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## Timing Control in Parkinson's Disease

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### 1. Introduction

Internal generation and modulation of timing may be an important underlying yet unrecognized mechanism of many symptoms in Parkinson's disease. It has been recently debated whether the basal ganglia or cerebellum might contribute to overall timing control during movement execution. As seen in basal ganglia disorders such as Parkinson's disease (PD) and Huntington's disease (HD), timing dysfunction is present and contributes to the ability to control everyday movements. In some cases, timing deficits may be associated with very debilitating movement impairments such as speech festination, balance control (falling) and freezing of gait.

One interesting example is how the 'shuffling gait' that is typical of PD can be improved with visual step cues spaced appropriately apart, even when dopaminergic medications are withdrawn. While this is a well known fact, it is important to consider whether the observed improvements in stride length may be the result of a spatiotemporal trade-off (Morris et al., 2001; 1994b). That is, while a larger stride length can be achieved with the use of visual step cues, a subsequent timing deficit (i.e. gait rhythmicity becoming even slower) may also result. However, unlike spatial parameters of movement like step length, timing dysfunction is resistant to the typical dopaminergic treatments used in Parkinson's disease (Blin et al., 1991). Thus, research has argued that spatiotemporal trade-off may be the result of a shift of focus to specific spatial components of movement (Georgiou et al., 1993; Zijlstra et al., 1998), while temporal control is simultaneously sacrificed. Alternatively, the inability to modulate timing during movement may be part of an underlying deficit in the ability to process interoceptive sources of feedback that guide the control of movement. If this were the case, then internal timing would be an important direction for therapeutic interventions which might have the potential to improve motor symptoms in PD.

Within this chapter we will examine timing deficits in upper limb repetitive and coordinated movements and also timing during gait in PD. Further, to evaluate how attention and processing of sensory feedback may contribute to timing control, we will take a close look at new methodologies to investigate timing control during gait in Parkinson's disease. Specifically we will evaluate the ability of individuals with PD (while "On" and "Off" their dopaminergic medication) to modulate spatial and temporal components of gait in self-paced, and temporally-cued conditions using an auditory stimulus, and further to determine whether this modulation is dependent on the dopaminergic system. The concept of evaluating timing error will also be introduced as a potential way to better understand

the motor symptoms of PD. The results of these studies will be discussed with respect to how the timing deficits might be an important underlying factor that contributes to the typical motor symptoms seen in Parkinson's disease.

## 2. Timing during upper limb movements

Control of upper limb movements is essential for many activities of daily living, and represents an area of concern for individuals with Parkinson's disease (PD). Many of the well known motor symptoms including tremor, rigidity and bradykinesia have an associated timing control deficit that has the potential to influence the execution of upper limb movements. For example, the dysfunctional motor output that leads to co-contraction of agonist and antagonistic muscles and hence the symptom of rigidity, has the potential to influence any sort of rhythmic movement behaviour that requires timing. Functionally, timing deficits could be reflected in upper limb tasks like typing or handwriting, where it has been commonly reported that 'hastening' (i.e. increased temporal frequency of tapping) is necessary to synchronize rhythmic hand movements requiring a frequency greater than 2Hz with tremor frequency of the hands (Freund, 1989).

It is also notable that many of the standard upper limb clinical tests, rate slowness as the low end of the severity spectrum while greater timing variability (in finger tapping, opening and closing hands, and wrist pronation-supination) represents an increased severity of motor symptoms. In these sorts of tests, the more the timing variability, the greater the severity of motor symptoms is rated.

As early as 1954, Schwab, Chafetz and Walker demonstrated that individuals with PD lacked the ability to maintain two concurrent voluntary motor activities. These observations were made during a rhythmic ergogram-squeezing task with one hand while connecting points on a triangle with the other. Results of this study indicated that the PD participants could do each task very well in isolation, but were unable to maintain both tasks at the same time. They concluded that individuals with PD have difficulty internally regulating continuous rhythmic movements, although the possibility that cognitive resource limitations associated with dual tasking needs to be considered. Since then, internal timing deficits have been commonly reported during upper limb movements in PD (Freeman et al., 1993; Nakamura et al., 1978; O'Boyle et al., 1996; Pastor et al., 1992; Yahalom et al., 2004; Ziv et al., 1999).

### 2.1 Timing during upper limb tapping movements

One of the simplest movements to evaluate clinical timing deficits is tapping. Due to its continuous rhythmical nature, timing deficits would be easily identified. It also the ideal type of clinical test for identifying unilateral deficits, since slowing of tapping frequency and increased in tapping variability are easy to recognize. O'Boyle *et al.* (1996) examined self-paced finger tapping in PD and found that relative to control participants, patients were unable to maintain their own self-selected frequency. Although, PD is typically associated with bradykinesia, they demonstrated that PD participants tapped faster during the self-paced tapping task when compared to healthy control participants. Additionally, they demonstrated that PD had a higher timing variability during the tapping task, which is interesting in itself, since self-paced timing might be considered the optimal state for the motor system to internally generate movement. Similarly, Pastor *et al.* (1992) examined rhythmic flexion-extension movements of the wrist and identified less accurate timing during movements at 2 and 2.5 Hz (but not slower required frequencies) in PD relative to healthy control participants.

In addition, they demonstrated that individuals who had moderate or severe PD were less accurate at all frequencies. The authors suggested that deficits were related to impairment in an internal timekeeper, and it could be argued that progressive neurodegeneration continues to further degrade timing control. This has been supported by other rhythmic unimanual tapping research in PD (Nakamura et al., 1978; Ziv et al., 1999).

Perhaps one of the most thorough evaluations of internal versus external timing control during upper limb tapping was published by Yahalom *et al.* (2004). Their group investigated a number of controlled frequencies that were both internally and externally generated. In this set of studies, self-paced tapping would have been considered as a baseline, and internally-generated tapping would have been considered the 'as fast as possible' frequency of tapping. External timing would have been evaluated by modifying the frequency required by an external auditory metronome. Results revealed that PD had difficulty with internally generated fast rhythmical movements (i.e. slowed tapping) but externally or self-paced tapping was preserved. In contrast to other studies, these findings might be difficult to interpret since self-paced movements might also be argued to be internally driven movements, whereas the deficits identified during fast rhythmical tapping movements might simply be the influence of the cardinal symptom of bradykinesia. One potentially interesting method of evaluating these sorts of deficits further, would be to externally pace movement at a pace that is faster than the internally-generated fast pace. If participants are still unable to match the fast required frequencies, it might be concluded that attempting to distinguish between externally and internally driven movements would be pointless. The other potential method to evaluate timing control would be to evaluate timing error (or timing accuracy) during the tapping, relative to the timing of the metronome. This alternative might be argued to be a better indicator of control, and will be discussed in the upcoming section on timing control during gait.

The other benefit of evaluating timing control in a motor skill as simplistic as tapping, is that unimanual tapping can easily be combined with other tasks. For example, unimanual tapping can easily be combined with the contralateral limb to evaluate bimanual finger tapping, or in some cases, lip tapping in internally and externally-paced situations in PD (Konczak et al., 1997a). In these experiments, results indicated that PD performed all tasks with reduced tapping amplitude and an increased variability. And that this performance was largely influenced by hastening. Their overall conclusion was essentially a replication of other researchers who argue that deficits in PD are associated with an internal cueing deficit. Oddly, since external cueing did not improve these impairments, the authors concluded that external cueing may have further negative effects of repetitive movements (Konczak et al., 1997a), although it might be important to evaluate how dopaminergic treatment response influences timing control during both internally and externally driven rhythmic movements, in order to make stronger conclusions on whether or not the basal ganglia are associated with internal versus external timing.

## 2.2 Timing during sequential upper limb movements

Generally research suggests that movement execution deficits observed with PD become even more pronounced when they involve coordination of multiple sequences of limb actions (Benecke et al., 1987). In a study involving a two-segmented movement, while individuals with PD displayed a marked delay between movement segments, the movement kinematics were similar to those of healthy control participants (Weiss et al.,

1997). One interpretation of these results is that individuals with PD have difficulty timing a switch between the sequential steps of a motor program, while others might argue that online integration of upcoming movement might represent a deficit in the ability to utilize sensory information in a closed-loop fashion to control movement. In a similar study Roy et al., (1993), observed a marked deficit during movement when participants with PD were required to produce different sequences of movements, as opposed to repeating the same sequence of movement repetitively. This finding would suggest that the difficulty making transitions between motor steps are accentuated in situations where different actions must be planned to complete the movement sequence (Brown & Almeida, 2011).

In contrast, Curra et al.,(1997) argue that individuals with PD may encounter a delay in the timing of movement execution when required to process a greater quantity of information per unit of time. In their sequential line drawing task, Parkinson's patients encountered more difficulty than healthy control participants in completing a full drawing sequence. However, when it was required to produce each segment with a step-wise cueing of the drawing sequence, PD patients were able to improve their performance. The results of these studies support the notion that individuals with PD may suffer from an attentional overload when selecting and preparing appropriate motor steps required for executing a movement sequence (Brown et al., 1993; Jones et al., 1994; Robertson & Flowers, 1990), while timing control itself is not impaired.

Sequencing difficulties of individuals with PD have also been documented in bimanual situations. Horstink (1990) noted that individuals with PD were unable to coordinate two separate plans of action for the upper limbs. While this perspective supports the idea of attentional overload, it may be of further interest since other studies of interlimb coordination have demonstrated that coordination deficits are not apparent when the movement tasks for each upper limb are related to a common goal. For example, Stelmach used a discrete bimanual targeting task in in-phase and anti-phase conditions of varying distances (Stelmach & Worringham, 1988). Unlike the findings of studies with different motor tasks for each limb, their results indicated that individuals with PD were able to coordinate movements as a single unit, and that deficits beyond typical bradykinesia were only present for asymmetrical movements. A detailed review of timing deficits that have been identified during bimanually coordinated movements is discussed further in the next section.

A number of studies have since confirmed that interlimb coordinated movements that involve a common goal between the limbs are less impaired in PD. This would suggest that strategies that help create a single movement goal for coordinated actions between two limbs may have important benefits in working toward improved coordination of timing between limbs. This may have even more important implications for basal ganglia disorders that are primarily or initially unilateral in nature, such as hemi-Parkinsonism, hemiballismus and even unilateral stroke of the basal ganglia. In therapeutic settings, important benefits might be achieved if interventions take into consideration coordinated movements that require both limbs to work together toward a common goal.

### **2.3 Timing during coordinated upper limb movements**

A wide variety of deficits have been found in individuals with PD during bimanual coordination. The most common measures used to describe coordination impairment are the accuracy and variability of the relative phase relationship between the upper limbs. Coordination accuracy and variability were found to be worse in PD during both



symmetrically performed (in-phase) movements while greater impairments were identified during non-symmetrical, unidirectional (anti-phase) movements (Serrien et al., 2000). PD were also found to have poorer coordination accuracy and greater variability during anti-phase (but not in-phase) during a medial-lateral sliding task (see Figure 1) and a pronation-supination task of the forearms (Almeida et al., 2002; Byblow et al., 2000).

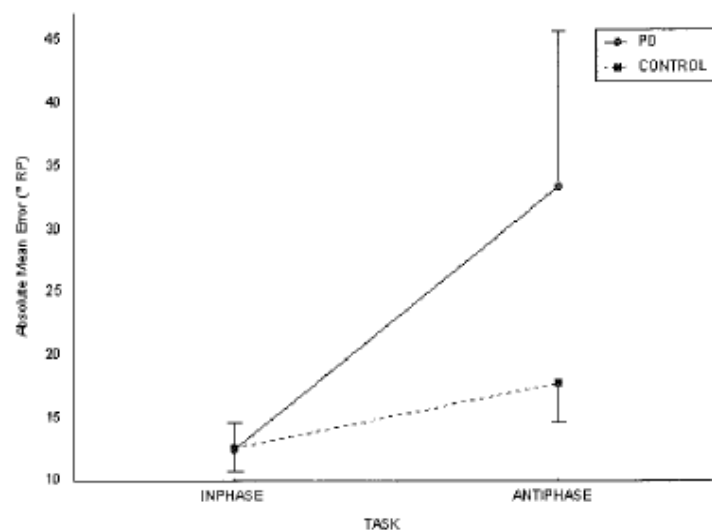


Fig. 1. Coordination accuracy as represented by absolute mean error in PD and healthy age-matched control participants (Almeida et al., *Movement Disorders*, 2002)

It is interesting to note however, that these results may be dependent on temporal parameters and requirements of the task. Some researchers would argue that timing demands might impose movement coordination to be dynamically self-organized. For example, Byblow and colleagues failed to identify coordination deficits in PD (Byblow et al., 2002), but it was proposed that this was a result of individuals with PD selecting a preferred frequencies of 1.02 Hz compared to a self-selected 1.56 Hz in healthy controls during a pronation-supination task. Similarly, no differences in relative phase were seen using a frequency of 0.6 Hz with wrist flexion-extension movements (Byblow et al., 2003). Together these experiments suggest that an externally-driven demand imposed by a fast paced metronome is critical to establish coordination deficits. Coordination performance has also been investigated using the number of successful trials. Individuals with PD were shown to have more unsuccessful trials during in-phase at high frequencies and anti-phase at low frequencies than healthy age-matched controls during bimanual circular drawing (Ponsen et al., 2006).

Coordination (i.e. accuracy and stability) involves the temporal and spatial coupling of the limbs (Swinnen, 2002). However (as previously mentioned), the individual assessment of amplitude and frequency are important to consider in bimanual coordination in PD due to the possible contributions of motor symptoms including bradykinesia (slowness of movement) and hypometria (reduced size of movement) (see section 2) to voluntary movement. In addition to coordination deficits, impairments in amplitude and frequency have been documented in individuals with PD while performing bimanual tasks. Smaller amplitudes were seen during both in-phase and anti-phase at a frequency of 1 Hz (Swinnen et al., 1997). During symmetrical (in-phase) triangle drawing, smaller amplitudes were seen but only symmetrical patterns were used (Swinnen et al., 2000). Smaller amplitudes of

movements were found predominantly with increasing the frequency from below to above the spontaneous transition frequency (Byblow et al., 2002). More variable amplitude was seen across all conditions for individuals with PD (Serrien et al., 2000). Amplitudes were found to be more variable in symmetrical triangle drawing (Swinnen et al., 2000). However, conflicting evidence has also found that amplitudes were not more variable during a cyclical flexion-extension task (Swinnen et al., 1997). The reason for this finding is unclear but it was suggested that the novel task used in this experiment could have resulted in variability of amplitude to be high across all participants.

Timing deficits as represented by a failure to follow a required frequency of movement has been even more commonly found in individuals with PD during bimanual coordination tasks. The frequency of movements in PD participants was found to be slower than healthy controls (see Fig. 2) only at a frequency of 1.75 Hz but not at 0.75 or 1.25 Hz (Almeida et al., 2002). Longer cycle durations were found in PD participants either when both arms moved 80 degrees or when one moved 80 while the other moved 40 degrees but not during movements of 40 degrees (Serrien et al., 2000). Longer cycle durations were also seen during both in-phase and anti-phase at 1 Hz (Swinnen et al., 1997). During symmetrical triangle drawing, longer cycle durations were seen with a goal of 1.5 seconds per cycle (Swinnen et al., 2000). As such, there may be value to evaluating error in ability to follow a required frequency. This notion will be considered during gait in more detail below.

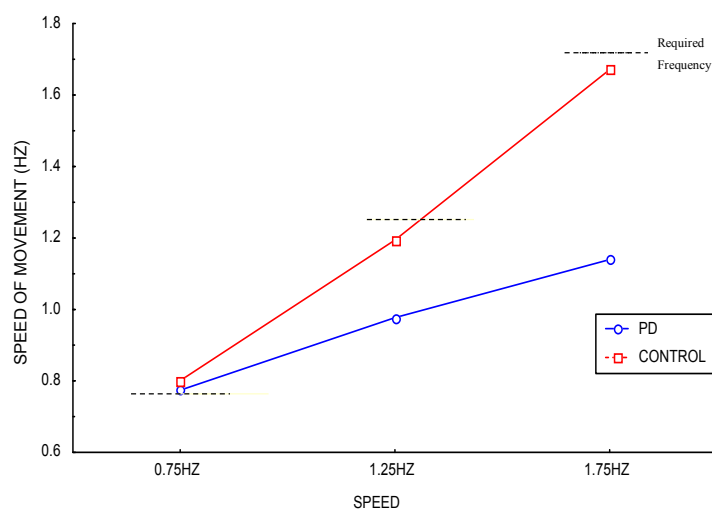


Fig. 2. Timing relative to required frequency during upper limb coordinated movements (adapted from Almeida et al., *Movement Disorders*, 2002)

In order to better appreciate timing deficits during coordinated limb actions, it may be valuable to consider what temporal demands might produce greater variability. For example, coordinated movements were found to be more variable at 1.0 Hz regardless of the complexity of required movement phase (Johnson et al., 1998). A slower and longer time to reach peak velocity as well as a longer time to reach peak negative and positive acceleration was seen in PD (Lazarus & Stelmach, 1992). A more variable frequency was seen at higher speeds and to a greater extent during anti-phase (Ponsen et al., 2006). More variability was seen in cycle durations during a cyclical flexion-extension task (Swinnen et al., 1997) and during in-phase triangle drawing (Swinnen et al., 2000). Thus, the use of auditory feedback to augment movement timing and performance has been controversial during upper limb bimanually coordinated movements in PD. Pacing was provided from a metronome for half

of the 20-second trials during an bimanual coordination task, and no difference in coordination, speed or size of movements was seen with the metronome (Almeida et al., 2002). Similarly, no effects of auditory cueing were seen on temporal, spatial, pattern switching or coordination in a bimanual coordination task (Byblow et al., 2000). Furthermore, no differences were seen in temporally regulating symmetrical bimanual triangle drawing with or without a metronome (Swinnen et al., 2000). Based on this evidence, it appears that auditory cueing does not negatively influence coordination performance in PD. However, research demonstrated that external cues from a metronome improved accuracy and stability of bimanual coordination during in-phase coordination but caused individuals with PD to switch from anti-phase to in-phase during anti-phase trials (Johnson et al., 1998). They suggested that this may have increased the complexity of the task. However, this may also have been the contribution of increased attentional demand as proposed by Almeida *et al.* (2003). Thus, it remains unclear whether timing devices such as an external auditory metronome might negatively affect coordination performance in PD. It is suggested that externally pacing devices may increase attentional demands or affect coordination through sensorimotor integration deficits.

### 3. Gait and timing control in Parkinson's

In comparison to upper limb pointing movements where eye-hand coordination is critical to our normal experience of executing a goal-directed movement, gait may be of particular interest when considering movement deficits because the lower limbs likely require greater integration of a variety of sensory inputs that are not as visually-based. To be explicit, while vision may be important in identifying the goal of a locomotor task or to evaluate how locomotion through the environment progresses, each lower limb can be efficiently controlled by spinal circuitry without a specific dependence on the visual system to monitor the trajectory and progression of each individual step throughout gait. In fact, while the upper limb motor system develops from childhood with a heavy dependence on visual guidance for reaching, pointing and grasping movements, would revert back to a greater dependence on vision in any neurologically-impaired state. Thus, it is important to consider how timing control might be differentially influenced in lower limb (in contrast to upper limb) systems.

#### 3.1 Typical gait deficits associated with Parkinson's

Although the control of gait may be one of the motor system's most useful and versatile capabilities, the contribution of the different sensory systems in a purposeful gait task is not often considered in PD or other basal ganglia disorders. That is, while upper limb pointing studies have been used to evaluate sensory guidance of goal-directed movement (as described above), investigations of gait in PD have spent more time attempting to quantify the unusual characteristics of PD gait rather than examining similar issues during goal-directed locomotion.

Traditionally, research into the gait deficits of PD has focused on differences between PD patients "On" and "Off" their dopaminergic medications, in self-paced walking tasks. Research has well documented the responsiveness of certain gait parameters to dopaminergic therapy in PD. The most typical finding is that both velocity and step length improve with dopaminergic treatment during conditions of self-paced locomotion in PD (O'Sullivan et al., 1998). As such, these studies have been interpreted as evidence that only



spatial impairments (e.g. decreased stride length) improve with dopaminergic treatment while temporal characteristics remain unchanged (Blin et al., 1991; Morris et al., 2001), thus concluding that the basal ganglia are involved in scaling movement amplitude (Morris, et al., 1998). The assumption would be that scaling of movement amplitude may be processed through the basal ganglia/supplementary motor-premotor cortex loop, while movement rhythmicity must be controlled by other neural structures such as the brainstem, spinal cord and cerebellum. This conclusion however may be premature, since these types of experiments do not specifically evaluate how individuals with PD are able to incorporate timing cues into an on-going locomotor behaviour.

In contrast, temporal characteristics such as cadence have been demonstrated to show no specific response to medications during self-paced locomotion (Blin et al., 1991; Morris et al., 1994a; O'Sullivan et al., 1998). Since step length and gait velocity both increase in response to drug therapy, while timing (which according to physics, is the only other factor that can contribute to gait slowness) is thought to remain constant, it is not surprising that researchers have been quick to assert that the underlying mechanism responsible for gait disturbance in PD involves the scaling and regulation of stride length.

Interestingly, many of the latest studies examining individuals with PD have determined that stride length regulation may not be the only contributing factor to gait disturbance. Hausdorff and colleagues have proposed that temporal measures, and specifically their stride-to-stride variability may be critical to evaluate since they have been demonstrated to be significantly associated with an increased rate of falling in PD (Hausdorff et al., 1998; Schaafsma et al., 2003). In both of these studies, stride-to-stride variability was investigated during self-paced gait over a large sampling period (80m). Although this variability was responsive to dopaminergic medication, individuals with PD in the "On" state were still considerably more variable than healthy control participants. Increased step-to-step timing variability has also been identified more frequently in those patients who experience episodes of freezing during gait (Hausdorff et al., 2003). This may have important implications for understanding the role of the basal ganglia in the control of timing, in light of recent research that has demonstrated dysfunctional cadence in the three steps proceeding an episode of freezing (Nieuwboer et al., 2001). As suggested by Morris and colleagues, hypokinesia and freezing are aggravated by a number of different ambulatory tasks (Morris et al., 2001) and so it is important to examine other gait tasks that involve a variety of goals rather than step length modulation, in response to visual cues.

However, there are a number of research groups that have argued that gait in PD can be improved through the use of timing cues (Earhart, 2009). Thaut and colleagues (Thaut et al., 1999) have acknowledged that important differences between timing associated-rhythm and auditory stimulation through music exist, but the argument that music might lead to auditory priming of timing control is an interesting one. Researchers have pointed out the suggested benefits of dance therapies such as tango (Hackney et al., 2007) and non-partnered dance (Hackney & Earhart) in PD. Thus, the potential for timing therapy to improve motor control in PD requires further consideration.

### **3.2 Freezing of gait and timing mechanisms in Parkinson's**

Interestingly, severe gait impairments during the on-going execution of movement may also be clinically evident as freezing and are most commonly identified in the gait of individuals with PD. Clinical evaluations have revealed that 14% of impairments associated with freezing phenomena occur during movement execution rather than more common initiation

problems (Giladi et al., 1992). Each example described in the study involves a shift in the sensory feedback experience, which may have resulted in an interruption in the on-going movement pattern. Examples include difficulty changing between a climbing and normal gait when reaching the last step of a staircase; continuing gait into an elevator before the door suddenly closes; maintenance of a consistent gait pattern over a change in floor texture and, difficulty switching between forward and side-ways step patterns. Common to these cases of severe movement impairment is the requirement for coordination between the lower limbs with feedback from the visual and proprioceptive senses, which provides a rationale for an examination into gait control in individuals with PD, and it may be important to consider how timing demands might contribute to these sorts of severe gait deficits.

Recent research has identified increases in timing variability as a marker that occurs prior to a freezing of gait episode (Hausdorff et al., 2003), and this has been used to predictably identify situations in which freezing of gait might most commonly occur. For example, our own research has identified an increase in timing variability prior to an unusually narrow doorway (Almeida & Lebold, 2010), and this can be identified in only those patients with PD who experience freezing of gait. Although more research is needed on this topic, anecdotal reports from patients who experience freezing of gait, suggest that if they focus on a single goal (such as timing their steps to dance through a doorway), that freezing episodes can be overcome. And so, in order to fully appreciate the potential underlying mechanisms for gait disturbance, it is important to decipher how gait parameters are modified while attempting to achieve a locomotor goal. As we will discuss later, modulating timing relative to an external rhythm might be such a locomotor goal.

### **3.3 External cueing and gait in Parkinson's**

The most common goal-oriented locomotor task employed to evaluate gait characteristics is the ability to follow or match gait characteristics to an external stimulus. Borrowed from the practice of physical therapy, external cueing has been argued to be a useful tool to bypass deficits associated with basal ganglia dysfunction (Rubinstein et al., 2002). The most universally known example is the improvement in step length that can be seen when visuospatial cues are provided in the form of parallel line in the path of a walk (Azulay et al., 1999; Azulay et al., 1996), compared to the typical shuffling and short-stepped gait of PD. Other sensory cues have also been studied and demonstrate improvements to the cadence (rate of stepping) and overall gait velocity, as a result of auditory cueing (Howe et al., 2003; McIntosh et al., 1997; Thaut et al., 2001), in spite of the fact that cadence control has been suggested to be intact in PD (Iansek & Morris, 1997; Morris et al., 1994b). Large clinical trials are now underway that are more thoroughly investigating the use of auditory cues as a therapeutic intervention for PD (Rochester et al., 2009). In many cases, when the instructions are specific to focusing on the timing of the task, PD performance can be improved with auditory cueing (Ringenbach et al., 2009).

## **4. Neural correlates of timing control in Parkinson's**

Imaging research has implicated the basal ganglia, and specifically the putamen in the neural network involved in timing control during movement (Harrington, Haaland, & Knight, 1998; Rao et al., 1997). Interestingly, the nigrostriatal projections to the putamen are believed to be involved in the loop producing motor dysfunction in PD. These projections

are part of a feedback loop between motor cortex, striatum, pallidum, thalamus and supplementary motor cortex (SMA) (Alexander et al.,1986), and are likely involved in the internal regulation of well-practiced, repetitive movements (Almeida et al., 2003). This parallel circuit may play a vital role in the sensorimotor integration of proprioceptive feedback from the limbs with other external stimuli. Integration of proprioceptive feedback and other sensory cues may be a critical aspect of internal guidance of movement that is rarely considered. Bearing this perspective in mind, a sample PD population with a dysfunctional timing neural network might be expected to demonstrate measurable deficits in temporal variability of gait such as cadence, step time and support time when integrating an auditory timing metronome, but not in tasks involving a self-selection of pace.

4.1 An integrated approach toward understanding timing control in gait

As previously mentioned, one of the most important ways to decipher the contribution of the basal ganglia system to movement control is to evaluate motor performance in a neurodegenerative population such as PD, when the patients are in the On and Off medication states. This allows us to make inferences about how movement control changes when the dopaminergic system has an opportunity to contribute to performance. And so, while we know that spatial parameters such as movement amplitude are strongly influenced by dopaminergic status, there would be a reasonably strong rationale to evaluate how timing control might also be influenced by dopamine. Thus, some of our own research has been focused on utilizing tasks that focus on the locomotor goal of modulating or maintaining timing in a movement task.

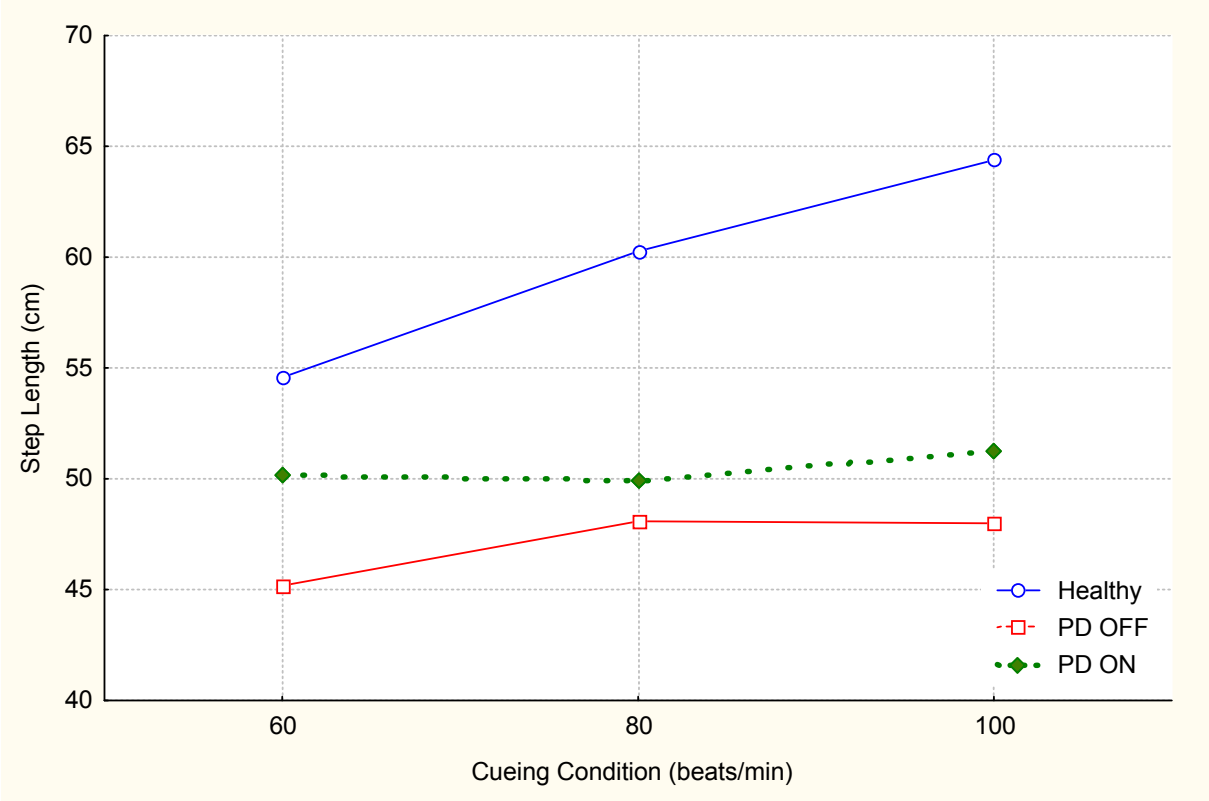


Fig. 3. Externally-paced step length for healthy participants, PD “Off “ and “On”. (adapted from Almeida et al., Movement Disorders, 2007)

Since some of our previous research has suggested that auditory timing cues may not be beneficial to upper limb repetitive and coordinated movements in PD (Almeida et al., 2002), we have been attempting to specifically evaluate the ability of individuals with PD (while “On” and “Off” their dopaminergic medication) to integrate an auditory timing cue to modulate the rhythmicity of gait. By manipulating dopaminergic status, we were able to acquire an important glimpse into whether this modulation might be dependent on dopaminergic system involvement (Almeida et al., 2007). As can be seen in Figure 3, only healthy control participants have a resulting increase in step length, when an increase in stepping frequency is prompted by an external timing device. In contrast, while PD participants show the expected step length increase (in response to dopaminergic medication), the same modulation of step length that occurs in healthy participants (when required to increase stepping frequency) does not occur.

This was the first study to demonstrate that while temporal characteristics were unaffected in the self-paced gait of PD patients (regardless of dopaminergic status and in comparison to healthy), PD patients “On” their regular dopaminergic therapy were more variable than both PD “Off” medication and healthy participants when required to integrate an external cue into the regular gait cycle. In fact, none of the timing measures (cadence, step time, double support time) yielded significant between-group differences during self-paced gait, although significant differences were apparent with the provision of external cue.

One of the most intriguing findings of this study (see figure 4a,b) was that temporal measures such as cadence, step time, and double support time identified that only the PD “Off” group now behaved similar to healthy participants, while PD “On” had greater difficulty maintaining appropriate timing in the two slowest cueing conditions (i.e. the PD “On” group performed least like the healthy age-matched participants). At 100 steps per minute, one might have expected that the behavioral response might become more automatically driven, implying less opportunity for supraspinal control. Thus, it might be expected that temporal differences between groups would be minimized. For example researchers have shown that galvanic vestibular stimulation has less of an effect at faster speeds of locomotion than during slower speeds (Jahn et al., 2000) arguing that the gain of this sensory regulation is down regulated at the higher speeds.

#### **4.2 A novel proposal for evaluating timing control in gait**

Given that timing modulation differences can be identified between the PD “On” and “Off” states, it seems important to determine whether these dopa-responsive changes are a specific issue of voluntary *control* over timing. One very common method identified for evaluating control and performance during upper limb tasks (described above) is to evaluate accuracy or error of performance. However, there have been very few applications to timing control during gait.

Thus, in order to apply measures of error to timing control during, the goal of our most recent research has been aimed at evaluating the influence of dopaminergic status on timing error (Almeida & Lebold, 2010). This can be achieved by comparing the specific goal of timing a heel strike on the ground relative to the auditory-paced signal from an external auditory metronome. Hence, a timing error could be calculated, with the prediction that if the basal ganglia truly contribute to temporal control, there should be identifiable differences in timing error that are specifically dependent on dopaminergic status.

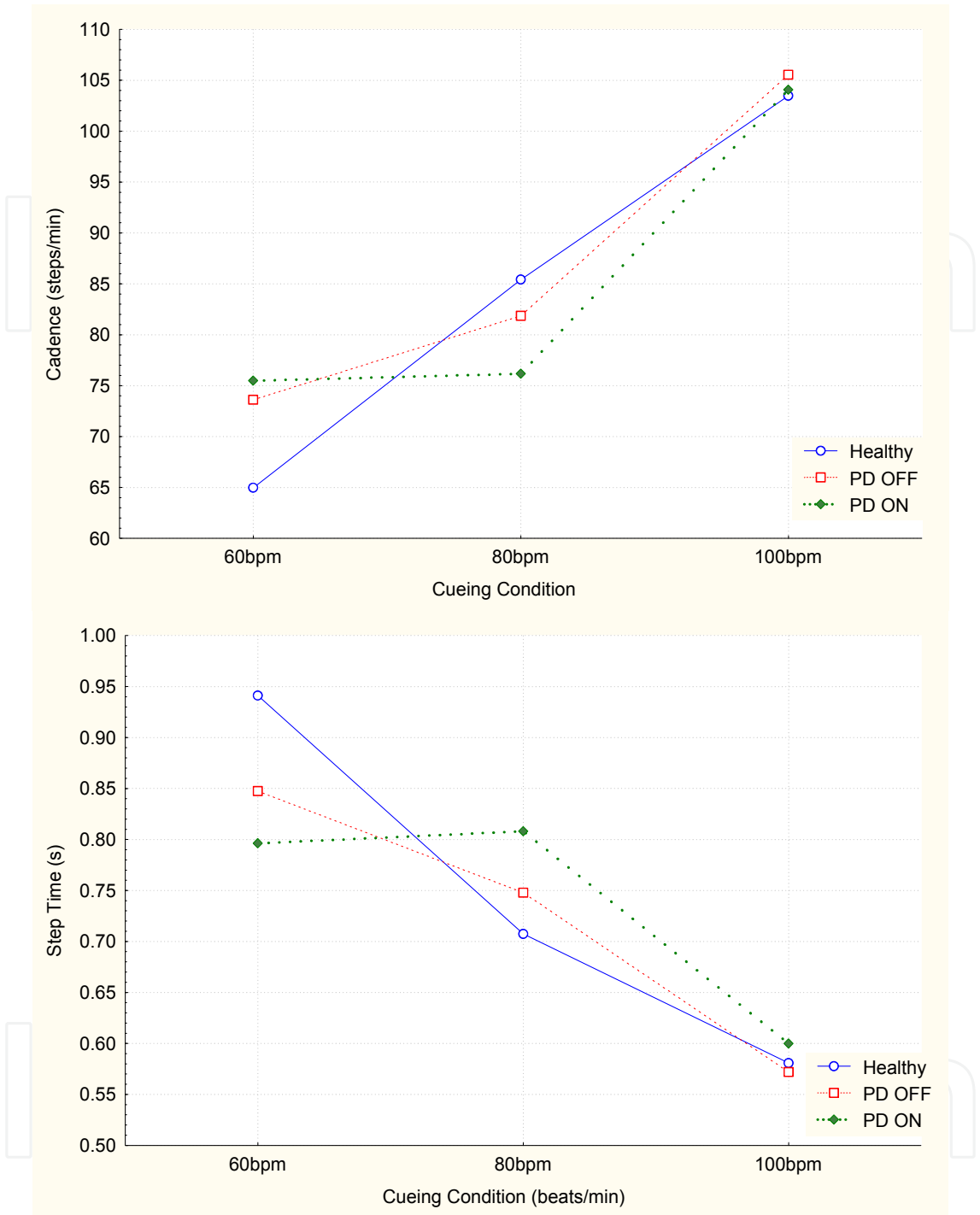


Fig. 4. a) Cadence of gait for the healthy participants, PD “Off “ and “On” in the externally-cued conditions, b) Step time for the healthy participants, PD “Off “ and “On” in the externally-cued conditions. (adapted from Almeida et al., Movement Disorders, 2007)

To test this hypothesis, eighteen PD participants were tested “On” and “Off” dopaminergic medication (consistent with our previous protocols), as well as a group of ten healthy, age-matched control participants. We required all participants to walk in 4 conditions paced by an auditory metronome (5 blocked trials per condition) over a computerized data-collecting and pressure-sensitive carpet (GAITRite®, CIR Systems, Inc., Clifton, New Jersey).



Conditions included self-paced Gait (SP), 30% slower than self-paced gait (-30% SP), 10% slower than self-paced gait (-10% SP) and 10% faster than self-paced gait (+10% SP), and timing error was calculated by comparing the onset of heel strike to the onset of the auditory cue, and averaged over the course of the trial. The error calculating software was created by CIR Systems, Inc., in collaboration with the researchers with the potential aim of creating a new clinical measure to evaluate neurological populations.

Perhaps more interestingly, the primary outcome measure, timing error identified a significant interaction ( $F(4,56)=4.87$ ;  $p<.0019$ ) between medication state and trial. Post hoc analysis revealed that while healthy control participants had a consistently lower timing error than PD, PD “Off” dopaminergic medication were initially less errorful (and behaved more like healthy control participants than PD “On”), but that with practice PD “On” gradually improved timing error while PD “Off” did not (Figure 6).

In addition, PD “Off” were identified to walk with overall greater step-to-step timing variability than PD “On”. This difference in variability was specifically identified in the slowest paced condition. Together, the overall interpretation of these findings is that timing variability (which has been linked to falls) and timing error measures reveal an interaction with medication state, suggesting that the basal ganglia may play a role in incorporating sensory timing cues into online control of gait in individuals with PD. Evaluating timing error may be in an important clinical indicator of motor control in PD and other neurological populations.

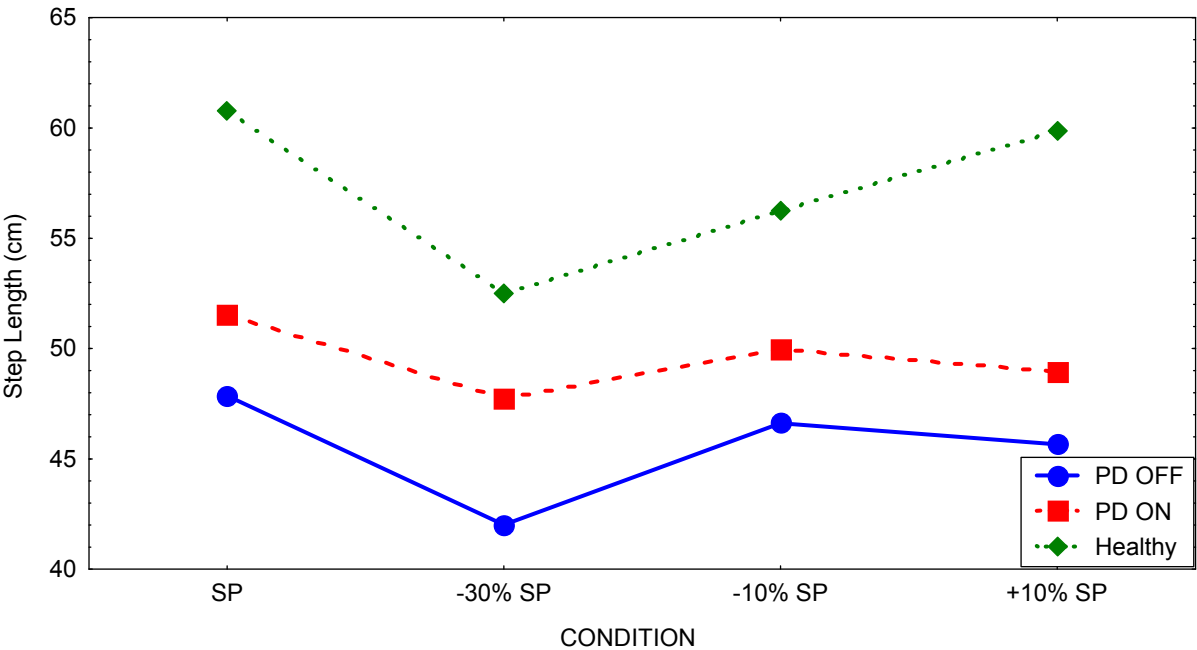


Fig. 5. Regardless of dopaminergic status, PD do not scale step length to the same extent as healthy control participants.

5. Conclusion

Deficits in timing control are evident in both unimanual and bimanual movements, across both the upper and lower limbs. Several methods of identifying timing deficits have been identified, with the important of error and variability being highlighted as important factors that reflect motor control deficits in PD. Although it is clear that amplitude is influenced by

basal ganglia dysfunction, it is important to consider how timing may be sacrificed in tasks where amplitude cues are the focus of the task. Similarly, the results of our own research suggest that amplitude (and specifically step length control) appears to be sacrificed when attention must be focused on the goal of modulating timing relative to an external auditory cue. Thus, consideration of sensory-related timing issues in PD may be an important approach in exercise rehabilitation interventions for PD and other basal ganglia-disordered populations.

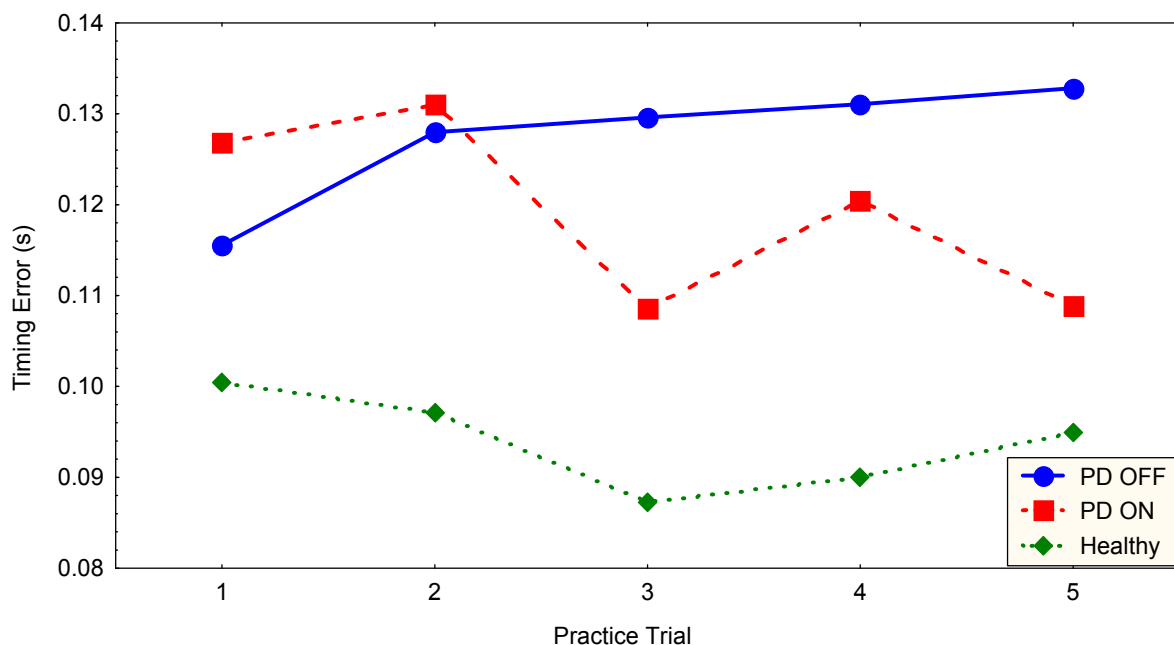


Fig. 6. A significant interaction between medication and trial revealed that with experience utilizing the metronome patients in the OFF state significantly increase their timing error, whereas PD ON improve timing error with practice.

The findings of our own studies on temporal characteristics of gait are consistent with the view that the basal ganglia may be involved in the neural network for precise modulation of timing of repetitive movement relative to external stimuli (Harrington et al., 1998; Rao et al., 1997) and are suggestive of an underlying mechanism for basal ganglia involvement in sensorimotor processing during movement.

In PD, where projections to specific basal ganglia nuclei (such as the putamen) that are implicated in the neural timing system are known to be affected, studies of repetitive finger tapping and lip movements have quantified a basic timing deficit (Freeman et al., 1993; Harrington et al., 1998; Konczak et al., 1997b; O'Boyle et al., 1996). Yet, external cues are heralded to be a potential method of overcoming basal ganglia-related movement impairments (Rubinstein et al., 2002) and a means of enhancing motor performance (Howe et al., 2003; McIntosh et al., 1997; Thaut et al., 2001). As seen in our studies, although provision of external auditory cues may improve certain characteristics of hypokinetic gait such as velocity and cadence, it may also contribute to greater step-to-step variability in PD which can lead to increased risk of falls, lack of stability and may lead to further impairments such as freezing of gait (Hausdorff et al., 1998; Hausdorff et al., 2003).

It is this within-trial variability that may provide insight into the sensorimotor mechanism underlying timing deficits in PD. Perhaps most interesting is the finding that group differences in variability (related to external cueing) are observable in measures of step time and double support time. This may be critically important to consider, in light of recent

research that has identified the relationship between step time variability and falls (Schaafsma et al., 2003) and freezing (Hausdorff et al., 2003) in PD. Double support time has been considered an important indicator of abnormal balance control in healthy, older adults and those with cerebellar dysfunction, as well as those with basal ganglia disease (Hausdorff et al., 1998). Increased double support time in medicated PD patients, in light of increased temporal variability may be representative of additional proprioceptive sampling that is required to verify that external cues are being used appropriately. Bearing in mind that the greatest increase in timing variability can be identified in PD "On", this may reflect an increased dependency on proprioceptive feedback for sensorimotor integration with the external stimuli in order to improve timing, with a faulty yet functioning basal ganglia providing input into the neural network for timing. It may be that the basal ganglia are specifically involved in interpreting and integrating proprioception during repetitive and automated movements such as gait. Therefore in timing modulation tasks, where the importance of proprioceptive integration is critical, differences between participants "On" and "Off" their dopaminergic medications can be identified.

Further in support of our view, it should be pointed out that all three groups experienced the most variability in timing at the slowest cueing condition, when there is the greatest opportunity to sample and integrate proprioceptive information with the auditory cues while maintaining balance. In the PD "Off" medication group, performance across temporal measures may approach that of healthy individuals because the basal ganglia loop is not centrally involved when medications are withdrawn. Under these circumstances, a mode of control similar to that for visual cues may be employed.

Finally, timing error was introduced as a novel and potentially interesting method of identifying timing control deficits. Although future research is necessary, evaluating timing error may be an important clinical indicator of disruptions to normal timing control in PD and other neurological disorders.

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## **Mechanisms in Parkinson's Disease - Models and Treatments**

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Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular mechanisms that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction, and oxidative stress may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons. Neurotoxin-based models have been important in elucidating the molecular cascade of cell death in dopaminergic neurons. PD models based on the manipulation of PD genes should prove valuable in elucidating important aspects of the disease, such as selective vulnerability of substantia nigra dopaminergic neurons to the degenerative process.

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