscle group and its antagonists are organized as normal movements with alpha-gamma coactivation (Hagbarth et al. 1975). The motor units, however, respond with abnormal clusters of action potentials - so called doublets and triplets (Young and Shahani 1979, Young 1985). What is more important, within the muscles themselves, the motor units are firing in a synchronous manner at regular intervals (Barbeau 1986). During an active muscle contraction the synchronized firing is lost and most PD patients show no other tremor. However, the tremor in the arms may still be present when walking, and when performing a repetitive arm abduction-adduction task (Jankovic and Frost 1981). Young (1985) has

found that when patients are asleep and activate their axial muscles to shift position, tremor can start and awaken them.

The PD tremor is increased by nervousness or fatigue and may disappear in sleep. It can be also suppressed by relaxation of the axial postural muscles (Delwaide and Gonce 1988). It may be completely absent when the subject is concentrating on some skilled task. PD resting tremor in the arms and legs responds to the use of anticholinergics and a combination of carbidopa and levodopa.

A variety of clinical and experimental findings suggest that parkinsonian resting tremor results from the involuntary activation of a central mechanism normally used for the production of rapid voluntary alternating movements. Magnetic field tomography studies showed that tremor in PD is indeed accompanied by rhythmic subsequent neural activation at the diencephalic level and in lateral premotor, somatomotor, and somatosensory cortex (Volkman et al. 1996).

Microelectrode recordings from the thalamus of PD patients revealed rhythmic neuronal activity associated with contralateral limb tremor (Jasper and Bertrand 1964, Albe-Fessard et al. 1966, Narabayashi and Ohye 1983). Some of this activity is simply being driven by muscle afferents but some neurons exhibit their own rhythmical activity (for review see Delwaide and Gonce 1988). Lee and Stein (1981) found neurons within the basal ganglia and the thalamus of PD patients that fire at the same frequency as the tremor, and hypothesized that damage to the inhibitory pathway between the substantia nigra pars reticulata and the striatum may lead to excessive striatal excitatory output facilitating oscillating bursts of activity in the thalamus. The tremogenic thalamic pacemaker would be included in a long hyperactive neuronal loop starting from the muscle spindles and going up to the thalamus, the motor cortex and returning to the muscular level via the pyramidal track (Delwaide and Gonce 1988).

Some physiological observations also support the theory that Parkinson tremor is a centrally driven rhythm that may be influenced by feedback effects. There is, for example, in PD patients a significant correlation between the peak of acceleration and the peak of rectified electromyographic activity from the muscle responsible for finger extension (Palmer and Hutton 1995). Such a correlation is not seen in age-matched control subjects.

The quality of motor control is affected by the tremor. Typically, the increase in the involuntary oscillations result in both a decline in sensory sensitivity, and in delayed movement initiation. Some patients with parkinsonism are not able to use visual information in a normal manner in a simple motor tracking task. The pathological tremor present in these individuals acts as noise and prevents them from performing normally (Vasilakos and Beuter 1993). On the other hand, a systematic phase relationship between tremor-at-rest and the onset of voluntary motor responses in PD has been recently documented (Wierzbicka et al. 1993, Staude et al. 1995). Reaction times of PD patients exhibit a significant dependence of mean values and variability on the current tremor phase at the onset of the voluntary motor response. Responses with an onset of contraction during the beginning of an EMG tremor burst are substantially delayed (on average 50 ms) and show more variability in comparison to responses initiated at later times in the tremor cycle. This effect can be explained by a simple gating process splitting the tremor cycle into two different system states that support or inhibit the initiation of voluntary motor responses (Wierzbicka et al. 1993).

Chronic thalamic stimulation, involving permanent implantation of deep brain electrodes and a pulse generator, effectively controls contralateral tremor (Benabid et al. 1996). It interesting that a low frequency (50 Hz) electrical stimulation of the ventral intermediate thalamic nucleus may increase tremor, while stimulation with a frequency greater than 100 Hz leads to suppression of the tremor (Alesch et al. 1995). The patient's ability to generate steady torque and rapid movements is also improved with moderate and high frequency stimulation (Pfann et al. 1996). However, even with motor improvements and with a decrease of tremor muscular activity abnormalities typical for PD remain.

RIGIDITY

Rigidity is manifested by increased resistance to passive movement throughout the range of motion of a joint. It is typically independent on movement velocity and is often described as "lead-pipe" rigidity; it persists as long as the stretch is maintained. The resistance to forced movement of the limb fluctuates in a jerky fashion and thus the rigidity may be regularly interrupted at a frequency of 5 to 6 Hz (cogwheel phenomenon).

The rigidity may affect the limbs, trunk, neck and other group of muscles. For example the characteristic immobile mask-like face of PD patients results from rigidity. PD rigidity differs from the rigidity of decerebra-

tion in that the force of resistance does not typically depend on the speed of displacement. In some patients however, the resistance to stretch is inversely proportional to velocity, being greatest when movement is slow (Delwaide and Gonce 1988). Both voluntary contraction and passive mobilization of the contralateral limb reinforce rigidity. Generally, reinforcement maneuvers are more affective if achieved by proximal rather than distal muscles and in a standing rather than a seated position (Delwaide and Gonce 1988). The latter observation indicates a role in rigidity of descending pathways, especially of the vestibulospinal tract.

Physiologically the only undisputed fact is that a dorsal root section reduces rigidity, evidencing that afferent input from joint, muscle, or cutaneous receptors is a contributing factor. A stereotaxic lesion within the ventrolateral nucleus of the thalamus, on the other hand, eliminates rigidity (Narabayashi 1985). Since the ventrolateral nucleus of the thalamus receives pallidal afferent inputs, rigidity in PD is interpreted as dysfunction of pallidal neurons caused by dopamine deficiency within the striatum (Narabayashi 1985).

Despite of a fact that there are well documented changes in Ia spinal interneuron activity in PD (Day et al. 1981), most authors advocate a concept of an increased long-loop reflex to explain rigidity (Mortimer and Webster 1978, Evarts and Vaughn 1981, Berardelli et al. 1983,1996, Dietz et al. 1988). The long-loop reflexes are commonly studied using limb or posture perturbation experimental models. In response to a movement perturbation, a sequence of three EMG bursts (M1-M3) appears in the muscle activity (Tatton et al. 1975, for review see Dienner and Dichgans 1986). The first of these corresponds to the stretch reflex (Lee and Tatton 1975) and is of normal amplitude in parkinsonians. The M2 burst involving supraspinal loop is significantly increased in PD rigidity.

POSTURAL INSTABILITY AND ABNORMALITIES

The parkinsonian posture is described in general as a "stooped posture" (Knuttson 1972, Murray et al. 1978, Barbeau 1986, Andrews 1987, Koozekanani et al. 1987, Beckley et al. 1991, Kitamura et al. 1991). The neck and head of PD patients are inclined forward. Their trunk is flexed forward and the dorsal spine shows kyphosis. The arms of parkinsonians are slightly abducted, the elbows are flexed and the hands are carried in front of the body with the fingers partially flexed. The hips and knees are flexed, and the ankle dorsiflexion angle decreases as the disability increases which causes the PD patients to stand more on their toes (Andrews 1987, Schieppati and Nardone 1991, Yekutiel 1993).

An important point made by Martin (1967) is that postural changes do not result from muscular weakness. Dietz et al. (1981) extended this observation to gait. Moreover, Martin stressed that the deficit in postural adjustment appears in the face of a dynamic perturbation such as tilt. These observations have been confirmed in a study by Traub and coworkers (1980). The postural impairment is not simply loss of planning or coordination, but rather a bias towards specific posture and gait (Calne et al. 1985).

Postural instability is one of the most disabling features of Parkinson's disease (Beckley et al. 1991, Bloem 1992). Many factors contribute to balance impairment of Parkinson patients, including disturbed postural reflexes and poor control of voluntary movement. Additional factors which place Parkinson patients at risk for falls are side-effects of medication (dyskinesias), gait abnormalities, muscular weakness in leg muscles and superimposed age-related changes such as reduced peripheral sensation.

Anticipatory postural adjustments, and postural reflexes are disturbed in Parkinson's disease (Traub et al. 1980). Studies of anticipatory postural adjustments show that parkinsonians have difficulty simultaneously performing two separate motor programs (Benecke et al. 1986), and they have also difficulty switching from one motor program to another (Benecke et al. 1987). This has led researchers like Rogers et al. (1987) to believe that the basal ganglia may play a role in linking the prime mover and postural components in balance control.

Andrews (1987) claims that vestibular control of posture is affected by damage to the basal ganglia. Since the proprioception from the neck is also impaired due to rigidity, both deficits would result in the decline of the vertical perception which the basic element of postural control. Thus it may lead to postural abnormality and postural instability due to impaired control of the center of gravity (Calne et al. 1985).

Results of studies of reflex postural responses are very controversial, but most agree that PD patients respond differently than controls. Some authors assume that peripheral and spinal mechanisms such as muscle spindles (Burke et al. 1977), and patterns of reciprocal inhibition (Obeso et al. 1985) function normally in PD subjects

amidst a higher level of background activity, suggesting that Parkinsonism is the result of hyperactivity in transcortical loops (Lakke et al. 1982, Delwaide 1985, Cody et al. 1986). Although the patterns of muscle innervation are correct, their anticipatory adjustments (Calne et al. 1985), and initiatory processes (Hallett et al. 1977) are impaired, with the prepared response falling short of what is required (Hallett and Khoshbin 1980). These authors have taken the position that spinal reflex activity in the muscles of PD patients is no different from those of normal tensed muscles, and that the problems most likely lie with transcortical loops. Delwaide et al. (1993) suggest however, that at least two spinal mechanisms behave abnormally in PD due to changes in the activity of descending spinal tracks. Increased excitability of Ia inhibitory spinal interneuron was associated with reduced excitability of Ib interneuron suggesting that the changes are due to the same mechanism. The reticulospinal tract appears to be mostly responsible for these changes. These changes may be seen in increased tendon jerks which are a feature of idiopathic parkinsonism. In most cases there is no correlation of reflex score such as in the tendon jerk with the severity of PD or with its cardinal signs (Hammerstad et al. 1994, Burne and Lippold 1996). However, in patients with asymmetric tendon jerks the side with the more active reflexes correlated with the side with greater parkinson signs. All these abnormalities strongly contribute to postural instability in parkinsonians.

Changes in PD postural control have been mostly reported in dynamic conditions. For example, in response to toe-up or toe-down platform tilts controls usually employ an ankle strategy (a sequence of posture stabilizing movements that starts in the ankle joint) PD patients, ON-medication, use a combination of an ankle and a hip strategy (Beckley et al. 1991). In response to forward or backward support surface translations, when controls would activate the muscles on the same side of the body as the direction of the perturbation, PD patients OFF--medication will reciprocally activate muscles on both sides of the joint (Horak et al. 1992). In response to such perturbation the gastrocnemius response is followed by significantly enhanced activation of the tibialis anterior (Dakof and Mendelsohn 1986). As a result, the angular rotation at the ankle joints is slower in PD than in normal subjects due to changes in intrinsic muscle stiffness. Similarly, healthy subjects while standing on a sinusoidally oscillating treadmill maintain equilibrium mainly by activating extensor muscles (Dietz et al. 1993). In contrast, PD patients use flexor activation for this purpose and they can not maintain balance with eyes closed. The timing and amplitude of programmed adjustments are inappropriate in PD and the reduced ability to activate the leg extensors is proposed to be due to an impairment of extensor load receptor.

A great number of electrophysiological studies have concerned the function of peripheral feedback in PD (for review see Dietz et al. 1988 and Beckley et al. 1991). The most evident finding of these studies is an enlargement of amplitude and duration of the medium (M2) loop muscular response (see Rigidity section) which, as suggested earlier, (Diener et al. 1983,1984) destabilizes upright posture. This increase significantly correlates with severity of the disease. Since the muscle spindle demonstrate normal alpha-gamma coactivation in PD, an increase of reflex gain at higher CNS sites has been postulated (Burke et al. 1977). Controversy persists as to whether M2 changes are caused by cortical or spinal reflex loop gain changes (Tatton et al. 1984).

Some patients with an akinetic Parkinson syndrome of the lower extremities and a poor response to L-DOPA have been described as having 'lower body Parkinsonism' (Trenkwalder et al. 1995). These patients are characterized by poor balance control which results in frequent falls. Normally it is not possible to differentiate lower body parkinsonism from standard PD patients in either static or dynamic posturographic tests. However, when lower body parkinsonism patients are placed on foam which results in both reduced somatosensory input as well as reduced stability they are not able to compensate for induced instability (Trenkwalder et al. 1995).

AKINESIA AND BRADYKINESIA

Akinesia and bradykinesia are two major functional impairments associated with Parkinson's disease (see Delwaide and Agnoli 1985 for review). Akinesia is defined as a lack or poverty of movement. According to Narabayashi (1985), akinesia in parkinsonism can be divided into three different parts: (1) slowness and unskillfulness of movement secondary to rigidity, (2) lack or poverty of movement even after complete abolition of rigidity and absence of muscular weakness, and (3) difficulty in initiation of movement also known as "freezing". These distinctions have been made based upon responsiveness to treatment. Stereotaxic thalamotomy within the ventrolateral nucleus of the thalamus has been shown to eliminate rigidity, and the first type of akinesia.

The lack of movement, the second type of akinesia, is helped in the majority of cases by Levodopa. While "freezing", the third type of akinesia, remains one of the most debilitating aspects of PD, and can appear even after complete relief of all other symptoms of PD. Freezing has been shown to be made worse by L-Dopa but is inconsistently relieved by norepinephrine therapy (Narabayashi 1985).

Akinesia is commonly attributed to globus pallidus disfunction. However, there is evidence that akinesia may also be caused by lesions of the supplementary motor area. Patients with such lesions share the same symptoms and signs as PD patients (Caligiuri et al. 1992). The supplementary motor area represents the "central timing system". Impairment of this system results not only in movement initiation delay but also in decline of movement synchronomy.

One of the main manifestation of motor impairments in PD is a slowness of movement or bradykinesia (Draper and Johns 1964, Flowers 1976, Evarts et al. 1981, Marsden 1985, Sheridab and Flowers 1990). In many cases movement velocity correlates well with the stage of the disease (Weinrich et al. 1988). An impairment of velocity control has often been associated with apparent deficits in the ability to increase muscle activity. Some research has found that motor units are recruited at higher thresholds than normal in PD (Palmer et al. 1991), and once recruited motor units fire at lower firing rates than normal (Delwaide 1985, Palmer et al. 1991).

Flowers (1976) has made several important observations about PD bradykinesia. Short ballistic movements are accomplished with normal speed while larger movements are performed more slowly than normal. Normal subjects perform larger movements with faster velocity, thus the time of movement is kept constant. In normal subjects the execution of single rapid one-joint movements is characterized by an electromyographic pattern composed of three discrete bursts of activity; two bursts (first and second agonist bursts) are present in the agonist muscle separated by an almost complete period of electrical silence (Berardeli et al. 1996). During this pause, another burst occurs in the antagonist muscle. If a rapid movement is executed during tonic activation of the agonist muscle, tonic activity is inhibited just prior to the first agonist burst onset (agonist inhibition). Similarly, if the movement is performed during tonic activation of the antagonist muscle, such activity is also inhibited prior to first agonist burst onset (antagonist inhibition). An equivalent of the kinematic features related to the EMG pattern described above is a symmetrical and unimodal velocity profile that is bell-shaped and shows an acceleration time roughly equal to the deceleration time. This holds true for movements performed under low accuracy constraints; as accuracy demands become stricter and stricter, the peak velocity decreases but, as long as the movement is made with one continuous trajectory, the velocity profile remains roughly symmetrical. The timing and size of the bursts vary according to the speed and amplitude of the movement. The origin of the EMG pattern is a central program, but afferent inputs can modulate the voluntary activity. The basal ganglia have a role in scaling the size of first agonist burst, reinforcing the voluntary command and inhibiting inappropriate EMG activity. The cerebellum, on the other hand, seems to play a role in timing the voluntary bursts and probably in implementing muscle force phasically. In PD force generation is slower than normal (Kaneoke et al. 1989, Jordan et al. 1992a, Stelmach et al. 1992) and additionally, there are disturbed reciprocal relationships that cause isometric contractions delaying movement (Lelli et al. 1991).

The basal ganglia contribute to the planning of movements (Hallet and Khoshbin 1980). Specifically, normal people perform movements of large amplitude with faster velocity while patients with PD have been shown to keep velocity the same for all movements (Draper and Johns 1964, Flowers 1976, Hallett et al. 1977, Hallett and Khoshbin 1980, Evarts et al. 1981, Hallett 1985, Flash et al. 1992). Hallett and Khoshbin (1980) and Berardelli et al. (1986) suggested that this is so because patients with PD do not increase the amount of muscular activity occurring in the first burst of muscle contraction that starts a fast movement. In their experiments, the duration of the initial burst appeared to be normal, but its size was not adjusted with the distance requirements. Stelmach and Phillips (1991) and Jordan et al. (1992a) also found that rate of force generation in PD is slower than normal.

Many mechanisms have been proposed for why PD patients move slowly. One possible explanation is that patients with PD loose the ability to "run" motor programs without conscious effort (Barbeau 1986). Other authors state that to maintain accuracy within acceptable limits, PD patients slow their movement down to a level where they can integrate feedback to execute the movement or to flow smoothly from one motor program to the next (Barbeau 1986, Beuter et al. 1992). Most of the studies on PD have clearly shown that parkinsonians are slower to react to an external stimulus (Bloxham et al. 1984).

Marteniuk and Athenes (1985) have suggested that, for normal subjects, simple arm movements such as aiming and reaching for a target object (Fitts-like task) are functionally related to the task demands. The control and organization of hand movements, in this case, is affected by the nature and the size of a target object. Specifically, the temporal location of the peak velocity (hence, the duration of acceleration and deceleration phases) occurred both relatively and absolutely earlier when the nature of the target object required greater terminal accuracy. Sanes (1985) reported results consistent with previous studies, that is, an increase in movement amplitude or a decrease in target width resulted in slower and less accurate movements for PD subjects. However, for movements with a low index of difficulty, PD subjects were as accurate and as fast as control subjects. Such results suggest the possibility that the poorer performance of PD subjects in aiming tasks is not solely related to slow speed but might also be a result of the relative inaccuracy of movement termination. Therefore the speed deficit might not be totally accounted for by a structural deficit in the basal ganglia. The involuntary movements of PD, most notably dyskinesia and tremor, could be significant factors in poorer performance by patients rather than deficits in motor programming and information processing (Sanes 1985).

PD patients have difficulty in initiating a motor plan but no difficulty in executing the plan once it has been initiated (Bloxham et al. 1984, Marsden 1985). Further, PD subjects are thought to be capable of adapting their motor plan to new or specific environmental circumstances, as well as capable of learning a novel motor skill (Marsden 1985, Frith et al. 1986, Verschueren et al. 1997). Some attempts have been made at examining the deficits in PD subjects when two motor programs are executed simultaneously with one limb (Benecke et al. 1986), or with two limbs (Schwab et al. 1954, Cohen 1970). The results obtained in these experiments have suggested to some authors that a major deficit of PD is an inability to execute concurrent or sequential actions (Schwab et al. 1954, Margolin and Wing 1983, Marsden 1985, Benecke et al. 1986, Rafal et al. 1987, Lang et al. 1990, Caligiuri et al. 1992).

LOCOMOTION

Two types of discoordination are manifested in parkinsonian gait. One is velocity dependent and hence related to bradykinesia which was discussed in the previous section. There are also altered coordination patterns (Beuter et al. 1992). The latter abnormalities include, beside the already mentioned postural deformities, the characteristic shuffling gait with small steps and poverty of movements in the trunk and in the upper limbs (Knuttson 1972, Murray et al. 1978, Stern et al. 1983b, Forssberg et al. 1984, Nutt 1988, Kitamura et al. 1991, Weller et al. 1992, Ueno et al. 1993). During locomotion PD patients show markedly reduced ranges of angular displacements in the hip and knee joints (Knuttson and Martensson 1986). When they move flexions and extensions appear in their normal sequences within the gait cycle, though the stride cycle is longer.

In the gait of parkinsonians, most of the normal EMG activation is well preserved expect that of the hip abductors where the activation is delayed compared to the normal pattern. The observed continuous muscle activity upon normal activation observed in PD can be regarded as equivalent to rigidity (Knuttson and Martensson 1986). Recently Gantchev et al. (1996) reported that coordination between the preparatory postural adjustment of the whole body and the actual stepping movement is impaired in PD. They showed that lengthening of the postural phase was a common deficit in all forward oriented movement tasks in parkinsonian patients. This is due to the impaired production of the requisite propulsive forces providing the forward acceleration of the center of gravity. Consequently, a shortening of the first step length occurs. Although the stepping movement can be improved with the aid of sensory cues, the postural phase will always be prolonged whenever a task requiring postural adjustment is performed. Studies of the Bereitshaft--spotential preceding movement have confirmed that PD subjects, in fact, exhibit an impairment of the preparation and assembly of the complex sequences of movement necessary to initiate gait (Vidailhet et al. 1993).

Gait deficit in PD also results in lesser tolerance for changes in movement conditions. In studies in which the postural requirements were reduced by supported stance (Schieppati and Nardone 1991) or by sitting (Horak et al. 1992) PD patients showed difficulty adapting their motor programs to new conditions. Lesser tolerance to changed movement conditions was also observed in split belt treadmill locomotion (Dietz et al. 1995). While healthy subjects easily tolerated these walking conditions, parkinsonians usually reached the limits of their walking capabilities. These patients showed a restricted range of stride frequencies.

Shuffling gait is a gait with shorter steps and higher cadence. In short steps with little lifting of the foot from the floor, short regular contractions are observed in the quadriceps brachii and tibialis anterior. Their antagonists show tonic discharges or small numbers of reciprocal potentials. Additionally, reciprocity of muscular contractions between tibialis anterior and triceps surae is not clear in PD gait (Yanagisawa et al. 1991).

Two type of rhythmic activities can be distinguished in the EMG of leg muscles: one results from locomotion and the second is characterized by rapid fluctuations. In shuffling gait, the rhythm of locomotion ranges between 1.1-1.4 Hz, whereas normal subjects move with a slower cadence - below 1.1 Hz (Blin et al. 1990). In force platform recordings of the shuffle gait, the two characteristic peaks in the vertical reaction forces i.e., "weight acceptance" and "toes push off" are missing (Hughes et al. 1990, Yanagisawa et al. 1991).

Very interesting results were presented by Morris and coworkers (1994). They demonstrated that walking slows down dramatically when PD subjects were asked to performed a long gait sequence. The observed slowing of the gait was primarily due to an inability of parkinsonians to generate steps of appropriate size. Thus, it seems that the fundamental deficit in gait hypokinesia might be in the regulation of stride length. At the same time the PD subjects showed no deficit in the regulation of cadence. The authors concluded that it is possible that cadence regulation is not under basal ganglia influence whereas stride length control is mediated by the basal ganglia. They also suggest that the reduced stride in the parkinsonians might be due to inadequate preparatory processes involving the interaction between supplementary motor area and the basal ganglia.

MOTOR BLOCKS

Freezing episodes and related phenomena (as a general term, motor blocks) are poorly understood, particularly disabling, and a therapeutically frustrating problem in Parkinson's disease. Freezing and hastening phenomena are motor symptoms frequently observed in PD, even when rigidity and tremor are well controlled by L-Dopa treatment (Mestre et al. 1992).

Freezing gait is a unique gait disorder manifested by start hesitation, as if the feet were "glued" to the floor, and gait arrests, often accompanied by festination, instability, and recurrent falls (Cooke et al. 1978, Yanagisawa et al. 1991, Achiron et al. 1993, Atchison et al. 1993). Different authors used different terms to define this abnormal gait: "lower body parkinsonism", "motor blocks", "apraxia of gait", "freezing in movement".

An abrupt inability to initiate voluntary movement, especially walking, is probably the most distressing phenomenon. The state of complete immobility and helplessness may last for seconds up to, occasionally, hours when the capacity for movement abruptly returns. Attacks seem to be unrelated to the timing of individual levodopa treatment but do tend to occur when the patient is physically tired. Frequency and severity of attacks may show considerable diurnal fluctuations and are related to the duration of the disease (Stern et al. 1980). It has been suggested that the increased sensitivity to visual stimulation and to modification of the visual environment can be an important factor leading to motor blocks (Mestre et al. 1992).

Distraction of attention can also result in freezing. This is the case in psychic stress and fatigue (Yanagisawa et al. 1991). In a study of 990 PD patients (Giladi et al. 1992), one third of them had motor blocks. Longer disease duration, longer duration of L-Dopa treatment, and higher Hoehn and Yahr rating were associated with the presence of motor blocks. According to these authors the three motor tasks that are most affected by motor blocks are speech, hand writing, and gait. In gait most of the freezing episodes appear during gait initiation, turning, and while passing narrow spaces or doorways. Twenty three percent of patients had blocks on open runways. Eleven percent of parkinsonians had blocks in speech and hand writing. A total of 22% of these patients had blocks at a time when they were experiencing the maximal beneficial effect from L-Dopa.

There are many maneuvers or tricks that are used to overcome the immobility (Knuttson 1972). Luria (1932) described a patient who became completely immobile whenever he attempted to walk but who could easily run upstairs. "Frozen" patients may move when a loud verbal command is given or when an accompanying person steps forward (Lang et al. 1990). Martin (1967), in his discussion of gait and posture impairments in PD patients, mentioned a potential benefit from using parallel line cues to overcome akinetic freezing. Generally, periodic visual or auditory stimuli improve the difficulty in walking as they form a rhythm adequate to maintain repetitive movements (Richards et al. 1994). The kinematic results of elderly control subjects showed that such visual cues cause longer stride lengths without significantly altering the stride duration or cadence. Auditory

cues on the other hand induce a faster cadence and a longer stride length. The results in the PD patients (OFF L-Dopa) showed that visual cues induce a longer stride length and a longer stride duration. Auditory cues caused shorter stride duration and a longer stride length. Richards et al. (1994) concluded that visual cues may exert their effect on spatial elements of movement (e.g., limb movement amplitude) and auditory cues act more on centrally controlled variables such as stride length and cadence. This also suggests that the motor program in PD is preserved and the problem is to access it or transform it into an action.

Motor blocks can be observed in the execution of many different motor programs involving different body segments. Narabayashi and Nakamura (1985) studied finger tapping in 123 parkinsonians. Seventy-two percent of their subjects could not make 50 to 100 taps above 2.5 Hz. The authors related the festination they observed to disturbances in rhythm formation due to norepinephrine deficiency in the central nervous system (Narabayashi and Nakamura 1985).

SENSORY SYMPTOMS

Although sensory symptoms were not originally described in Parkinson's disease, in recent years it has been increasingly recognized that painful sensations and paresthesias occur in approximately 40% of patients (Shulman et al. 1996). PD patients often describe a sensation of internal tremor, a feeling of tremor inside the chest, abdomen, arms, or legs that cannot be seen. The frequency of other sensory symptoms (aching, tingling, burning) was higher in the PD patients with internal tremor (73%) than in those without (45%). Internal tremor is associated with anxiety which can also affect motor performance.

CONCLUDING REMARKS

Significant progress in the understanding of PD symptoms has been made in the recent years. However, many unresolved problems still remain. For example movement impairments as observed in parkinsonism could be also due to perceptual, predictive, executional, or motor sequencing deficits (Cassel et al. 1973, Cooke et al. 1978, Sharpe et al. 1983, Stern et al. 1983b, Bloxham et al. 1984). Hence it has been difficult to infer, without ambiguity, either the specific process(es) involved in an impairment, or its pathophysiological correlates. Therefore, it is naive to suggest that motor deficits associated with PD subjects are localized purely in the basal ganglia. The basal ganglia mediate between higher and lower brain structures, receiving, for example, inputs from cortical areas and the substantia nigra, and innervating thalamic and midbrain nuclei (DeLong et al. 1983, Tatton et al. 1984). Given these interconnections and the distributed nature of the neural processes, consideration must be given to the inputs the basal ganglia relay, how they process these inputs, and what structures are modulated by their outputs. Thus it is necessary to consider the neural flow of activity during movement production from cortex, to basal ganglia and down to muscles. Does each structure deal with its inputs adequately, and how long does it require to do so? Any consideration of structural impairment requires an assessment of motor functioning, and so the functional correlates of movement production should be documented. Cognitive neuroscience faces the task of supplementing the neurophysiological data base with detailed descriptions of how and when a structural deficit is causing an impairment of function.

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Received 25 September 1997, accepted 20 January 1998