Slowness of Movement in Parkinson's Disease

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Loss of the ability to move is the most characteristic and fundamental motor deficit in Parkinson's disease. Parkinsonian patients exhibit akinesia (inability to initiate movement), hypokinesia (reduced movement), and bradykinesia (slowness of the movement itself). (All these phenomena will be subsumed under the title akinesia.)

Rigid muscles may contribute to akinesia, but they are not the cause. This is evident from the effects of both stereotactic surgery and treatment with levodopa. Stereotactic thalamotomy is an effective means of abolishing contralateral rigidity (and tremor), but does not relieve akinesia, which progresses to cause increasing disability. Levodopa therapy, on the other hand, dramatically relieves akinesia, even in those who have undergone previous stereotactic surgery.

The akinesia of Parkinson's disease represents a major negative symptom and, as such, probably gives the best clue as to what goes wrong with basal ganglia function in that condition (1,2). However, analysis of the pathophysiology of akinesia has proved difficult. One is dealing with higher-order motor function in all its complexity.

Normal Movement

Two approaches have been employed to investigate events in the brain before the initiation of movement in Parkinson's disease; (a) the study of reaction times, and (b) the investigation of the Bereitschaftspotential.

REACTION TIMES

Patients with Parkinson's disease, on average, take longer than normal to move to an external visual, auditory, or peripheral kinesthetic stimulus (3–5). Unlike normal subjects, patients with Parkinson's disease who know what is required seem less able to use advance information to initiate the response to a simple cue.
Normals knowing what is required can select and prepare the movement to deliver it more quickly than parkinsonian patients. However, the extent of impairment of simple reaction times does not correlate closely with clinical akinesia.

The difference between simple and choice reaction times (central delay) gives some indication of the ability to formulate the correct response to a stimulus to move. The central delay is thus a measure of the time taken to select the correct motor programme to respond to the choice signal. The overall conclusions from such experiments (5,6) is that the difference between simple and choice reaction times in patients with Parkinson’s disease is no greater than normal. Furthermore, parkinsonian patients respond to the choice correctly. Bloxham et al. (6) point out that the major deficit in Parkinson’s disease is the prolonged simple reaction time, whereas choice reaction times are similar to normal. This can be interpreted to indicate a failure to prepare a movement known to be required in advance, a failure to hold that movement in store, or a failure to deliver the prepared stored motor programme.

Patients with Parkinson’s disease, under some circumstances, can make use of a warning before the imperative cue to improve reaction time in the same way as normal subjects (4,7). This indicates that they can select the correct motor programme in response to the warning for subsequent delivery when the instruction to move occurs. They can also correct wrong moves when the cue is false (8,9), albeit more slowly than normal. This also suggests that parkinsonian patients do prepare motor programmes in advance of a stimulus to move. The sum of evidence suggests that the delayed response to a simple trigger to move is due to failure to hold or deliver the stored motor programme with normal speed.

Patients with Parkinson’s disease can learn motor tasks and can formulate an “internal plan” of a motor sequence (10). Despite earlier claims to the contrary, they can also take predictive motor action in a learned motor task (6,10). Thus, having learned a new motor sequence to track a target, they can move in advance of their perception of the target to anticipate its track, albeit less successfully than normal subjects (11,12). In visual tracking of known targets, parkinsonian patients exhibit greater error than normal, and are more dependent on visual feedback.

The ability to deliver motor commands in advance of perception of a target means that parkinsonian patients must be able to select a sequence of motor programmes in preparation to move. However, they are still more heavily dependent on visual information than normals; if the target is made to disappear, they often fail to execute the known required movement (13,14).

These data suggest that patients with Parkinson’s disease can: (a) correctly perceive the stimulus to move; (b) take appropriate action by selecting the correct motor programme to prepare for movement; (c) learn new motor tasks and try to deliver appropriate motor programmes in advance of any feedback; (d) but either cannot hold, or cannot deliver, these prepared motor programmes in response to their established internal plan of action; (e) as a result, they are less successful in employing predictive motor action, and are more dependent on visual feedback to achieve movement.

A crucial question is whether parkinsonian individuals cannot store and hold selected motor programmes, or whether they cannot deliver those held in store.
Unfortunately, too little is known about motor "memory," or motor programme storage and retrieval to comment further.

BEREITSCHAFTSPOTENTIAL

Several lines of evidence emphasise the role of the supplementary motor area (SMA) in the breakdown of motor control in Parkinson’s disease. Anatomical studies of primate basal ganglia systems show that a major portion of pallidal output is directed to the nonprimary motor areas of frontal cortex, in particular to the supplementary motor area (15,16). In humans, cerebral blood flow studies have suggested that the SMA is crucial to the organisation of sequential hand movements (17,18), and an abnormality of sequencing hand and elbow movements has been demonstrated in a patient with unilateral SMA damage (19). A similar disturbance of sequenced hand and elbow movements has been demonstrated in patients with Parkinson’s disease (20) (see Sequential Motor Actions in Parkinson’s Disease, below).

Kornhuber and Deecke (21) suggested that the activity of the SMA may be studied by averaging surface electroencephalographic (EEG) activity during the organisation and performance of a self-paced voluntary movement. Such a movement is preceded by an EEG potential called the Bereitschaftspotential (BP) after Kornhuber and Deecke (21). Kornhuber and Deecke (22) and Deecke (23) argued that the BP may reflect activity in the SMA, because its maximum amplitude is at the vertex (overlying the SMA) for several different types of voluntary movement (eye, hand, arm, and foot). In a recent review, Tamas and Shibasaki (24) divided the BP into an early and a late component. The late component is lateralized to the hemisphere contralateral to the limb movement and is thought to represent activity in the motor cortex (25), perhaps due to input from the dentatothalamic tract (26,27). The early component is not lateralized and reaches its maximum amplitude over the midline. Boschert et al. (28) concluded that it is the early BP, rather than the late component, which reflects SMA activity.

If the main functional target area for pallidal output is the SMA, one would anticipate an abnormality of the BP in Parkinson’s disease and the abnormality might selectively affect the early BP.

Initial BP studies from different laboratories suggested that there was an abnormally small BP in Parkinson’s disease (23,29). However, recently certain methodological difficulties in this earlier work have been reassessed (30,31); it has been suggested that the apparently smaller BP observed in Parkinson’s disease could have arisen as a result of problems triggering the averager due to the gradual onset of electromyogram (EMG) activity in akinetic patients (32). In addition, it has become clear that the amplitude of the BP is critically dependent on age. Barrett et al. (33) and Deecke (23) found that older normal subjects have a smaller BP than do younger control subjects. Consequent on improved triggering and the use of older normal subjects for comparison, Barrett et al. (32) have suggested that no difference exists between the BP of normal old subjects and patients with Parkinson’s disease.

Treatment of patients with Parkinson’s disease may also confound BP studies.
Dick et al. (34) pointed out that the oral administration of levodopa alters the amplitude of the BP, particularly of the early BP, in both patients with Parkinson’s disease and normal subjects. Some of the patients studied by Barrett et al. (32) may have been receiving drug therapy. This would have caused an increase in the early BP component, which could have hidden any decrease in its size. When drug administration was withheld, Dick et al. (34) found, like Barrett et al. (32), that the peak BP negativity of patients with Parkinson’s disease was normal for simple finger extension movements; however, unlike Barrett et al. (32), Dick et al. (35) and Simpson and Khuraibet (36) found a smaller early component of the BP in patients with Parkinson’s disease.

The decreased amplitude of the early BP from midline leads in patients with Parkinson’s disease may be due to impaired SMA function. However, there is as yet no definitive proof that the early component of the BP arises in SMA.

With regard to the later lateralized components of the BP, the results in Parkinson’s disease show a more prominent negativity than normal in this late phase of the BP.

What then does the defective early BP and the prominent later negativity reflect in terms of the breakdown of movement control in Parkinson’s disease? Goldberg (37) has suggested that there are two distinct systems for the control of voluntary movements. The first is a predictive, feedforward mode whereby the subject decides “internally” the format of a desired movement. The second is a responsive mode whereby the subject responds to environmental cues, which themselves determine how a motor response is organised. On the basis of embryological, anatomical, and modern neurophysiological evidence (primate lesion studies, cortical single unit studies and blood flow studies), Goldberg (37) suggests that these two systems are anatomically distinct; the former involves the medially situated SMA; the latter involves the dorsolateral prefrontal area (PMA).

Connectivity studies in primates suggest that the major input to SMA is ultimately derived from the basal ganglia (15,16), whereas the dorsolateral PMA has a significantly greater input from areas of sensory cortex, particularly the visual cortex (38). It is tempting to suggest that patients with Parkinson’s disease rely on the dorsolateral system of motor control because their medial system is defective. This would be consistent with the inordinate dependence of parkinsonian patients on visual information for the successful initiation and performance of a variety of movements.

This model of SMA and premotor area function permits an interpretation of the BP findings. The impaired early BP may reflect poor cortical activation of the medial predictive system, involving SMA and basal ganglia, used to generate internally generated movement. The augmented negativity in the late phase of the BP may reflect compensatory overactivity of the lateral externally responsive system, involving the dorsolateral PMA and visual (and other) sensory systems.

**SIMPLE LIMB MOVEMENTS**

When a patient with Parkinson’s disease attempts a self-paced, simple fast movement of one joint of the upper limb, the movement is executed slowly (3).
reaction paradigms it is the movement time, rather than response time, that is most compromised in Parkinson's disease (5).

A normal person who executes a simple fast or ballistic movement shows a stereotyped pattern of EMG activity in agonist and antagonist muscles (accompanied as necessary by similarly stereotyped activity in synergists and postural fixators). The agonist fires first to generate the impulsive force required to produce the fast movement; the antagonist then fires to provide any required braking force; the agonist may then fire again to provide any required final correction. Normal subjects make larger movements with faster velocities. Movement of increasing amplitude and velocity are achieved by increasing the size and, to a lesser extent, the duration of the first agonist burst of EMG activity. The parkinsonian patient activates agonist and antagonist muscles in the correct sequence and brings in appropriate anticipatory activity in postural muscles (39). In other words, the selection of muscles and the relative timing of their activation is correct, so the basic form of the motor programme is preserved.

The reason why a fast ballistic movement in Parkinson's disease is slow is that the force of the initial impulsive activity in the agonist is inadequate. This is because the size of the initial EMG burst in the agonist is reduced (40). This is true even for distal limb movements involving no postural support (41).

The size of the first agonist burst can be graded to make larger movements in parkinsonian patients (42), but it is consistently underscaled for the amplitude of movement intended. As a result, the velocity of the resulting movement is too slow and the displacement achieved undershoots the point of aim. The latter is finally reached by a subsequent series of additional small bursts of EMG activity, which adds to the overall delay in achieving the required movement. Parkinsonian patients, unlike normals, tend to make movements of different size at the same velocity (3,40).

As a consequence of their inability to produce large agonist bursts to initiate movement, parkinsonian patients are particularly impaired in making high-velocity movements (11). Normal subjects make an initial fast movement to within ±20% of the target position, and then make a small number of corrections to hit the point of aim. In contrast, parkinsonians creep by small steps towards the required position, and appear inordinately dependent on visual information to achieve their objective (11). It is as if parkinsonian individuals cannot employ accurate preprogrammed or “open-loop” ballistic movements without the need for feedback, but are constrained to operate in a “closed-loop” mode requiring visual information (11,13,14).

Sanes (43) has extended these observations on movement accuracy by assessing how well patients with Parkinson's disease adapt to Fitts' law (44). In normal subjects executing rapidly alternating movements, Fitts showed that movement time varied systematically with changes in movement amplitude and target width, providing accuracy was held constant. Movements that are easier, because they are smaller or directed to larger targets, are performed more rapidly. Sanes (43) found that parkinsonian patients had exaggerated difficulty in coping with larger movements (target size held constant), or smaller target sizes (target separation...
held constant). These results are consistent with a deficit in executing high-velocity movements, but also point to the conclusion that the greater the difficulty in the task, requiring more movement accuracy, the greater the problem for the parkinsonian patient.

Failure to scale the initial agonist activity appropriate to the intended amplitude and velocity of movement is undoubtedly a fundamental abnormality of limb motor control in Parkinson’s disease. Parkinsonian individuals appear unable to decide in advance, or to deliver, the size of agonist muscle activity required to generate fast large movements to the target they know they wish to achieve.

Is this, however, sufficient to explain all of the akinesia so characteristic of that illness? There are good reasons to think not. For example, there is no close correlation between the extent of slowness of such simple ballistic movements of a single joint and the degree of clinical disability. Patients who are remarkably mobile when taking dopaminergic therapy show only modest improvement in their capacity to execute such simple movements, compared with their performance when drugs are withdrawn and they are dramatically immobile (42).

**COMPLEX LIMB MOVEMENTS**

Motor behaviour in daily life demands much more complex motor control than that required for the regulation of simple single movements of one joint. Many goal-directed motor acts require the performance of a series of movements, sequentially and/or simultaneously, at different joints and of different limbs. For instance, to drink we need to advance one or both arms to the cup, grasp it, then lift it to the lips, before engaging the sucking and swallowing mechanisms. Each of these actions involves an individual motor programme, but the whole act requires appropriate sequencing and superimposition of the individual motor programmes into a coherent motor plan, so as to achieve a smooth and accurate overall performance.

Patients with Parkinson’s disease exhibit many problems in executing complex motor actions such as repetitive, simultaneous, or sequential motor acts (45). Commonplace clinical observation reveals that parkinsonian patients have particular difficulty in repeatedly tapping the finger on the thumb or the ball of the foot on the floor. The initial movement is slow and undershoots, but subsequent repetitions progressively decrease in amplitude and velocity until the movement may cease. There is a progressive decrease in the size of letters in micrographia. More complex motor acts, involving switching from one to another motor programme in a sequence, or the execution of two different motor acts with opposite limbs, are obviously compromised (46).

These clinical observations suggest that there is something more to the motor deficits of Parkinson’s disease than just the underscaling of the initial agonist burst. For this reason, analysis has turned to the examination of simultaneous and sequential movements. The BP preceding such simultaneous and sequential movements is larger and longer than that before similar simple movements (47), suggesting greater activation of premotor cortical areas with complex movements.
SIMULTANEOUS MOTOR ACTIONS IN PARKINSON'S DISEASE

The basic paradigm that has been used for testing the execution of simultaneous voluntary movements is as follows: Patients and controls are asked to perform a fast isotonic elbow flexion (flex) and an isometric opposition of the thumb to the fingers against a strain gauge to exert a force (squeeze), separately or simultaneously. Duration of the elbow flex movement time is measured from the velocity signal; duration of the finger/thumb squeeze is measured from the force signal. Starting and target positions, as well as the elbow position and hand force, are displayed to the individual on an oscilloscope screen. The individuals are asked to undertake (a) elbow flex by itself, (b) hand squeeze by itself, or (c) both movements simultaneously (squeeze and flex).

The results may be summarized as follows (48).

1. The movement times of flex and squeeze vary from trial to trial in each individual, but there is no correlation between them in the simultaneous flex-and-squeeze task, in either normal people or parkinsonian patients. This indicates that the complex task is executed by superimposition of two separate motor programmes, rather than by the use of a new single generalized motor programme (49,50).

2. The separate individual movements of flex or squeeze with the same arm are performed more slowly by the parkinsonian patients than by the normal individuals.

3. When the two movements are performed simultaneously with the same arm (flex and squeeze), there is no change in the duration or speed of either movement in normal individuals compared with their performance of each movement by itself.

4. However, in the parkinsonian patients there is an additional slowness of both movements when performed together with the same arm, compared with that seen for the separate movements alone.

5. Similar results have been obtained when patients and controls squeeze with one arm but flex with the opposite limb. However, the extra slowness of the movements when done together by the parkinsonian patients is less marked than when the same arm is used for both tasks.

The conclusion is that patients with Parkinson's disease have added difficulty (expressed as extra slowness) when they try to execute two motor programmes simultaneously, especially with the same arm. In other words, they have added difficulty superimposing two motor programmes simultaneously for separate joint movements, over and above the difficulty that is evident when they execute either movement by itself.

SEQUENTIAL MOTOR ACTIONS IN PARKINSON'S DISEASE

The same paradigm has been used to test sequential motor action (20). Patients and controls are instructed to (a) squeeze with the right hand, then flex the right elbow, and (b) squeeze with the left hand then flex with the right elbow. They are
given two instructions: (a) move as rapidly as possible, and (b) start the second movement immediately after the end of the first. Their performance on these ipsilateral and contralateral sequential tasks has been compared with their performance when they undertake the individual movements by themselves. In addition, the interval between the onset of the first movement and that of the second (the interonset latency, IOL), and the interval between the termination of the first movement and the onset of the second (the pause) also has been measured, as has the total time taken to complete both movements.

The results may be summarized as follows (20).

1. As with simultaneous movements, there is no correlation between the times for squeeze and flex in sequential movements, or between movement times and the pause between movements, in either normal individuals or parkinsonian patients. Again this indicates that the complete movements of squeeze-then-flex are executed by two separate motor programmes.

2. The separate single movements are slower in the parkinsonian patients than in the control individuals, and there is a further decrease in speed in the parkinsonian patients when the two movements are executed sequentially. Similar results have been observed for the bilateral squeeze with the left hand, then flex with the right.

3. The IOL between the beginning of the first squeeze and the second flex movements is automatically chosen at -244 ms by normal individuals (51). The first movement is completed in ~150 ms, so there is a pause of some 70–100 ms before the second movement is started. This pause occurs despite the instruction to execute the second movement as soon as possible after the first. When normal subjects are asked to vary the interval between the two movements, by making it shorter or longer at will, it transpires that at IOLs of <~200 ms the speed of the second elbow flex decreases; the shorter the IOL <200 ms, the slower the second movement. This is interpreted to indicate that normal individuals automatically switch from one motor programme to another with an optimal minimal delay of a little longer than ~200 ms, to execute the second movement with maximum speed (51). This optimal interval between movements corresponds to the known maximum rate of tapping movements of the hand at ~5 Hz.

4. Patients with Parkinson’s disease find it difficult to learn the sequential task of squeeze-then-flex. When they have done so, the IOL is longer than normal (~425 ms), as is the pause between the two movements (~171 ms). If they try to execute the two movements with IOLs of <400 ms they find it extremely difficult; when they succeed the speed of the second movement declines progressively (20,52). In other words, the optimum interval between movements, so as to maintain the speed of the second movement, is considerably longer in the parkinsonian patients than in the controls.

Patients with Parkinson’s disease thus have added difficulty when attempting to execute two motor programmes sequentially with the same or opposite arms. They perform the individual movements in the sequence more slowly than when each is carried out alone, and the interval between the two movements is prolonged. It turns out that the extra slowness in executing such a complex motor
sequence is more closely related to the degree of clinical bradykinesia than to the slowness of single movements.

Berardelli et al. (53) have obtained similar results in a study of the ability of patients with Parkinson's disease to execute the fast, complex arm movements required to draw triangles and squares on a writing tablet. The movements were accurate, but the time taken to trace the geometric figures, and the pauses at the angles, were prolonged. They concluded that the parkinsonian's difficulties in generating two joint ballistic movements were due to problems in running the motor programmes required to generate complex arm trajectories.

CONCLUSIONS

The studies reviewed here have shown that damage to the basal ganglia in Parkinson's disease causes (a) slowness of single simple arm movements with one joint, and (b) extra difficulties in the execution of simultaneous or sequential complex arm movements with two joints.

Can the first abnormality explain the second? Is the difficulty that patients with Parkinson's disease have in single movements sufficient to explain their problems with movement sequences?

The more recent findings presented here suggest that the slowness of simple single movements (due to an underscaling of the size of the first agonist EMG burst) is not in itself sufficient to explain the added problems encountered in complex simultaneous and sequential motor acts. Not only does the performance of two movements expose an extra slowness of each component, but in the sequential task there is also extra delay between the two movements in parkinsonian patients compared with normal individuals.

It might be predicted that the extra problems encountered with two motor programmes would become even more evident if even longer sequences involving three or more motor programmes were examined. Indeed, the extra slowness and delay of the next movement in a long sequence might become more evident as the sequence progresses, to produce the progressive fade and collapse of complex repetitive or sequential motor actions so characteristic of Parkinson's disease. As suggested earlier (2,46), "each motor programme in itself is imprecise, so it is not altogether surprising that, when repeated, the whole sequence is in error. However, the details of the impairment of repetitive action suggests that there is more than this. The critical feature is that, as the sequence is continued, the individual movement or motor programme progressively degrades. The time to initiation gets slower and the size of the movement progressively fades. Thus, the final movement in a sequence is far worse than when that individual movement is performed by itself. Repetition of the movement unearths a greater deficit than is apparent in single movements. Likewise, when two movements are made together, they are each performed much worse than if they are undertaken alone. This suggests that there is a fundamental breakdown in the capacity to run the sequence of movements that comprises a motor plan. In particular, there appears to be a major problem in switching from one motor programme to another. In

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other words, the sequence of the motor plan does not run smoothly in Parkinson’s disease."

Such problems might explain many of the characteristics of parkinsonian akinesis. For example, the fatigue of repetitive tapping of fingers or feet, or the progressive nature of micrographia or hypophonia, might all represent the compound effect of difficulty in generating long sequences of movement.

The deficit in sequencing arm movements seen in patients with Parkinson’s disease leads to the following proposition. Perhaps the motor basal ganglia are more concerned with directing what happens to the next movement in a sequence than with the initial movement.

It has been difficult to correlate the pattern of single-unit discharges in the basal ganglia of subhuman primates with a single motor act (54). Single units in the output zones of globus pallidus interna and substantia nigra pars reticulata show somatotopic organization, with correlation between cell discharge in localized regions and active movements of specific body parts. However, such neuronal discharges do not clearly or consistently precede the first EMG changes in muscles; overall, changes in neuronal discharge seem to occur later in the basal ganglia than in the motor cortex.

This is not surprising, because the basal ganglia receive a readout of the motor cortex output that drives the movement itself, via corticostriatal pathways from sensorimotor cortex to putamen. Putamen units (and probably those of the globus pallidus) fire in relation to the direction and amplitude of the movement (rather than to the activity in the individual muscles involved), suggesting that these basal ganglia areas monitor parameters of the movement. The suggestion is that this information is used to set up the premotor areas to select the correct parameters for the next movement. To test this hypothesis, those who record the activity of basal ganglia units in awake performing primates would need to correlate such neuronal discharge with the next movement the animal performs, not with the immediate obvious motor action as has been done so far.

How would such a theory explain the slowness of a simple single one-joint movement? Why do parkinsonian patients underscale the size of the first agonist EMG burst in relation to the amplitude and velocity required to execute the desired movement? One suggestion is that such simple movements are defective because they must be based on what has gone before. In other words, the correct setting of the parameters of the motor programme required to execute even a single movement must depend on information about the motor state before its execution. If the readout of existing motor activity from sensorimotor cortex delivered to the basal ganglia is mishandled, the output of the basal ganglia to premotor areas might misdirect the selection of parameters for even a simple subsequent single movement.

Such a hypothesis has the attraction of encompassing all the defects of movement demonstrated in Parkinson’s disease within one basic abnormality, namely a failure of basal ganglia direction of premotor areas to select the correct parameters for subsequent motor programmes. As a result, the individual motor programmes necessary for complex actions are specified incorrectly, and the linkage of motor programmes into a unified motor plan collapses.
REFERENCES

SLOW MOVEMENT IN PARKINSON’S DISEASE