Pathophysiology of bradykinesia in Parkinson’s disease

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Summary
Bradykinesia means slowness of movement and is one of the cardinal manifestations of Parkinson’s disease. Weakness, tremor and rigidity may contribute to but do not fully explain bradykinesia. We argue that bradykinesia results from a failure of basal ganglia output to reinforce the cortical mechanisms that prepare and execute the commands to move. The cortical deficit is most apparent in midline motor areas. This leads to particular difficulty with self-paced movements, prolonged reaction times and abnormal pre-movement EEG activity. Movements are often performed with normally timed EMG bursts but the amount of EMG activity is underscaled relative to the desired movement parameters. There are also abnormalities in sensory scaling and sensorimotor integration. The brain appears to be able to compensate to some degree for the basal ganglia deficit. There is overactivity in the lateral premotor areas during task performance and movements can be speeded by giving sensory cues. Attention to movement is also beneficial. However, we propose that the engagement of compensatory processes may also lead to reduced performance in other tasks. For example, patients’ problems in performing more than one task at the same time could result from lack of sufficient resources both to compensate for their basal ganglia deficit and to run two tasks simultaneously. Surgical therapies are unlikely to work solely by normalizing basal ganglia output to that seen in healthy individuals. It seems more plausible that surgery removes an interfering signal that allows more efficient compensation by other structures.

Keywords: bradykinesia; Parkinson’s disease; movement; motor control

Abbreviations: BP = Bereitschaftspotential; CNV = contingent negative variation; fMRI = functional MRI; MEG = magnetic electroencephalography; SMA = supplementary motor area

Introduction
The term bradykinesia was first used by James Parkinson to describe one of the cardinal features of the disease that now bears his name. It is now recognized, however, that bradykinesia may be part of the motor dysfunction in many movement disorders.

Bradykinesia is often used synonymously with two other terms: akinesia and hypokinesia. Strictly speaking, bradykinesia describes the slowness of a performed movement, whereas akinesia refers to a poverty of spontaneous movement (e.g. in facial expression) or associated movement (e.g. arm swing during walking). Other manifestations of akinesia are freezing and the prolonged time it takes to initiate a movement. Hypokinesia refers to the fact that, in addition to being slow, the movements are also smaller than desired, as in the micrographia of patients’ handwriting. Although these three symptoms are related, they must also be separate to some extent, since they may not be well correlated with each other in individual patients (Evarts...
Parkinson’s disease patients often appear clumsy, and it is likely that this results from several aspects of the motor disorder.

In this review we will use the term ‘bradykinesia’ to encompass all these problems of slowness or absence of movement. However, where we think that separate mechanisms are involved we will always define the particular functional deficits that we think are relevant in each case. Before discussing the central mechanisms of bradykinesia and how they relate to the basal ganglia dysfunction that is at the heart of Parkinson’s disease, it will be useful first to consider other secondary factors that can contribute to bradykinesia.

**Secondary causes of bradykinesia**

There are five factors that can potentially contribute to bradykinesia in Parkinson’s disease. These are muscle weakness, rigidity, tremor, movement variability and slowing of thought.

**Muscle weakness**

Several studies (Stelmach and Worringham, 1988; Stelmach et al., 1989; Jordan et al., 1992) have compared the strength of patients with Parkinson’s disease and healthy age-matched subjects. All of them found a mild reduction of strength in a variety of muscle groups, even though this sometimes failed to reach statistical significance. One probable reason for this lack of agreement is that it is difficult to match patient and control groups for the amount of daily exercise and diet.

A recent study by Corcos and colleagues attempted to resolve this problem by measuring strength at the elbow in patients when ON and OFF L-dopa following overnight withdrawal of therapy (Corcos et al., 1996). When OFF medication, there was a 30% reduction in the strength of maximum elbow extension and a 10% decrease in elbow flexion. Because intrinsic muscle properties could not have changed in the short period between the OFF and ON conditions, the difference in strength must have been due to an inability of patients to activate the elbow muscles maximally. In that study, the patients appeared to be highly motivated to produce strong contractions when OFF and ON therapy, so that lack of volitional drive was not thought to be a factor. A later study by Brown and colleagues on the wrist extensors showed that one physiological reason for the reduction in strength is the persistence of action tremor during maximal contraction (Brown et al., 1997). Tremor at ~10 Hz in patients OFF therapy prevents maximum fusion of motor unit contraction and can contribute to weakness. However, this cannot account for the decrease in strength in all muscle groups, so that other, presumably central, factors must also be involved. The conclusion is that patients with Parkinson’s disease can be weak in some muscle groups and this will inevitably contribute to slowness of movement.

It is not clear whether attention might affect the results of strength testing. The fact that patients fail to energize their muscles fully, especially when OFF drug treatment, indicates only that they lack some part of the normal volitional input to lower motor centres. Why this occurs is unclear. There is no obvious lack of effort by patients and there does not appear to be any lack of concentration. Patients will frequently say they are trying as hard as possible. Similarly, the existence of physiological differences in the EMG activity in patients compared with normal subjects suggests that the voluntary drive to contract is not organized in the same way as usual. However, phenomena such as paradoxical kinesia suggest that there are mechanisms that can overcome this apparent lack of volitional drive but this is probably not an attention-related phenomenon.

**Rigidity**

Long-latency stretch reflexes are enhanced in Parkinson’s disease (Tatton and Lee, 1975; Berardelli et al., 1983; Rothwell et al., 1983). They could potentially contribute to bradykinesia if they were elicited in an antagonist muscle during an active isotonic contraction of the agonist. Johnson and colleagues tested this hypothesis by using a torque motor to stretch muscles unexpectedly during active sinusoidal movements of the wrist (Johnson et al., 1991). They showed that reflexes elicited in the antagonist muscle were not suppressed as much as in normal subjects, and that the degree of abnormality was related to the amount of clinical bradykinesia. The one flaw in this argument was that the amount of activity in the antagonist muscle during unperturbed flexion/extension movements was no greater than that seen in normal subjects. Thus, there was no evidence in the actual movements tested that antagonist co-contraction could have been a limiting factor. Indeed, co-contraction has never been described as an important feature even in very rapid movements, in which the triphasic ballistic movement EMG pattern has been analysed in some detail. The conclusion must be that the role of rigidity in bradykinesia has yet to be proven conclusively.

**Rest and action tremor**

We noted above that action tremor can contribute to weakness in Parkinson’s disease. In addition, rest and action tremor can also be a factor in prolonging reaction times. Hallett and colleagues and Wierzbicka and colleagues showed that patients with Parkinson’s disease tend to time the onset of agonist muscle activity at the elbow or wrist with the time of activation of the same muscle in any ongoing tremor (Hallett et al., 1977; Wierzbicka et al., 1993). This could, on average, slow the initiation of any movement.

Action tremor can also be a factor in pacing the speed of voluntary alternating movements. Logigian and colleagues showed that voluntary movements are entrained by action tremor if patients attempt to move at frequencies close to
that of their natural action tremor (Logigian et al., 1991). The extent of the entrainment depends on the amplitude of the patients’ ongoing tremor.

**Movement variability**

The movements of patients with Parkinson’s disease are less accurate than normal, particularly if they have to move as fast as possible (Sanes, 1985; Sheridan and Flowers, 1990; Phillips et al., 1994). In other words, the speed–accuracy trade-off is less efficient in patients than in healthy subjects. Sheridan and Flowers suggested that bradykinesia might be due to an active strategy of patients to move more slowly in order to improve their accuracy (Sheridan and Flowers, 1990). Although this is a plausible strategy, other factors must also be involved since bradykinesia remains in tasks in which spatial accuracy constraints have been removed (Teasdale et al., 1990).

**Bradyphrenia**

Slowness of thought, or bradyphrenia, could lead to bradykinesia by interfering with movement planning and, for example, increasing reaction time. Whether bradyphrenia exists in Parkinson’s disease has been controversial. In part, this is due to the fact that many patients with Parkinson’s disease do develop dementia from several aetiologies, and there is certainly slowing of thinking in dementia (Berry et al., 1999). Additionally, there is slowing of thought in ageing and depression (Cooper et al., 1994), and these factors need to be considered. Lastly, many ‘cognitive’ studies have employed procedures that have required a motor response, so that bradykinesia might cause an apparent bradyphrenia (Rafal et al., 1984). Confusion has arisen from a number of studies that have not taken these factors into consideration. Moreover, thinking is not just one process and whether it is slow might depend on the nature of the task. Some studies have claimed to find bradyphrenia (Cooper et al., 1994; Pate and Margolin, 1994), but most have not (Rafal et al., 1984; Duncombe et al., 1994; Howard et al., 1994; Spicer et al., 1994). It is likely that bradyphrenia is not responsible for slowing when dementia is not present and the patient is not on drugs, such as anticholinergics, that might interfere with cognitive processes.

**Primary bradykinesia**

Although all the factors above can contribute to bradykinesia, they must be distinguished from the core disorders of central movement control that are responsible for primary bradykinesia. In this section we describe those features of bradykinesia that cannot be explained by secondary factors.

Bradykinesia could potentially be due to slowness in formulating the instructions to move (programming) or to slowness in executing these instructions. Although programming and execution are usually thought of as separate and sequential operations, they could well overlap, at least to the extent that programming could continue during execution. It is possible, therefore, to study some of the processes involved in programming if we confine ourselves to measurements such as reaction times or EEG/magnetic encephalography (MEG) studies made before the onset of movements. Measurements made after movement onset may reflect both execution as well as programming.

**Preparation to move: studies of reaction times**

Patients with Parkinson’s disease react more slowly than healthy subjects of the same age and this contributes to akinesia. The more advanced the disease, the slower the reaction times. A question is whether patients are slow in starting to move because they have a problem in preparing the instructions to move, or whether the problem is in releasing those instructions.

Some information about preparatory processes can be obtained by comparing reaction tasks in which the movement component is constant but the amount of preparation is variable. In a simple reaction task, the same response is made on every occasion and healthy subjects can prepare the response fully in advance of the imperative signal. In a choice reaction task, the response depends on the reaction signal. Subjects know the set of possible moves they might have to make but not the precise one that will be needed on any particular trial. They cannot prepare the movement fully in advance and have to complete more of the preparation after the imperative signal is given. The result is that choice reaction times are longer than simple reaction times.

Simple reaction times are prolonged in Parkinson’s disease (Heilman et al., 1976; Evarts et al., 1981; Rafal et al., 1984; Bloxham et al., 1987; Sheridan et al., 1987; Hallett 1990; Jahanshahi et al., 1992, 1993; Kutukcu et al., 1999; see also Zimmerman et al., 1992; Harrison et al., 1993; Revonsuo et al., 1993). The situation with choice reaction times is more complex. Some authors have reported that they are the same as normal (Evarts et al., 1981; Bloxham et al., 1987; Sheridan et al., 1987) and have suggested that patients have slow simple reaction times because they fail to take advantage of the opportunity to programme their response fully in advance. However, other authors have reported that choice reaction times are longer than normal (Wiesendanger et al., 1969; Stelmach et al., 1986; Mayeux et al., 1987; Dubois et al., 1988; Lichter et al., 1988; Reid et al., 1989; Pullman et al., 1988; Jahanshahi et al., 1992; Brown et al., 1993b). It is not clear why there is so much variety in the results reported. Some may arise because different patient groups were studied at different stages of the disease; some may be due to elements in the design of the task, such as stimulus–response compatibility, which may be handled differently in patients with Parkinson’s disease (e.g. Brown et al., 1993b). Whether or not patients can take full advantage of prior programming, there is evidence that patients are likely to
be slower than normal in preparing expected responses (Jahanshahi et al., 1992).

In contrast to the disagreement over the extent of programming deficits in Parkinson’s disease, there is much clearer evidence that slowness in executing motor commands is an important factor in prolonging reaction times. The reason is that motor excitability has to build up to a certain threshold level before movement or even EMG activity can be detected. If this is slow, the threshold is reached later than normal. For example, EMG activity in patients usually rises slowly after its onset, and this can delay the time at which movement is detected. The same argument can be applied to the interval before the onset of EMG: motor excitability has to build up to threshold before motor neurones are discharged. Experiments with magnetic transcranial stimulation have confirmed that pre-movement excitability increases more slowly than normal in patients with Parkinson’s disease (Pascual-Leone et al., 1994). The conclusion is that little of the increase in simple reaction times is due to problems in starting the commands to move. The deficit arises either because the wrong (slow) commands have been chosen or because the correct commands are executed more slowly than normal.

Our conclusion from these reaction time studies is that slowness in simple reaction tasks is as much due to problems in the execution of a stored motor command as it is to maintaining that command in store at an appropriate state of readiness. The situation for choice of reaction tasks requires further study.

Preparation to move: activation of specific brain areas

EEG, MEG, PET, functional MRI (fMRI) and magnetic stimulation techniques have all been used in an attempt to understand which parts of the motor system are functioning abnormally in akinetic patients with Parkinson’s disease. However, because brain activity during movement reflects both outgoing motor commands and the sensory input that results from moving, studies of motor activity have concentrated on the period just before the onset of movement when changes in sensory input are minimal. In most instances, the movements are self-paced; reaction tasks involve pre-movement sensory input that can complicate the interpretation of the data obtained. A general finding from these studies is that there is underactivity of midline [supplementary motor cortex (SMA) and nearby areas] cortical motor areas, perhaps coupled with extra activation of lateral premotor areas. The former may be related to difficulties in preparing instructions to move; the latter may be an active process of compensation and may be related to the improvement in performance that can be observed when external cues are given to guide movement (see below).

The pre-movement EEG potential, sometimes called the Bereitschaftspotential (BP), is a slowly rising negativity that occurs over widespread areas of the scalp before the onset of a self-paced voluntary movement. It has two major components. The early component (sometimes known as BP but here referred to as BP1) begins 1–2 s before movement. It is bilaterally symmetrical and is largest at the vertex. The second component (sometimes known as NS1 or NS’ but here called BP2) rises more steeply, beginning ~650 ms before the onset of EMG activity. Recent recordings from subdural electrodes suggest that the BP1 predominantly reflects bilateral activity in the motor and supplementary motor areas, whereas the BP2 also has a contribution from the contralateral motor and premotor cortex (Ikeda et al., 1992).

In early studies, there was some debate over whether the BP was abnormal in Parkinson’s disease. Some of the controversy was resolved by Dick and colleagues, who showed that L-dopa could affect the amplitude of the BP both in normal subjects and in patients, and that a difference between patients with Parkinson’s disease and normal subjects was crucially dependent on the level of dopaminergic function (Dick et al., 1989). They went on to show that the BP in patients OFF therapy was reduced in the early part (BP1) but larger than normal in the later part (BP2) (Dick et al., 1989). The net effect was that the peak BP was virtually the same in the patients as in normal subjects. They suggested that underactivity of a source in the SMA was responsible for the reduction of the early component, and that this was compensated for by overactivity in lateral motor areas nearer the time of onset of movement. Recent studies have tended to confirm this idea. For example, Jahanshahi and colleagues noted that pre-movement EEG activity was normal in patients with Parkinson’s disease when they performed an externally triggered task compared with the reduction that is seen in self-paced movements (Jahanshahi et al., 1995) (Fig. 1). Cunnington and colleagues proposed that underactivation of the SMA in Parkinson’s disease patients made them more reliant on external cues so that they did not use predictive models when cues were available (Cunnington et al., 1995, 1997). Pre-movement activity could, however, be induced in patients if they were asked to attend to the time of the next movement, and this improved task performance (Cunnington et al., 1999). The authors suggested that attentional processes allow lateral premotor systems, which are less impaired by basal ganglia dysfunction, to compensate for deficiencies in midline motor systems that are normally active in internally generated tasks.

In these early studies the subjects repeated the same movement over many trials. Later studies have required the subjects to choose to make different movements (e.g. moving a joystick up, down, left or right) on each trial. In healthy subjects, the BP is much larger than when subjects make the same movement on each occasion, perhaps reflecting the additional processing necessary to choose between movements on each trial (Touge et al., 1995; Praamstra et al., 1996a, b, 1998; Dirnberger et al., 2000). Praamstra and colleagues used dipole modelling to show that the most likely source for the extra activation was the SMA (Praamstra et al.,...
Pathophysiology of bradykinesia in Parkinson’s disease

Fig. 1 (A) Premotor potentials preceding self-initiated movements for normal subjects (continuous line) and patients with Parkinson’s disease (broken line). (B) Premotor potentials preceding externally triggered movements for normal subjects (continuous line) and patients with Parkinson’s disease (broken line). The mean time of stimulus presentation is 253 ms prior to EMG onset for patients with Parkinson’s disease and 212 ms for normal subjects. Pre-movement EEG activity was normal in patients with Parkinson’s disease when they performed an externally triggered task compared with the reduction that is seen in self-paced movements. From Jahanshahi et al., 1995.

1996b). This extra activation is lacking in patients with Parkinson’s disease, consistent with the model outlined above.

Abnormalities in cortical activation prior to and during movement have been also found with the technique of event-related desynchronization (Defebre et al., 1996; Magnani et al., 1998). The amount of power in the alpha (10 Hz) and beta (20 Hz) ranges of EEG activity decreases ~1 s before the onset of movement and remains lower than at rest while movement occurs. It has been suggested that the 10–20 Hz rhythm occurs because the activity of cortical neurones tends to become synchronized during periods of relative inactivity. If so, event-related desynchronization is a measure of cortical activation that reflects uncoupling of the population activity into more discrete temporal and spatial patterns. In patients with Parkinson’s disease the duration of the event-related desynchronization prior to voluntary movements is shorter and the pattern of movement-related attenuation of the alpha and beta rhythms during various types of motor tasks is abnormal. Brown and Marsden found that dopaminergic stimulation in Parkinson’s disease restores the movement-related attenuation of the alpha and beta rhythms (Brown and Marsden, 1999). This effect was specific for the motor areas involved in the motor task and correlated with the improvement of bradykinesia. Wang and colleagues reported similar findings in their study of simple and complex movements (Wang et al., 1999). The above studies suggest that the basal ganglia have a role in releasing cortical elements from idling rhythms during voluntary movement. In a recent report, Brown carried this idea one stage further by examining the effect of dopaminergic stimulation on the coupling of activity between different nuclei of the basal ganglia (Brown et al., 2001). They recorded local potentials from patients with implanted electrodes in the subthalamic nucleus and internal pallidum, and found that they were coupled by activity at 20–30 Hz when the patients were OFF medication, whereas ON medication this changed to 60–70 Hz.

**Motor execution**

*Single ballistic movements at a single joint*

Single movements made as fast as possible about a single joint are slower than normal in patients with Parkinson’s
Part of this slowing may be due to weakness of the agonist muscle discussed above, but much must be due to other factors. For example, even though maximum contraction strength of the biceps decreases by 10% in the OFF condition, the speed of elbow flexion may halve. Similarly, EMG records show that there is no excessive co-contraction of the antagonist that might slow the movement down more than expected from the decline in strength. It seems instead that slowness of movement is caused by problems in recruiting the appropriate level of muscle force sufficiently fast.

There are two parts to this problem. First, patients may find it difficult to activate a muscle rapidly. This is certainly true in more advanced disease: it can take several seconds for some patients to produce a maximum voluntary contraction (e.g. Corcos et al., 1996). However, the rate of contraction is not the only cause of bradykinesia in simple movements. The fastest movements are accompanied by a triphasic EMG pattern in which the time and duration of the bursts varies in a highly predictable way depending on the amplitude and other parameters of movement. This pattern is present in patients with Parkinson’s disease, but the first agonist burst is small. As Hallett and Khoshbin pointed out, the result is that patients often add further bursts of EMG to the pattern in order to achieve enough force to move the limb to the required end position (Hallett and Khoshbin, 1980). Despite this, if patients aim for a movement of larger amplitude, the size of the agonist burst can increase. In effect, this means that the size of the agonist burst is not always a limiting factor in slowing movement: if the burst for the large movement had been used for the smaller movement the speed would have been normal. The conclusion is that there is a second cause of bradykinesia in simple movement: inappropriate scaling of the dynamic muscle force to the movement parameters (Berardelli et al., 1986b).

Simultaneous, sequential or repetitive movements

If any additional complexity is added to a simple movement, either by repeating the movement or by combining it with other tasks, bradykinesia becomes more prominent. Clinical tests of bradykinesia often make use of this phenomenon. Repetitive sequential movement involving isolated finger movements, hand opening/closing or wrist pronation/supination become smaller (hypo-kinesia) and slower with repetition of the movement (‘fatigue’) (Agostino et al., 1998). Schwab and colleagues asked patients to squeeze a sphygmomanometer bulb in one hand and outline a drawing with the other (Schwab et al., 1954). They had much more difficulty if they had to do both tasks together than if each one was performed alone. Indeed, in most cases, patients tended to alternate between the tasks rather than perform them at the same time.

Experimental studies have analysed these features of bradykinesia in some detail. In essence, they show that bradykinesia is more than the slowness seen in simple single movements. There are additional problems in combining or sustaining complex movements. Benecke and colleagues examined rapid elbow flexion movements combined with a simultaneous or sequential hand movement performed with either the same or the opposite arm (Benecke et al., 1986, 1987). In contrast to normal subjects, in whom there was no decrement of performance when two tasks were combined, patients with Parkinson’s disease showed (i) a marked slowing of movement over and above that seen in each task alone when both had to be performed together, and (ii) a longer pause between each element of a sequential task. Indeed, these two extra deficits correlated better with clinical measures of bradykinesia than the slowness in each simple movement.

Similar problems in performing simultaneous movements have been described in bilateral reaching (Stelmach and Worringham, 1988; Castiello and Bennett, 1997) and cranking tasks (Johnson et al., 1998). In sequential movements, prolonged pauses between each element have been observed.
in everyday movements, such as rising from a chair to pick up an object or drinking from a cup (Bennett et al., 1995). Elements of fatigue have also been reported in longer-lasting sequences of movements (Berardelli et al., 1986a; Agostino et al., 1992, 1994).

What is the nature of the extra deficits in performance of complex movements?
The problem of combining tasks or switching from one task to another is not confined to movement. It can be observed in cognitive tasks or combined cognitive and motor tasks (Brown and Marsden, 1991; Oliveira et al., 1998). Such observations are important since they indicate that the extra deficit seen in complex movements is not necessarily a purely motor problem. They raise the possibility that global processing mechanisms, perhaps involving attention, are also a factor. Brown and Marsden suggested that patients either have a limited processing resource that interferes with their ability to run more than one task at the same time, or that they have difficulty in switching this resource between tasks (Brown and Marsden, 1991). An alternative is that the global resource is the same in patients, but that tasks are performed less automatically than in normal subjects. In this case, each task would consume more of the processing resource, and lead to difficulties in performing several tasks at once, or in switching between tasks. Effectively, patients may be trying to compensate for lack of basal ganglia input by devoting more resources to each single task they perform. When required to perform more than one task at once, this becomes a limiting factor.

Sensorimotor processing
Some authors have reported abnormalities in sensorimotor processing in Parkinson’s disease. Schneider and colleagues reported a decrease of precision in two-point discrimination and proprioceptive position sense (Schneider et al., 1986) and Klockgether and colleagues, in a study of arm movements testing the effects of both visual and kinaesthetic information, suggested that peripheral afferent feedback is impaired in patients with Parkinson’s disease (Klockgether et al., 1995). A problem in matching somatosensory and visual inputs was demonstrated by Demirci and colleagues (Demirci et al., 1997). The authors postulated that this was due to an abnormality of sensory scaling and drew parallels with the abnormal scaling of motor output reported by Berardelli and colleagues (Berardelli et al., 1986b).

A deficit in sensorimotor integration may also be observed in precision grip/lift tasks. These are complex acts that are performed by gripping an object with the correct amount of force so that it does not fall between the fingers when it is lifted off a supporting surface. Parkinsonian patients take longer to develop peak grip force and show a pronounced slowing in the rate at which grip force is generated. They also squeeze the object more than normal when lifting it in the air (Fellows et al., 1998). The authors thought that the latter effect was due to problems in sensorimotor processing. We conclude that kinaesthesia may have a role in the pathophysiology of Parkinson’s disease, but that its importance still needs to be clarified.

Abnormalities in the contingent negative variation (CNV) can also be explained in terms of abnormal sensorimotor processing. The CNV is a slow negative potential that occurs between a warning (S1) and an imperative (S2) stimulus. It is best recorded at frontal and central electrodes and reflects processes related to planning a forthcoming movement and anticipation of the imperative stimulus. Activity of the prefrontal cortex contributes to the amplitude of the CNV. In Parkinson’s disease, the amplitude of the CNV is reduced by an amount related to the severity of disease and levodopa treatment (Amabile et al., 1986; Ikeda et al., 1997; Gerschlager et al., 1999). In general, the CNV is more clearly affected in Parkinson’s disease than the (single movement) BP. The reason for this may be as follows. In a CNV task, S2 acts as a trigger for the final movement, whereas in a self-paced task there is no trigger. Thus, if patients OFF therapy fail to prepare for the forthcoming movement in the S1–S2 interval, they can still rely on S2 as an external trigger to retrieve the instructions to move. In such conditions, the CNV would be substantially reduced because there would effectively be no contribution at all from processes involved in movement preparation. In contrast, in a self-paced task, preparation of some kind must have been complete before the movement; hence the effect on the BP will always be less pronounced than on the CNV.

Transcranial stimulation
Studies using electrical and magnetic stimulation techniques have shown that the corticomotoneurone connection is normal in Parkinson’s disease (Dick et al., 1984). Indeed, movements that are elicited by direct stimulation of the motor cortex are the same whether the stimulus is given when patients are immobile and OFF therapy or dyskinetic and ON therapy. As noted above, this means that bradykinesia is not primarily the result of any deficit in the final output pathways of the motor areas of the cortex. Despite this, cortical stimulation has revealed subtle changes in cortical circuits. Some of these may contribute to bradykinesia whilst others may be compensatory.

Most authors report that the motor cortex of patients with Parkinson’s disease has the same threshold for stimulation as in healthy subjects (Priori et al., 1994; Valls-Solè et al., 1994; Ridding et al., 1995). However, when patients are tested at rest, the slope of the input–output relationship between stimulus intensity and response size is steeper than normal. Perhaps as a result of this, voluntary contraction facilitates responses less than in normal subjects (Valls-Solè et al., 1994) (Fig. 3). The implication is that the distribution of cortical excitability at rest is skewed towards higher values.
Fig. 3 Mean motor-evoked potential (MEP) area in normal subjects and in patients with Parkinson’s disease at various stimulus intensities and degrees of muscle activation. In Parkinson’s disease, the slope of the input–output relationship between stimulus intensity and response size was steeper than normal. From Valls-Sole et al., 1994.

than normal. Although this could be the result of a primary basal ganglia deficit, it seems likely that it could also be an attempt to compensate for the slow recruitment of commands to move by making it easier to recruit activity from a resting state.

There are also changes in the excitability of cortical inhibitory circuits. A suprathreshold stimulus given whilst the subject makes a tonic voluntary contraction evokes a muscle twitch that is followed by a postexcitatory silent period. The disappearance of voluntary activity during the period of silence is thought to be due to the activation of cortical GABAergic inhibitory systems that suppress motor cortical output for 100–200 ms (Fuhr et al., 1991). The silent period is shorter in bradykinetic patients (Cantello et al., 1991; Priori et al., 1994) and is normalized by treatment with l-dopa (Priori et al., 1994). Cortical inhibition can also be tested in subjects at rest using the double-pulse paradigm of Kujirai and colleagues (Kujirai et al., 1993). Again, in patients the amount of inhibition is smaller than normal (Ridding et al., 1995). With long interstimulus intervals and larger (suprathreshold) conditioning and test stimuli, a different type of abnormality is found. The test response is significantly inhibited at 100 and 150 ms (Berardelli et al., 1996b); this suggests that patients with Parkinson’s disease have reduced facilitation during voluntary muscle activation. It may be that these effects on inhibition and excitation reflect reduced facilitatory input to the cortical excitatory and inhibitory circuits from basal ganglia. Both could affect the speed of recruitment of cortical motor output in bradykinesia.

Recent transcranial magnetic stimulation studies have shown that it is sometimes easier to disrupt activity in motor areas of the cortex in patients than in healthy subjects. For example, Cunnington and colleagues showed that single-pulse stimulation over the SMA early before the onset of movement could disrupt task performance in patients, whereas it may have no noticeable effect in healthy subjects (Cunnington et al., 1996). Presumably, the compromised activity in midline cortical areas in patients is more readily disrupted than usual.

Metabolic imaging (PET and fMRI studies)
Data from metabolic studies are consistent with the electrical data above, and reveal a relative underactivation of midline motor areas in many tasks that is sometimes accompanied by an increase in activation of the lateral premotor areas. The studies give more information than EEG or MEG about the precise cortical areas involved, but a special paradigm has to be used to distinguish preparation and execution.

Many studies have used a self-paced joystick movement task in which subjects choose on each trial which direction to move (up, down, left or right). There is less activation compared with that at rest in the anterior SMA, anterior cingulate cortex, dorsolateral prefrontal cortex, basal ganglia and thalamus in patients than in healthy subjects (Jenkins
and supplementary motor cortex, as well as in the ipsilateral cerebellum, increased as the movement sequences became longer or more complex. In patients, there was overactivity compared with normal subjects in the premotor and parietal cortices. The conclusion is that the parkinsonian brain may recruit additional circuits during movement that compensate for the primary basal ganglia deficit.

**Bradykinesia and other basal ganglia diseases**

In Parkinson’s disease, slowness of movement (bradykinesia) occurs in conjunction with a reduction in the amount of spontaneous movement (hypokinesia or akinesia). However, in two other basal ganglia diseases, Huntington’s disease and dystonia, bradykinesia co-exists with hyperkinesia. One conclusion from this is that bradykinesia has a different mechanism from hypo- or hyperkinesia. However, analysis of the nature of the bradykinesia indicates that even this one symptom may have more than one cause. The maximum speed of simple voluntary arm movement is slower than in healthy subjects in patients with either Huntington’s disease or dystonia (Heftner et al., 1987; Thompson et al., 1988; van der Kamp et al., 1989; Berardelli et al., 1998, 1999), but the pattern of EMG activity underlying the slowness of movement in patients with either of these conditions differs from that in patients with Parkinson’s disease. In Huntington’s disease and dystonia, the EMG bursts are often prolonged and the final position and peak velocity are more variable than in Parkinson’s disease.

Patients with Huntington’s disease are also abnormal in executing simultaneous and sequential movements (Thompson et al., 1988; Agostino et al., 1992) and, like patients with Parkinson’s disease, have difficulty in performing a sequence of movements without external cues (Georgiou et al., 1995).

**Experimental parkinsonism and lessons from surgery**

The majority of the basal ganglia output, particularly that in the ‘motor loop’ (Albin et al., 1989; Alexander and Crutcher 1990a; Alexander et al., 1990b), projects back to the cortex via the thalamus. The projection neurones of the main output nuclei (the internal globus pallidus and the substantia nigra pars reticulata) are GABAergic and inhibitory. When the present model of basal ganglia function was being developed in the late 1980s, it was proposed that there was a direct relationship between the level of discharge in the output nuclei and the amount of observable movement, a high output causing hypokinesia and a low output causing hyperkinesia (Wichmann and De Long, 1996). Several observations seemed to confirm this idea. The level of resting pallidal discharge was increased when monkeys were made parkinsonian by injection of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (DeLong, 1990) and microelectrode recordings...

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**Fig. 4** Comparison of the adjusted mean regional cerebral blood flow between normal subjects and patients with Parkinson’s disease for self-initiated movements relative to the rest condition. The areas showing differentially greater activation during the self-initiated movements for normal subjects than for parkinsonian patients were the anterior cingulate, the supplementary motor areas bilaterally, the left putamen, the left insular cortex, the left lateral premotor cortex, the right parietal area 40 and the right dorsolateral prefrontal cortex. From Jahanshahi et al., 1995.
made during neurosurgery suggested the same might be true in human patients with Parkinson’s disease (Hutchinson et al., 1997). Indeed, injection of apomorphine to reduce bradykinesia during the course of surgery for Parkinson’s disease produced a reduction in the firing rate of pallidal neurones (Hutchinson et al., 1997; Merello et al., 1999) (Fig. 5). The most recent recordings from patients undergoing pallidotomy for hemiballism or dystonia also suggest that, in these hyperkinetic conditions, pallidal neurones fire at rates substantially less than those observed in patients with Parkinson’s disease (Lenz et al., 1998; Vitek et al., 1999).

However, a simple relationship between the level of pallidal activity and movement cannot fully explain some of the most important results of stereotaxic surgery. Marsden and Obeso called this ‘the paradox of stereotaxic surgery’ (Marsden and Obeso, 1994). Since its revival in the early 1990s, pallidotomy has been used to treat several hundred patients worldwide, yet lesioning this major output of the basal ganglia never results in hyperkinesias, as might have been predicted if there were a strict relationship between movement and pallidal output. In fact, the opposite is observed: pallidotomy is an excellent procedure to reduce or even abolish the drug-induced dyskinesias that are common after several years of L-dopa treatment. Pallidotomy has even been used successfully to treat hyperkinetic basal ganglia disorders, such as hemiballism and dystonia (Lozano et al., 1997; Suarez et al., 1997; Vitek et al., 1999). Despite its success in treating or preventing hyperkinesias, pallidotomy has only a mild effect on bradykinesia or hypokinesia. In patients with Parkinson’s disease, there is only a 30% improvement in clinical bradykinesia scores in patients OFF treatment with L-dopa and virtually no effect on clinical scores evaluated in the best ON condition (e.g. Samuel et al., 1998).

Explanations that try to account for this basic paradox fall into two main categories: (ii) physiological abnormalities due to changes in neural noise; and (ii) anatomical explanations due to the anatomical complexity of the basal ganglia output structures. At the present time it is not possible to determine whether any of these explanations is true.

The physiological (neural noise) explanation suggests that the mean level of discharge from the globus pallidus internus and substantia nigra pars reticulata is not the only important physiological measure of basal ganglia function. The temporal and spatial pattern of output, as well as its absolute level, is likely to be relevant. This pattern might help focus cortical activation so that appropriate muscles are activated and others suppressed during the performance of a task (e.g. Mink, 1996). It is speculated that this output becomes disordered in Parkinson’s disease. Certainly, in human patients and in monkeys rendered parkinsonian by MPTP, there is an increase in the temporal variability of pallidal discharge and there is a tendency for the discharge to be more synchronized between distant cells than in the healthy state (Bergman et al., 1998).

It is reasonable to imagine that pallidotomy removes input to the thalamus from a noisy and disordered system. If one pattern of noise gave rise to bradykinesia, then this might explain the 30% improvement in OFF-treatment clinical scores; if another pattern provoked dyskinesias, then lesioning would abolish these also. Nevertheless, the most important feature of this development of the basal ganglia model, and one that is often not appreciated by those who use it, is that there is no implication that lesioning the pallidum in any way normalizes basal ganglia function. Unlike the simple model, in which lesioning reduces, and therefore normalizes, the overall level of pallidal output, the newer model views the lesion as a means to remove basal ganglia output completely. The implication is that if the lesion causes any improvement in function this must be due to other parts of the brain being able to compensate more readily for the usual basal ganglia contribution. This proposal is explored below.

The anatomical solution to the paradox of pallidal surgery is that the arrangement of pallidal output is more complex than had been envisaged originally (for a review, see e.g. Parent and Hazrati, 1995). Results of chronic high-frequency stimulation of the globus pallidus internus, which produces an effect similar to that of a reversible lesion, are particularly suggestive. The electrodes that are usually implanted have four possible stimulation sites that allow activation of different areas inside the globus pallidus internus. With this technique, Krack and colleagues found that there are two different functional zones within the globus pallidus internus (Krack et al., 1998). Stimulation in the ventral zone was able to reduce drug-induced dyskinesias and improved rigidity but had the side-effect of abolishing the anti-kinetic effects of L-dopa treatment. Stimulation at a more dorsal site near the border of the globus pallidus internus and the globus pallidus externus improved OFF-drug bradykinesia but could also induce dyskinesias in some patients. If effects on bradykinesia and dyskinesias can be separated anatomically, it is possible that the initial model of basal ganglia function can still be applied. Reducing output in one part of the system might reduce bradykinesia, whereas interrupting function in another part of the loop might abolish dyskinesias. In contrast
with the physiological explanation above, this theory still implies that improvement in motor function is the consequence of normalizing basal ganglia output rather than removing it entirely.

At this point it is useful to enquire further into the details of the effects of surgery on bradykinesia in patients with Parkinson’s disease. The results suggest that surgery may produce a combination of normalized function and improved compensation.

**Neurophysiological studies of the effect of surgery and deep brain stimulation on bradykinesia**

A large number of clinical studies have examined the effectiveness of pallidotomy; rather fewer have been published on chronic stimulation of the subthalamic nucleus or globus pallidus. However, a general rule is that, in terms of bradykinesia, pallidotomy produces an improvement of ~30% in OFF-period symptoms on the side contralateral to the lesion that is sustained for 2 years or more after the operation. There is less effect on measures of postural stability or on the best ON-therapy scores (Bronstein et al., 1999; Lang et al., 1999). Pallidal stimulation has similar effects, but is considered to be potentially safer in terms of adverse cognitive side-effects if bilateral procedures are performed (Brown et al., 1999). Chronic stimulation of the subthalamic nucleus may be more effective than pallidotomy or pallidal stimulation in improving OFF-treatment bradykinesia scores. Improvements in balance and posture are also more evident (Limousin et al., 1998). It is usually possible to reduce the dose of L-dopa, and this ameliorates problems with dyskinesias.

Several studies have used physiological techniques in addition to clinical measures to try to understand more precisely the nature of the improvement produced by these procedures in patients OFF their normal drug therapy. In general, the main improvement is in execution rather than preparation for movement. Thus, both pallidotomy and stimulation of the subthalamic nucleus speed up simple and complex movements and improve the recruitment of maximum muscle force (Pfann et al., 1998; Brown et al., 1999; Kimber et al., 1999; Limousin et al., 1999; Siebner et al., 1999). However, there is much less effect on reaction times and no effect on the early (BP1) component of the BP (after pallidotomy; Limousin et al., 1999). Interestingly, the late (BP2) component of the BP is improved, which is consistent with the idea that one effect of surgery is to improve compensation by non-midline cortical structures.

**Functional imaging studies of the effect of surgery and deep brain stimulation on bradykinesia**

Many imaging studies have been driven by the model of basal ganglia function outlined in the early 1990s. Overactivity of the inhibitory output projections from the basal ganglia to the thalamus in Parkinson’s disease was supposed to remove facilitatory thalamocortical drive, particularly to midline cortical motor areas (anterior SMA and cingulate cortex). PET and fMRI activation studies had shown (see above) that these areas were less activated during movement in patients, and therefore pallidotomy was expected to improve activation by restoring normal levels of basal ganglia output (e.g. Ceballos-Baumann et al., 1994).

Most studies on movement-related changes in metabolic activity have reported similar findings both after pallidotomy (Grafton et al., 1995; Samuel, 1997a, b) and during subthalamic nucleus stimulation (Limousin et al., 1997; Ceballos-Baumann et al., 1999). In tasks in which a free-choice joystick movement is used, increased activation of preSMA and anterior cingulate cortex is usually accompanied by increased activation of the dorsolateral prefrontal cortex. Although most reports of activation-induced metabolism suggest that there is no change in the primary motor cortex, there are some suggestions that stimulation of the subthalamic nucleus may reduce activity in the resting state (Limousin et al., 1997; Ceballos-Baumann et al., 1999). Whether this is related to a general reduction in rigidity or other involuntary muscle activity or to reduced input to the cortex via pathways direct from the subthalamic nucleus is not known.

Surgery also appears to produce increases in the activation of the premotor areas, even though these are not normally underactive, and may even be overactive, in Parkinson’s disease. This has been noted in both a prehension task (Grafton et al., 1995) and in a freely selected joystick movement task (Ceballos-Baumann et al., 1999). In an [18F]fluorodeoxyglucose-PET study carried out in patients at rest, Eidelberg and colleagues found increases in metabolism in the premotor cortex as well as in the dorsolateral prefrontal cortex and motor cortex, ipsilateral to a pallidotomy (Eidelberg et al., 1996). Thus, it appears that lateral premotor areas may also be involved in recovery after surgery.

**Conclusion**

The term ‘bradykinesia’ is often used to cover a range of related problems in the control of movement. However, in all cases the principal deficit is that movements are slow. The data reviewed here suggest that, although secondary factors such as muscle weakness, tremor and rigidity may contribute, the principal deficit is due to insufficient recruitment of muscle force during the initiation of movement. The result is that patients’ movements undershoot their targets and end by approaching it in several smaller steps. The two distinguishing features of parkinsonian bradykinesia are (i) that patients underscale muscle force and (ii) that the deficit is often ameliorated when external cues (vision, sound) are given to guide the movement. The former has led to the suggestion that bradykinesia is a problem of scaling motor output appropriately to the task rather than to any intrinsic limitation in motor execution. The latter is usually interpreted...
in terms of the preferential access of basal ganglia motor output to medial rather than lateral motor cortical areas. Medial cortical areas are more active in association with internally generated movements, whilst lateral areas are more active during externally cued movement. In summary, bradykinesia seems to result primarily from the underscaling of movement commands in internally generated movements. This may well reflect the role of the basal ganglia in selecting and reinforcing appropriate patterns of cortical activity during movement preparation and performance.

Recent imaging and EEG studies have shown that other regions of the CNS can adapt to the primary basal ganglia deficit of Parkinson’s disease. Thus, the clinical presentation of bradykinesia may be a mixture of the primary deficit and compensatory processes. We raise the possibility that some aspects of bradykinesia, such as the long intervals between successive elements of a sequence, difficulty in doing two things at the same time and the progressive slowing of long sequences of movement, are the result of this interaction. This line of argument can be followed further. One of the new understandings of basal ganglia pathophysiology is that disease may make the basal ganglia output noisy. Surgical interventions may work in part by removing or reducing this noise. The implication is that surgery improves function both by normalizing basal ganglia output and by allowing other structures to compensate better for the underlying deficit.

References


Pathophysiology of bradykinesia in Parkinson’s disease


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