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# Motor and Perceptual Timing in Parkinson's Disease

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## Abstract

Neuroimaging has been a powerful tool for understanding the neural architecture of interval timing. However, identifying the critical brain regions engaged in timing was initially driven by investigation of human patients and animals. This chapter draws on the important contribution that the study of patients with Parkinson's disease (PD) has made in identifying the basal ganglia as a key component of motor and perceptual timing. The chapter initially describes the experimental tasks that have been critical in PD (and non-PD) timing research before systematically discussing the results from behavioural studies. This is followed by a critique of neuroimaging studies that have given insight into the pattern of neural activity during motor and perceptual timing in PD. Finally, discussion of the effects of medical and surgical treatment on timing in PD enables further evaluation of the role of dopamine in interval timing.

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## Keywords

Parkinson's disease • Basal ganglia • Dopamine • Motor timing • Perceptual timing • Temporal processing • Internal clock

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## Introduction

Psychological research has a long history of being informed by clinical populations. Atypical performance in a patient group open a window

for understanding the neural mechanisms of a given psychological process. This has been particularly true of Parkinson's disease (PD) and research into interval timing, with a focus on both motor and perceptual timing in the milliseconds and seconds range. The following chapter summarizes the contribution that research on PD has made to the field of interval timing. Starting with descriptions of the key timing tasks used, the chapter then goes on to review evidence from behavioural studies of motor and perceptual timing in PD. This is then supplemented by a summary of neuroimaging

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studies of timing in PD, as well as investigation of studies that have analyzed treatment effects. To enable conclusions to be drawn we will present the percentage of studies showing evidence of impairment in PD across a range of different task factors. We have a relatively small pool of studies, which differ in terms of methodology and experimental rigor, which means that the calculation of percentages has limitations. However, whilst recognizing this caveat, it also proves a valuable approach for identifying patterns in the results across tasks.

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### **Parkinson's Disease as a Model of Basal Ganglia Mediated Dysfunction in Temporal Processing**

Parkinson's disease (PD) is neurodegenerative movement disorder associated with the loss of dopamine producing neurons in the substantia nigra pars compacta, a midbrain structure. This pathological process has implications for the efficacy of the nigrostriatal dopaminergic pathway that transmits dopamine from the substantia nigra to the striatum, the input area of the basal ganglia. Thus, PD is a disorder of dopamine deficiency within the basal ganglia, a group of closely connected nuclei that play an important role in the control of movement, cognition and motivation. The cardinal symptoms of PD include akinesia, bradykinesia, rigidity and tremor. Akinesia translates as 'lack of movement' and manifests as symptoms including difficulty initiating movement, and reduced frequency and amplitude of spontaneous movements. Affected movements include blinking, facial expression and gesticulation during speech. Akinesia also leads to the characteristic shuffling and short stepping during walking, alongside reduced arm swinging. Bradykinesia refers to the slowness in executing movements, whereas rigidity is due to increased muscle tone. These features are seen alongside a characteristic 4–6 Hz tremor present at rest. Other clinical symptoms can include pain, sleep disturbance, psychiatric disturbance including depression, apathy and anxiety, cognitive impairment, and

dementia in the later stages (see [1] for a review). The most common treatment for PD is dopaminergic medication to increase the amount of dopamine in the brain and redress the neurochemical imbalance in the basal ganglia. A more invasive surgical treatment option is to directly stimulate key targets in the basal ganglia using chronically implanted electrodes, a technique called deep brain stimulation (DBS).

The slowness of movement in PD has led to interest in characterizing the temporal processing profile of patients with this disorder. From an initial case study exploring motor timing in PD [2], the field has expanded to encompass a range of motor and perceptual timing tasks. Testing patients both 'on' and 'off' medication or DBS has also enabled researchers to directly evaluate the impact of the efficacy of dopaminergic neurotransmission and the manipulation of striato-frontal connectivity on timing performance. This research has dovetailed with the quest to characterize the neural substrates of an 'internal clock' that meters time (e.g. [3]). Thus, investigation of temporal processing in PD has been instrumental in the argument that the basal ganglia are a critical component of the internal clock. This argument has been bolstered by more recent neuroimaging research that has found evidence of basal ganglia activation during a range of tasks involving temporal processing (see [4] for a review).

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### **Tasks Commonly Used to Study Perceptual and Motor Timing**

Motor timing can be considered as any temporal process where the temporal decision is intrinsically tied with movement. For example, the split second adjustments required to catch a ball or the ability to clap in rhythm with others. In contrast, perceptual timing is a subjective judgment of perceived time and is not defined by movement. For example, perceptual timing processes enable a person to judge that their kettle has boiled or to estimate that a friend travelling a familiar route will have returned home. Perceptual timing sometimes includes a motor element and there is some grey area in these distinctions. However,

commonly motor timing is a description reserved for repetitive and continuous movements (e.g. clapping in time with music), as opposed to a discrete movement that may be employed to indicate a temporal decision but can be separated from the perceptual decision (e.g. returning to the kitchen because the kettle is judged to have boiled). Studies have shown a significant correlation between performance on motor and perceptual timing tasks (e.g. [5, 6]), leading many to assume a common neural substrate.

Classic motor and perceptual timing tasks are summarized in Table 1 and the most frequently used with PD patients are described in more detail below. Figure 1 illustrates the duration discrimination, time estimation, time production and time reproduction tasks. Tasks commonly use a computerized presentation of simple auditory (e.g. pure tone) or visual (e.g. small square) stimuli to denote the intervals being timed. The duration being estimated can either be 'filled' e.g. a stimulus such as an auditory tone is present for the duration of the interval, or 'unfilled' e.g. the onset and offset is bounded by two short auditory tones but the actual interval is empty (e.g. [25]). For certain tasks, sometimes the interval is filled with counting or reading aloud random numbers (e.g. [30]), which will be discussed in more detail below. The **duration discrimination** task is the most popular 'pure' method of measuring perceptual timing. The task is considered pure as movement is not tied to the temporal decision. In this task, two durations are presented, typically sequentially (although see [24] for an alternative approach), and the participant has to make a discrimination based on their durations. This might be to judge which interval is longer (e.g. [20]), or to decide whether the second interval is longer or shorter than the first (e.g. [11]). Either a set number of trials and duration differences are presented [24] or, more commonly, an adaptive staircase is presented to calculate the threshold at which (for example) 75 % of discriminations are correct (e.g. [20]). It is important in studies with a patient population that group differences can be designated as specific to the process of interest and not to the general perceptual and cognitive demands (e.g.

stimulus detection, attention, memory, decision making). This issue is particularly pertinent when investigating a clinical group such as PD, where cognitive deficits are well documented (e.g. [38]). Unfortunately, most timing tasks cannot be matched with an adequate control task and researchers rely on carefully matched groups (age, IQ, education), as well as screening for cognitive impairment and psychiatric problems (depression, apathy and anxiety) that may additionally impact on timing performance. An advantage of the duration discrimination task is that control tasks can be used. Most studies of PD have used an auditory version of the duration discrimination task and a sound intensity or frequency discrimination control task (e.g. [11, 12, 25]). Line length or colour discrimination are common options when a visually presented duration discrimination task is used, although not all studies include such a control task (e.g. [22, 24]). Typically, control discrimination tasks are performed with proficiency by PD patients (e.g. [11, 25]), which adds weight to the argument for a specific timing deficit. However, a major caveat is that all of these control tasks can be solved in the first few hundred milliseconds; for example, it is not necessary to attend to the stimulus for its entire duration to decide its frequency. This is in contrast to the duration discrimination task, which makes it intrinsically more cognitively demanding. The neuroimaging field has led the way in designing inventive control tasks that match well for additional demands, including attention, working memory and motor preparation. These are covered comprehensively in seventh chapter of this book.

**Time estimation** assesses how well a participant can apply temporal labels to intervals of time. For example, the participant is presented with an interval and asked to estimate its length to the nearest second (e.g. [29]). Rather than relying on direct comparative judgments, this task assesses the ability to map understanding of the common units of time to an internal sense of time passing. A very similar task, which also relies on the participant's ability to label units of time, is the **time production** task. Here, the participant is asked to indicate when

**Table 1** Summary of motor and perceptual temporal processing tasks, the key processes measured, and studies that have used the tasks in Parkinson's disease

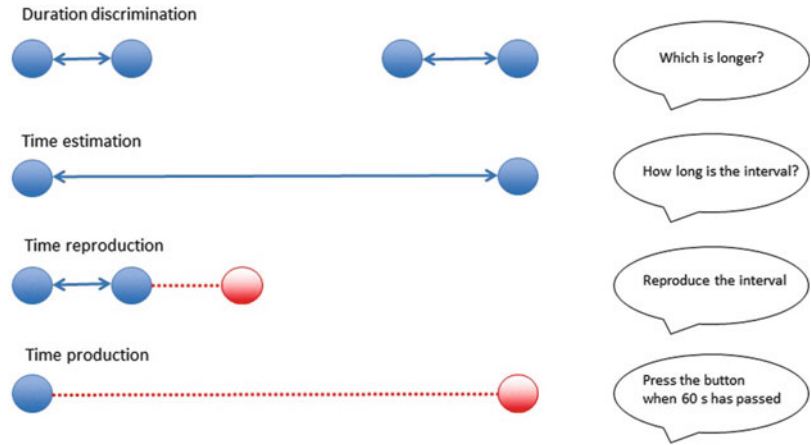
Task	Description	What is measured	Studies using task
<i>Motor timing</i>			
Synchronization-Continuation task/ repetitive tapping task	Tap in time with a regularly paced stimulus (synchronization phase) and then maintain the rhythm (continuation phase) in the stimulus's absence	Paced and unpaced motor timing	Cerasa et al. [7]; Claassen et al. [8]; Duchek et al. [9]; Elsinger et al. [10]; Harrington et al. [11]; Ivry and Keele [12]; Jahanshahi et al. [13]; Jones et al. [14]; Joundi et al. [15]; Merchant et al. [6]; O'Boyle et al. [16]; Pastor et al. [17]; Spencer and Ivry [18]; Wojtecki et al. [19]
<i>Perceptual timing</i>			
Duration discrimination	Pairs of intervals are presented. Participants indicate which is longer/shorter	Detection of a temporal difference between two durations	Guehl et al. [20]; Harrington et al. [11]; Harrington et al. [21]; Hellström et al. [22]; Ivry and Keele [12]; Rammsayer and Classen [23]; Riesen and Schneider [24]; Wearden et al. [25]; Wojtecki et al. [19]
Peak-interval procedure	Participants reproduce a learnt interval by pressing a response button repeatedly within the boundaries of its judged offset	Reproduction of a learnt interval	Malapani et al. [26]; Malapani et al. [27]
Temporal bisection	Participants learn short and long standard intervals. They then classify subsequent intervals as more similar to the short or long standards	Classifying stimuli based on duration	Merchant et al. [6]; Smith et al. [28]; Wearden et al. [25]
Temporal generalization	Participants learn a standard interval. They then judge if subsequent intervals are the same length as the standard	Judge if stimuli is same or different to a standard	Wearden et al. [25]
Time estimation	A temporal interval is presented. Participants are asked to estimate the duration, using seconds and minutes	Assigning a temporal label to a duration	Lange et al. [29]; Pastor et al. [30]; Riesen and Schneider [24]; Wearden et al. [25]
Time production	Participants press a button when a defined interval of time (e.g. 60 s) has elapsed	Subjective time sense for a given unit of time	Jones et al. [31]; Lange et al. [29]; Perbal et al. [32]; Wild-Wall et al. [33]; Wojtecki et al. [19]
Time reproduction	A temporal interval is presented. Participants press a button to indicate when an identical interval has elapsed	Reproduction of a presented interval	Jones et al. [31]; Koch et al. [34]; Koch et al. [35]; Koch et al. [36]; Merchant et al. [6]; Pastor et al. [30]; Perbal et al. [32]; Torta et al. [37]; Wojtecki et al. [19]

Stimuli are typically simple pure tones or simple visual displays (e.g. a square on a computer screen)

they think a pre-specified period of time has elapsed, for example, to press a button when they think 60 s has passed (e.g. [31]). The **time reproduction** task requires the participant to attend to an interval and then reproduce the duration by pressing a response button when they think an identical period of time has elapsed (e.g. [31]). The latter three tasks can vary in their design, but one crucial feature is whether participants are instructed to count. Counting out

the intervals, at a self-paced and self-preferred [32], self-paced but specified (e.g. 1 s) (e.g. [29, 30]), or externally paced [30] rate, introduces a timed motor element that can confound interpretation. It becomes unclear whether the task is measuring perception of a discrete interval or the ability to time a short continuous sequence that is intrinsically tied to motor production. Thus, many purported perceptual timing tasks have an implicit motor timing element. As an

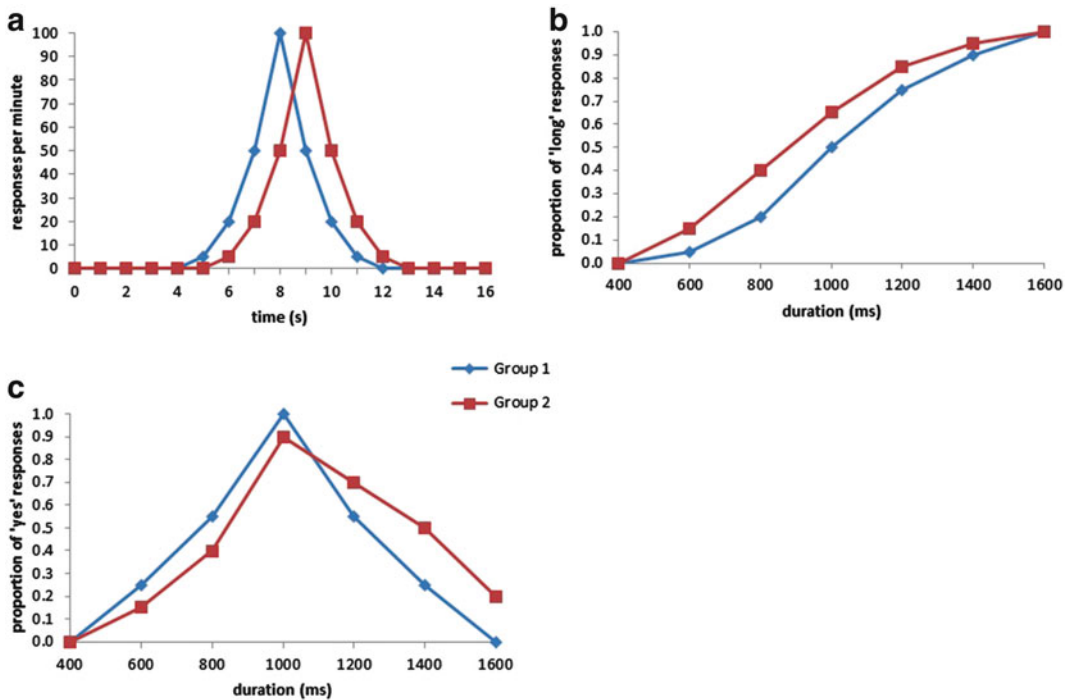
**Fig. 1** Illustration of the four most popular perceptual timing tasks. *Blue circles* indicate stimulus presentation (auditory or visual) and *red circles* indicate the participant's response



additional confound, the psychophysical properties of chronometric counting and interval timing are different, with only the variance in interval timing conforming to the scalar property [39]. Arguably, chronometric counting may still activate the internal clock (e.g. to generate individual counts), but it is a less pure measure of internal timing processes and results in more precise estimations [40]. Cognizant of these issues, some studies take the opposite approach and require that random numbers are read aloud to inhibit counting (e.g. [24, 26, 35]). However, managing the competing demands of two separate tasks is differentially more demanding for PD patients than healthy controls (e.g. [32, 41]) and the confounding motor element is still present. Some researchers have asked participants not to count (e.g. [31]). The downside of this is that the data become more noisy as it is difficult to control what strategies participants employ when timing intervals.

Three classic tasks from the animal timing literature, the **peak interval procedure**, the **temporal generalization** task and the **temporal bisection** task, have been used to good effect when investigating perceptual timing in PD. All three tasks plot a response curve and schematic examples of these curves, along with interpretation of results can be seen in Fig. 2. Malapani and colleagues have used an adaptation of the peak interval procedure in humans [26, 27]. The task can be thought of as a time reproduction task in

which many intervals are reproduced and then plotted to produce a frequency distribution. The participants are first trained in the target duration by monitoring the length of time a rectangle is displayed on a computer screen. In the testing phase, the rectangle appears but remains on the screen for a longer period. Participants have to press a button when they think the target duration has elapsed. Unlike a classic time reproduction task the participants are told to make multiple guesses on each trial, pressing the button before the estimated duration has elapsed and continuing until they judge it has passed. Feedback regarding accuracy is provided. This procedure enables responses to be plotted, showing a peak at the time where responses are most frequent. With time plotted on the x axis, a curve with a peak shifted to the right would imply relative overestimation, whereas a peak shifted to the left would imply underestimation. The human version of the temporal bisection task (e.g. [25]) has participants learn two standard durations, one 'short' and one 'long'. Once learnt, the participant is presented with a range of intermediate durations, spaced at equal intervals, as well as the standard durations. They have to classify each duration as more similar to the 'short' or 'long' standards that they learnt. The data produces a sigmoid curve, plotting the probability of making a 'long' response as a function of stimulus duration. With durations plotted on the x axis, a leftward



**Fig. 2** Schematic illustration of the (a) peak interval procedure, (b) temporal bisection task and (c) temporal generalization task. For each illustration, Group 1 illustrates typical performance, while Group 2 illustrates

relative overestimation compared to Group 1. For (a) the duration being reproduced is 8 s, for (b) the standard durations are 400 and 1,600 ms, and for (c) the standard duration is 1,000 ms

shift in the curve reflects a relative overestimation of time. The bisection point (or point of subjective equality) is the duration at which long and short responses occur with equal probability. In the human version of the temporal generalization task (e.g. [25]), participants are initially presented with examples of a standard duration that becomes learnt. During the testing phase, a range of different durations are presented including the standard duration. After each interval presentation the participant responds 'yes' if they judge that the interval is the standard duration and 'no' if they think otherwise, with feedback given. The proportion of 'yes' responses for each duration are plotted to create a temporal generalization gradient, which illustrates the probability of a response as a function of signal duration. With duration plotted on the x axis, a rightward skew of the generalization function would indicate overestimation of the

standard duration, whereas a leftward skew would suggest underestimation.

Motor timing is almost exclusively measured using the **synchronization-continuation task**, also known as the repetitive tapping task. The task assesses the ability to entrain a motor response to a regularly paced cue and then to maintain the learnt rhythm without the pacing cue (all studies discussed in this chapter use an auditory cue). Thus, there are two phases to the task, which are analyzed separately. In the synchronization phase the participant is required to tap in time to regularly paced stimuli, typically a pure tone. Tapping usually uses the index finger of the dominant hand and the inter tone interval of the pacing tone is generally within the range of a couple of seconds, most commonly around 500 ms. After a certain number of taps the tone ceases and the participant has to maintain the entrained rhythm as accurately as possible. This



is the continuation phase. The accuracy of the tapping rate, usually measured by the mean inter-response interval, is important in determining whether tapping is unusually slow or fast. For measuring the variability of responses, Wing and Kristofferson [42, 43] proposed a model that decomposed tapping variability into 'clock' and 'motor' components. The model assumes that a centralized internal clock that meters time can be dissociated from a motor implementation process, which is triggered by the clock. Although highly influential, the model has certain caveats. First, it assumes that the clock and motor processes are independent and second it does not allow for drift in the length of the participant's taps, despite this being a common phenomenon (e.g. [44, 45]). The Wing and Kristofferson [42, 43] model was designed to delineate the variability of unpaced tapping, which has meant that very few studies report performance on the synchronization section of the task. However, the synchronization phase provides important information about motor timing performance, particularly as a comparison with the continuation phase. For example, performance on the continuation phase would be interpreted differently if the ability to keep pace with the tone in the synchronization phase was poor, compared to if it was good.

It is important to note that varying durations have been used in behavioural timing studies. Perceptual timing tasks range between 50 ms and 120 s, which is in contrast to a far narrower span of between 250 and 2,000 ms for motor timing (see Tables 2 and 3). For perceptual timing tasks, time estimation and time production tasks tend to use longer intervals than the duration discrimination and time reproduction measures. As duration discrimination and time reproduction tasks involve remembering an interval within a trial, the durations are kept short to reduce interference from cognitive demands. A complete understanding of motor and perceptual timing in PD requires direct comparison of task performance using the same durations. Particularly as different time ranges (e.g. millisecond vs. seconds-range) are thought to recruit different neural regions (e.g.

[3, 46]) and patients with PD can show differential performance across different time ranges (e.g. [14]).

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## Behavioural Studies of Temporal Processing in Parkinson's Disease

### Perceptual Timing in Parkinson's Disease

A summary of the results from four of the most popular perceptual timing tasks can be seen in Table 2. When investigating perceptual timing in a group with a movement disorder the most effective tasks, and certainly the most easily interpretable, dissociate movement from the temporal decision. The duration discrimination task fits this criterion and performance of patients with PD is compromised in six of ten tasks (60 %) across nine published studies (see Table 2). Using a slightly different paradigm, where a ball moved across a computer screen, individuals with PD showed difficulty at distinguishing velocities as low or high speed [47]. However, the same individuals were successfully able to predict the time at which the moving ball would reach the bottom edge of the screen. This indicates intact temporal prediction in PD, which has also been reported elsewhere [48].

Other perceptual measures that are dissociated from motor performance are the temporal bisection and temporal generalization tasks. Using temporal bisection, Merchant et al. [6] found evidence of increased variability when patients were tested 'off' medication, while Smith et al. [28] found impairment in PD patients tested 'on' medication in both the visual and auditory modality for durations of 1–5 s, although not for a shorter range of 100–500 ms. However, Wearden et al. [25] draw attention to a probable miscalculation of the key timing variables in Smith et al. [28]. In contrast, Wearden et al. [25] found no evidence of impairment in either the temporal bisection or temporal generalization task within the milliseconds range (100–800 ms), and no effect of dopaminergic medication on

**Table 2** Summary of findings from studies of perceptual timing in patients with Parkinson's disease when compared to healthy controls

Study	Medication state	Modality	Counting	Type of interval	Standard duration	Results
<i>Duration discrimination</i>						
Guehl et al. [20] <sup>a</sup>	Off	Auditory	No	Unfilled	50 ms	Impaired
Harrington et al. [11]	On	Auditory	No	Unfilled	300 and 600 ms	Impaired
Harrington et al. [21] <sup>c</sup>	Off	Auditory	No	Unfilled	300 and 600 ms	Impaired
Hellström et al. [22]	On	Auditory	No	Filled	400, 800, 1,200, 1,600 ms	No impairment at group level, although gender differences reported
Ivry and Keele [12]	On	Auditory	No	Unfilled	400 ms	No impairment
Rammsayer and Classen [23]	On	Auditory	No	Unfilled	50 ms	Impaired
Riesen and Schnider [24]	On	Visual	No	Filled	200 ms and 1 s	Impaired
Wearden et al. [25]	On & Off	Auditory	No	Short delay condition: both; long delay condition: filled	400 ms with short delay between the two tones (1,100 ms); 350–650 ms with long delay (2, 4, 8 s)	Short delay: No impairment Long delay: Impairment
Wojtecki et al. [19] <sup>a</sup>	Off	Auditory	No	Unfilled	1,200 ms	No impairment
<i>Peak-interval procedure</i>						
Malapani et al. [26]	On & Off	Visual	Random number	Filled	8, 21 s	Impaired accuracy for 21 s. Greater variability for 8 s (Off only)
<i>Temporal bisection</i>						
Merchant et al. [6]	On & Off	Auditory	No	Filled	350, 1,000 ms	Greater variability (Off only)
Smith et al. [28]	On	Both separate	No	Unfilled	100, 500 ms and 1,000, 5,000 ms	Impaired for long (1,000, 5,000 ms) intervals
Wearden et al. [25]	On & Off	Auditory	No	Filled	200, 800 ms	No impairment
<i>Temporal generalization</i>						
Wearden et al. [25]	On & Off	Auditory	No	Filled	400 ms	No impairment
<i>Time estimation</i>						
Lange et al. [29]	On & Off	–	Yes	Filled	10, 30, 60 s	Underestimation (Off only)
Pastor et al. [30]	Off	Visual	Yes	Filled	3, 9, 27 s	Underestimation
Riesen and Schnider [24]	On	Visual	Random number	Filled	12, 24, 48 s	No impairment
Wearden et al. [25]	On & Off	Auditory	No	Filled	10 durations between 77 and 1,183 ms	No impairment
<i>Time production</i>						
Jones et al. [31]	On	Auditory	No	Unfilled	30, 60, 120 s	Overestimation
Lange et al. [29]	On & Off	–	Yes	Filled	10, 30, 60 s	Overestimation (Off only)

(continued)



**Table 2** (continued)

Study	Medication state	Modality	Counting	Type of interval	Standard duration	Results
Perbal et al. [32]	On	Visual	Yes, and a random number condition	Filled	5, 14, 38 s	Counting condition: No impairment Random number condition: underestimation
Wild-Wall et al. [33]	On	Visual	No	Filled	1,200 ms	No impairment
Wojtecki et al. [19] <sup>a</sup>	Off	Visual	No	Unfilled	5, 15 s	Underestimation at 15 s
<i>Time reproduction</i>						
Jones et al. [31]	On	Auditory	No	Unfilled	250, 500, 1,000, 2,000 ms	Reduced variability. Violation of Scalar property
Koch et al. [34] <sup>a</sup>	Off	Visual	Random number	Filled	5, 15 s	Overestimate 5 s, Underestimate 15 s
Koch et al. [35]	Off	Visual	Random number	Filled	5, 15 s	Left-hemi PD: Overestimate 5 s, underestimate 15 s Right-hemi PD: Overestimate 5 s
Koch et al. [36]	On & Off	Visual	No	Filled	Short: 400, 450, 500, 550, 600. Long: 1,600, 1,800, 2,000, 2,200, 2,400 ms	Standard condition: Underestimation of long intervals. 1 h delay between short and long trials: No impairment
Merchant et al. [6]	On & Off	Auditory	No	Unfilled	350, 450, 550, 650, 850, 1,000 ms	Increased variability
Pastor et al. [30] <sup>b</sup>	Off	Visual	Yes	Both	2, 3, 4.5, 6, 9 s	Overestimation
Perbal et al. [32]	On	Visual	Yes, and a random number condition (during encoding only)	Filled	5, 14, 38 s	Counting condition: No impairment Random number condition: increased variability
Torta et al. [37] <sup>a</sup>	On & Off	Both	No	Both	Seconds-range, varied for each participant	Unfilled: No impairment Filled (simple motor task during encoding phase): Underestimation (off only)
Wojtecki et al. [19] <sup>a</sup>	Off	Auditory	No	Unfilled	5, 15 s	No impairment

<sup>a</sup>Patients had undergone STN DBS, data in the table are reported when stimulation was turned off

<sup>b</sup>Pastor et al. [30] tested five variations of the time reproduction task. As all tasks produced the same result we present the data as one result in the table, with reference to the different manipulations discussed in the chapter

<sup>c</sup>Data collected during a neuroimaging (fMRI) experiment

**Table 3** Summary of findings from studies of the synchronization-continuation task in Parkinson's disease when compared to healthy controls

Study	Medication	Duration (ms)	Synchronization: variability	Synchronization: accuracy	Continuation: variability	Continuation: accuracy
Cerasa et al. [7] <sup>a</sup>	Off	750	Increased	PD = Controls	PD = Control	PD = Control
Duchek et al. [9]	On	550	–	–	Decreased (MV) PD = Control (SD)	PD = Control
Elsinger et al. [10] <sup>a</sup>	On & Off	600	Increased	PD = Control	Increased	Faster
Harrington et al. [11]	On	300, 600	–	–	Increased (CV, TV)	PD faster
Ivry and Keele [12]	On	550	–	–	PD = Control	PD faster
Jahanshahi et al. [13] <sup>a</sup>	On & Off	1,000	PD = Control	PD = Control	PD = Control	PD = Control
Jones et al. [14]	On & Off; De novo	250, 500, 1,000, 2,000	No consistent pattern across durations	Faster at 250 ms	No consistent pattern across durations	Faster at 250 ms
Joundi et al. [15] <sup>b</sup>	On	500, 2,000	Increased (CoV)	PD = Control	Increased (CoV, MV)	PD = Control
Merchant et al. [6]	On & Off	350, 450, 550, 650, 850, 1,000	–	–	Increased (SD)	Not reported
O'Boyle et al. [16]	On & Off	550	–	–	Increased (CV, MV, TV) (only CV sig. when On)	PD faster (only sig. when On)
Pastor et al. [17]	On & Off	400, 500, 667, 1,000, 2,000	–	PD slower at 400 and 500 ms	Increased (CV, MV, TV)	PD slower at 400 and 500 ms
Spencer and Ivry [18]	On & Off	550	–	–	PD = Control	PD = Control
Wojtecki et al. [19] <sup>b</sup>	Off	800	PD = Control	PD = Control	PD = Control	PD = Control

CoV coefficient of variation, SD standard deviation; using the Wing and Kristofferson [42, 43] model: CV clock variance, MV motor variance, TV total variance. The Wing and Kristofferson model is only applied in the continuation phase

<sup>a</sup>Data collected during a neuroimaging (PET or fMRI) experiment

<sup>b</sup>Patients had undergone STN DBS, data reported in the Table are when stimulation was turned off

performance. Of the studies that have reported on the time estimation and time production tasks, both of which require application of a temporal label to intervals, 50 % (2 of 4) of time estimation tasks and 67 % of time production tasks (4 of 6) record impairment in PD (see Table 2). The time reproduction task is a significant source of difficulty in PD on 67 % (8 of 12) occasions. However, the pattern of findings is inconsistent, with reports of both increased and reduced variability and of over and underestimation. Notably, the time reproduction

task has the greatest motor demand of all perceptual tasks, with a short temporal decision (commonly < 5 s) having to be made precisely through a motor response. However, studies that have required two different intervals to be reproduced in the same session have found that the longer interval is underestimated, while the shorter interval is overestimated (see below for a full description of this 'migration' effect) (e.g. [34–36]). This effect is not compatible with a simple motor explanation (e.g. slowed motor execution).

The pattern of findings for different tasks can prove illuminating. Lange et al. [29] and Pastor et al. [30] report a compelling finding of underestimation in patients with PD when deciding the length of a temporal interval (time estimation) and overestimation when producing a temporal interval (time production). This pattern is consistent with an internal clock that runs at a slowed rate. However, in both studies the participants were trained to count aloud at a rate of 1 digit per second, which does not give a true estimate of perceptual deficits (see above). However, Jones et al. [31] found similar evidence of overestimation in time production in PD but this time in a condition where participants were explicitly told not to count (although see [19] for a different pattern of results).

Perceptual timing research in PD has uncovered another important phenomenon, the 'migration' effect. When presented in consecutive blocks, it has been noted that shorter intervals (<10 s) are overestimated while longer intervals ( $\geq 15$  s) are underestimated, causing an apparent 'migration' [26, 27]. Using the peak interval procedure in a series of experiments that manipulated task factors including medication state, Malapani and colleagues concluded that two types of dysfunction were evident in PD [27]. First, when individuals with PD learn an interval 'off' medication they subsequently overestimate the interval when medicated; this indicates a storage dysfunction. Second, when individuals with PD reproduce the intervals when 'off' medication (regardless of their medication state when learning) they produce the migration effect; this indicates a retrieval dysfunction. Importantly, the data indicate that the memory for the learnt durations is the source of the temporal deficit, rather than the 'clock' process itself. Using the time reproduction task, a similar migration effect was reported for intervals of 5 and 15 s [34, 35]. In a study using shorter intervals (500 and 2,000 ms), Koch et al. [36] found significant underestimation of the 2,000 ms in PD group. However, when the short and long intervals were separated by a delay of an hour, the migration effect disappeared. Thus, Koch et al. [36] suggest the

phenomenon has a general cognitive explanation, such as set-shifting. In a novel re-working of the time reproduction task, Torta et al. [37] required the time taken for the participant to perform an activity (unscrewing a bolt from a nut) to be reproduced, without replication of the activity (participants had to tap a desk to mark the onset and offset of the interval). This meant that a filled interval was learnt in the context of a dual task and reproduced in an unfilled context. Whereas performance was unimpaired in a standard version of the time reproduction task, the group with PD significantly underestimated on the motor version. The authors interpret the data in terms of attentional allocation (e.g. [49]), arguing that the motor task is demanding for the patients and therefore routes attention away from the secondary task of time perception. The relative lack of attention given to temporal processing leads to underestimation.

### The Importance of Cognitive Factors

These findings lead to an important area of debate, does the temporal deficit in PD reflect the dysfunction of critical timing regions or is impairment of global cognitive processes (e.g. attention, memory, executive skills) the root cause? One way of testing the specificity of the temporal deficit is to use carefully selected control tasks. Studies have commonly found a deficit on the duration discrimination task in PD, while performance on other types of discrimination task (e.g. frequency) remains unaffected (e.g. [11]). However, as discussed above, whether these control tasks are sufficiently cognitively demanding is questionable. Using a rhythm discrimination task, Grahn and Brett [50] showed that participants with PD were as proficient as controls when the rhythm did not contain a beat but showed poorer performance when a beat was present. This study is particularly notable as rhythms with a beat structure are easier to discriminate than non-beat rhythms. A specific deficit in the easier beat condition suggests that global and non-specific cognitive or perceptual difficulties are not the explanation.

Another way for testing the independence of the temporal deficit is to measure the extent to

which cognitive impairment is correlated with timing task performance. Using exploratory factor analysis, Jones et al. [31] found that the time production of seconds range intervals (30–120 s) and a measure of attention (Paced Auditory Serial Addition Test) formed a common factor, distinct from time reproduction (250–2,000 ms) and a warned and unwarned reaction time task. This supports the hypothesis that cognitive mechanisms relate to the production of time intervals in the seconds-to-minutes range, a cognitive load that is not common to all timing tasks. In a rigorous study testing participants with PD on five different perceptual timing tasks, Wearden et al. [25] found that the only task that significantly discriminated the group with PD from the control group was a duration discrimination task that required the standard interval to be held in memory for 2–8 s. Wearden et al. [25] comment that studies that find temporal processing differences in PD tend to use tasks where two stimuli have to be processed. They therefore suggest a cognitive explanation for the difficulties, for example, impaired sequential processing or attention-switching. This interpretation aligns with Riesen and Schnider [24] who found impairment on a duration discrimination task using an unusual protocol where the two intervals were presented simultaneously but with different onsets and offsets. They suggest their results may be best explained by a failure of divided attention or working memory, although further research using additional manipulations (e.g. a comparison with sequential durations) would be needed to more fully support this interpretation. Guehl et al. [20] reported that participants with PD were impaired on a duration discrimination task with a standard interval of 50 ms (defined by two clicks) and a comparison interval that was longer to varying degrees. However, they were unimpaired on a very similar duration discrimination task where trains of clicks paced at 50 ms intervals were used. Participants had to determine which of the two trains of isochronous clicks had one long interval (>50 ms) in the middle. Thus, although the durations were identical the context they were embedded in was different. One interpretation

suggested by the authors was that the first task requires a greater allocation of attentional resources, as the onset of the stimuli cannot be predicted as easily. However, Merchant et al. [6] found that performance on a range of cognitive tasks (working memory, go/no-go reaction time and verbal learning) did not discriminate those with PD who did well or poorly on a range of motor and perceptual timing tasks with intervals  $\leq 1$  s. This suggests that impaired memory and attention were not driving timing difficulties in their sample. However, surveying across all of the studies, there seems to be evidence that cognitive factors can influence performance on perceptual timing tasks in PD, which aligns with the documented cognitive deficits of this group. Of course, this does not preclude that genuine clock dysfunction is also present. Certainly, data such as those presented by Grahn and Brett [50] are compelling. Also, the finding of duration discrimination deficits using very short intervals (50 ms) (e.g. [20, 23]) compared to preserved performance using equivalent tasks with much longer durations (e.g. [19, 22]), albeit in different samples, would not be predicted by a purely cognitive explanation.

### The Importance of Task Factors

Across the range of most common perceptual timing tasks (Table 2), 23 of 37 tasks (62 %) demonstrate a different pattern of performance in PD. This is perhaps low given the publication bias for positive findings. However, both the heterogeneity of PD and the effects of aging on temporal processing (see [33]), which means a well-matched control group is critical, may in part explain the mixed findings. Another reason for the variation in the results is task differences. When looking at relevant tasks (peak-interval procedure, time estimation, time production, and time reproduction) that included a timed motor element, 4 of 6 (67 %) of the tasks that using counting reported between-group differences, whereas 5 of the 6 (83 %) that used random numbers reported differences. For both, this is higher than for tasks where no counting was included (6 of 11, 55 %). Therefore, the presence of a paced element, which may change

the nature of the temporal and cognitive processes being utilized, is more likely to produce impairment. Another important distinction is the length of the intervals being used. Previous research has suggested that the time range may affect the type of timing and the pattern of neural activation (e.g. [46]). A particular emphasis has been placed on millisecond vs. seconds-range timing (e.g. [3]). If millisecond-range timing is defined (arbitrarily) as between 1 and 1,000 ms and seconds-range timing as intervals >1,000 ms, 6 of 15 (40 %) millisecond-range tasks find evidence of impairment compared to 16 of 26 (62 %) seconds-range tasks. If the cutoff is increased to 5 s and above then the proportion of longer interval tasks that the PD group perform poorly on increases to 71 % (12 of 17). This suggests that temporal processing in the seconds-range is more challenging, which may relate to the additional cognitive demands (e.g. [31]). It is worth commenting that this is collapsing across all studies and the pattern is more nuanced if a task breakdown is used. For example, for the duration discrimination task, both studies that used very short millisecond standard intervals of 50 ms reported impairment [20, 23], whereas the studies with durations from 200 to 1,600 ms presented with more mixed results. Importantly, although it has previously been suggested that the basal ganglia are only implicated in seconds-range timing [3], this does not seem to be the case when reviewing the studies. These data complement neuroimaging work that has found the basal ganglia are active in both millisecond and seconds-range temporal processing [46].

Focusing on the five types of task that present a stimulus to be timed (time reproduction, duration discrimination, temporal bisection, temporal generalization, and peak-interval procedure), there are group differences for 9 of the 16 (56 %) tasks using the auditory modality but for 9 of the 11 (82 %) tasks that use the visual modality. Modality of presentation is known to have an effect on temporal processing, with auditory stimuli judged as longer than equivalent visual stimuli [51]. Further, temporal sensitivity is poorer in the visual modality in healthy adults

and children [52]. Zélandi and Droit-Volet [52] also found that temporal performance in the visual modality was significantly associated with visual selective attention, but that there was no equivalent association in the auditory modality. It was concluded that temporal processing in the visual domain is more cognitively demanding. This task-related difference may therefore indicate the influence of general cognitive factors on performance on these tasks for individuals with PD. An alternative interpretation is that there are separable modality-specific neural clocks and that the visual clock is more compromised. However, recent research reports that auditory judgments are influenced by the presentation of visual durations, and vice versa, which suggests that visual and auditory durations are timed by a 'common code' and not by modality-specific processors [53]. As the tasks using visual cues were more likely to be seconds-range than the auditory tasks, further studies are needed to corroborate the interpretation that the auditory domain is differentially more demanding in PD.

Looking across all the tasks in Table 2, of the 14 using unfilled intervals, 9 showed differences between groups (64 %), which contrasts with 15 of the 25 tasks using filled intervals (60 %). However, if the 13 tasks that used counting, random numbers or motor activity are removed and the focus is just on tasks that used simple visual stimuli or pure tones to fill the interval, then just 5 of the 12 (42 %) studies with filled interval tasks reported a deficit in PD. Filled intervals are routinely judged as longer than unfilled intervals (e.g. [54]), with animal research suggesting that filled intervals are also timed with more precision [55]. Therefore, when comparing across studies it appears that tasks that are unfilled (compared to filled) and visual (compared to auditory) are more demanding for individuals with PD. Wearden et al. [25] required participants to complete both unfilled and filled versions of the duration discrimination task. Supporting the pattern across studies, the difference between the PD and control groups appeared more marked in the unfilled condition, although a direct comparison across stimulus

type was not reported. On the other hand, Pastor et al. [30] found no difference in the time reproduction of filled and unfilled intervals in PD, although participants were given no specific instructions in the unfilled condition so may have used the counting that they were trained to apply in the filled condition. It has been suggested that the internal clock ticks at a slower speed for unfilled and visual intervals (i.e. producing less clock ticks per unit of time) compared to their filled and auditory equivalents, and that this explains the relative overestimation in the filled and auditory versions in healthy populations (e.g. [51, 54]). Why auditory and filled durations produce a faster clock is not clear, although it may relate to differences in arousal. Further, it remains to be established why stimuli that induce a slower clock pace are more problematic in PD and whether this relates directly to their hypothesised slowed clock (e.g. [30]) or to generic cognitive demands. Future research would benefit from exploring this finding.

In summary, individuals with PD often perform poorly on measures of perceptual timing, implicating the basal ganglia in interval timing. These results have been interpreted in terms of a slowed internal clock, but it is likely that compromised cognitive functioning also influences performance. The data suggest both millisecond and seconds-range perceptual timing are impaired in PD, and cognitive factors may be more important for longer durations. Finally, stimuli that are unfilled and presented in the visual modality are the most challenging in PD. Greater consideration needs to be given to the extent to which these stimulus properties influence temporal processing in PD and what they can tell us about the role of the basal ganglia in timing. Finally, greater consideration of the interaction between time-dependent computations and supportive cognitive processes is required.

### Motor Timing in Parkinson's Disease

As mentioned previously, investigation of motor timing has focused on the synchronization-

continuation task, with the majority of studies only investigating continuation performance. However, although both healthy participants and those with PD perform better at synchronization than continuation tapping (e.g. [14]) there is no convincing evidence that the pattern of impairment in PD differs significantly between the two phases (e.g. [14, 15, 17, 19], although see [10]). A summary of the studies into motor timing in PD can be found in Table 3.

There have been varied results for accuracy on the synchronization-continuation task. Tapping rate in PD has been shown to be faster [10–12, 14, 16], slower [17], and unimpaired [7, 9, 13, 15, 18, 19]. To help make sense of these inconsistencies it is important to focus on the differences between the tasks used. Notably, there is a cluster of studies compatible with the hypothesis that accuracy of repetitive finger movement is only impaired at rates faster than 500 ms, at slower rates patients with PD are able to demonstrate preserved performance (e.g. [7, 9, 13–15, 18, 19]). This pattern is also observed in tasks that have just measured synchronized tapping [56–58]. In contrast, many studies report that individuals with PD tap significantly faster than a control group at intervals of 300–600 ms [10–12, 16]. One interpretation of these findings is that individuals with PD are demonstrating festination at these shorter intervals. Festination is a clinical phenomenon often observed in PD and is the tendency to speed up when performing a repetitive movement. Experimentally it is identified when movement speed exceeds that in a control group by a specified margin (e.g. 2 standard deviations) and has been recorded for a variety of movement types, including oral, finger and wrist (e.g. [56, 59–61]). Reflecting these findings, other studies demonstrating the phenomenon of festination report it in movement rates of 500 ms and faster [56, 59–61]. In contrast, two studies [17, 59] found evidence of slowed tapping at short intervals (200–500 ms), but they used repetitive wrist movements, making a comparison with the traditional synchronization-continuation tasks difficult.

It appears that the interval range of 400–600 ms is of critical importance in PD, as



this is the threshold at which performance switches from impaired to unimpaired. It has been suggested that movement rates of around 500 ms (i.e. movement frequencies of 2 Hz) are associated with a transition in control strategy. At this faster rate, the timing of continuous movements to a cue shifts from a synchronization strategy (i.e. individually controlled movements), to a syncopated strategy (i.e. control over the rhythm of movements rather than each individual movement, as indicated by a lag in producing the movement) [62]. While slower movements can be executed in a closed-loop fashion, where motor commands are continuously compared to afferent information, the execution of faster movements depends on a motor program being generated before movement onset and controlling performance in the absence of feedback (e.g. [63]). This dissociation is supported by neuroimaging (positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)) evidence that the pattern of sensorimotor activation during repetitive index finger tapping is different for slower (0.25–0.5 and 0.5–1 Hz) compared to faster (1–4 and 1.5–5 Hz) rates of movement [64, 65]. Thus, in PD the difference in motor control strategy may make timing faster movements differentially more demanding. Using an electroencephalogram (EEG) to measure  $\beta$  band oscillations, Toma et al. [62] found that timing a repetitive thumb movement with a slow pacing signal (below 2 Hz) activated motor cortical areas (i.e. event-related desynchronization of neuronal populations) and was followed immediately by deactivation (i.e. event-related synchronization). In contrast, for faster movements (above 2 Hz) the motor cortical areas were continuously activated without any synchronization. It has been suggested that the impairment of faster repetitive movements in PD may relate to a difficulty in the desynchronization of elevated  $\beta$  band oscillations [57]. Logigian et al. [56] argue that there is 'attraction' of repetitive voluntary movements to the strong neural synchronization that drives pathological tremor in PD. As such, the movements become 'entrained' to the tremor rate.

Reviewing the findings for variability, a majority of studies reported elevated levels of variability on the synchronization-continuation task in PD (e.g. [6, 7, 10, 11, 15–17]) but other studies found no impairment [12, 13, 18, 19] or decreased variability [9]. There is no consistent pattern that relates timing variability to interval length, although Jones et al. [14] observed that variability for both patients with PD and healthy controls was lowest at 500 ms. Five hundred milliseconds is close to the natural tapping rhythm (i.e. when tapping at their most comfortable pace) of individuals with and without PD [58]. Combined with the pattern of findings from the accuracy of synchronization-continuation performance, the variability results again suggest the importance of evaluating the shorter interval ranges when investigating motor timing performance in PD.

In summary, ten (77 %) of the thirteen studies report group differences in the variability and/or accuracy of motor timing, making motor timing more discriminating than perceptual timing. However, close analysis of the pattern of findings suggests that focus should be given to intervals under 600 ms, with particular emphasis on identifying the shift from impaired to unimpaired accuracy at around 400–600 ms. This may reflect the conceptual and neural shift in the way that the shorter intervals are timed, with the timing and production of shorter intervals being more demanding in PD.

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## Neuroimaging Studies of Temporal Processing in Parkinson's Disease

Although highly informative, behavioural studies only provide a limited window on the role of the basal ganglia in temporal processing. The basal ganglia are a highly connected set of structures and the pathology in also PD influences the functioning of these other regions. PD is associated with excessive inhibitory outflow from the basal ganglia, which means that cortical sites are not adequately activated. The frontostriatal motor loop is particularly affected, which implicates the supplementary motor area (SMA) and pre-SMA [66]. As the disease



progresses more widespread areas of the frontal cortex are implicated. As such, it is feasible that cortical, as well as subcortical, dysfunction is driving the temporal deficits observed in PD. One obvious way to test this hypothesis is to use neuroimaging techniques to reveal the extent of cortical and subcortical patterns of neural activation during a timing task. A handful of studies have used imaging to examine the neural substrates of perceptual and motor timing in PD. The results of these studies are summarized in Table 4.

To date, only two studies have investigated the neural correlates of perceptual timing in PD. In the first study, Harrington et al. [21] scanned 21 patients with PD both 'on' and 'off' dopaminergic medication and 19 healthy controls during a duration discrimination task. Standard durations of 1,200 or 1,800 ms were presented followed by a comparison duration and participants had to decide if the comparison was longer or shorter than the standard. Data were obtained during both the encoding and decision phases of the task. Striatal dysfunction was found in both phases, highlighting its key role in timing. However, activation in distributed areas of the cortex were also recorded. During the encoding phase, activation interpreted as part of a working memory network (middle frontal-inferior parietal regions, supplementary motor area (SMA), and lateral cerebellum) was dysfunctional, whereas during the decision making phase activation in regions relevant to executive processes and memory retrieval were atypical (posterior-cingulate, parahippocampus). Dopamine medication did not alleviate the timing deficits on the task in the patients, and effective connectivity between the striatum and cortex was modulated by dopamine medication in the decision phase. Specifically, there was greater connectivity between the striatum and medial frontal gyrus, SMA, pre- and postcentral cortex, insula and parietal cortex 'off' compared to 'on' medication. This authors interpreted this as reflecting excessive synchronicity in corticostriatal circuits. In contrast, the connections between the striatum and left superior frontal gyrus were greater 'on' than 'off' medication.

In another fMRI study, Dušek et al. [67] scanned 12 PD patients 'on' and 'off' medication in the encoding and reproduction phases of a time reproduction task with short and long intervals (range 5 to 16.82 s). Medication had no effect on performance of the task. However, in the reproduction phase, significantly greater activation in the precuneus was found 'on' than 'off' medication, which was not present during a control random button pressing task. It was concluded that differences in activation of the precuneus during retrieval of an encoded duration may underlie the time perception deficits in PD (as documented in the 'migration effect' for example), which is partly alleviated by dopaminergic medication.

As shown in Table 4, the neural correlates of motor timing in PD has been investigated in four studies, three of which employed the synchronization-continuation task [7, 10, 13], whilst Yu et al. [80] just used the synchronization phase. Elsinger et al. [10] and Jahanshahi et al. [13] assessed patients both 'on' and 'off' medication, whereas Cerasa et al. [7] and Yu et al. [80] only scanned patients in the 'off' state after overnight withdrawal of dopaminergic medication. The study of Jahanshahi et al. [13] was the only one with an additional reaction time task to control for the non-temporal aspects of the synchronization-continuation paradigm, such as anticipation of the tone, motor preparation, and execution of a motor response. For the controls, relative to the control task, motor timing in the synchronization and continuation phases was associated with increased activation in the right middle frontal gyrus (BA 8) and the left caudate compared to the PD patients. In contrast, compared to the controls, PD patients showed greater activation of the midbrain/substantia nigra, vermis and the cerebellar lobule V during motor timing relative to the control task. Thus, while the controls were recruiting fronto-striatal areas more than PD, the patients were relying on the vermis and cerebellum for motor timing. For both groups, the internally controlled timing in the continuation phase was associated with significantly greater activation of the DLPFC compared to the externally paced

**Table 4** Summary of imaging studies of perceptual or motor timing in Parkinson's disease

Study	Imaging technique	Sample	Medication state	Task	Duration	Main findings
Cerasa et al. [7]	fMRI	10 PD 11 HC	Off	S-C finger tapping	750 ms	See Table 3 for behavioral results. No differences between S and C phases for either PD or HCs except in visually related areas. During S phase, relative to HCs, PD showed increased activation in cerebellum, putamen, SMA and thalamus, inferior frontal gyrus, frontal operculum, lingual gyrus and insula. In the C phases, relative to HCs, PD showed greater cerebello-thalamic activation
Dušek et al. [67]	fMRI	12 PD	On & off	Time Reproduction & Control random button pressing	5, 5.95, 7.07, 8.41, 10, 11.89, 14.4, 16.82 s	A 'migration effect' was observed, with intervals $\leq 11.9$ s overestimated and intervals $\geq 14.1$ s underestimated in the 'off' compared to the 'on' medication state. Significantly greater activation in the precuneus 'on' than 'off' medication during the reproduction but not encoding phase
Elsinger et al. [10]	fMRI	10 PD 13 HC	On & off	S-C finger tapping	600 ms	See Table 3 for behavioral results. PD less activation in SMC, cerebellum and SMA than HCs. SMA, thalamus and putamen active in PD during the C phase when on but not off medication. NB. Direct statistical comparison of the conditions not reported.
Harrington et al. [21]	fMRI	22 PD 10 HC	On & off	Duration discrimination	1,200, 1,800 ms	See Table 2 for behavioral results. Striatal dysfunction evident in both the encoding and decision phases when PD were compared 'off' to HCs. During encoding, PD also showed underactivation of a working memory network (middle frontal-inferior parietal, SMA, lateral cerebellum). During the decision making phase there was abnormal activation of regions involved in executive processes and memory (posterior-cingulate, parahippocampus). Connectivity between the striatum and areas of frontal and parietal cortex was greater 'off' than 'on', and the putamen showed greater connectivity with the left superior frontal gyrus 'on' compared to 'off'

*(continued)*

**Table 4** (continued)

Study	Imaging technique	Sample	Medication state	Task	Duration	Main findings
Husárová et al. [68]	fMRI	20 PD 21 HC	Off	Target interception task	Not applicable	Similar hit ratios in the two groups, but the groups differed in the distribution of early errors relative to hits and in trial by trial adjustments of performance. During successful trials, more activation in the right cerebellar lobule VI in HC than in PD. In HCs compared to PD, successful trial by trials adjustments were associated with higher activity in the right putamen and cerebellar lobule VI
Jahanshahi et al. [13]	PET	8 PD 8 HC	On & off	S-C finger tapping & Control RT task	1,000 ms	See Table 3 for behavioral results. Relative to control task, motor timing (S + C) associated with greater fronto-striatal activation for HCs, but greater activation of the cerebellum, vermis, midbrain/substantia nigra for PD. Relative to S, C associated with greater activation of DLPFC for both HC and PD. Cortical activation more predominant 'on' medication, whereas pallidal and cerebellar activation more evident 'off' medication. Greater caudate-frontal connectivity 'on' medication and greater striatal-cerebellar connectivity 'off' medication
Yu et al. [80]	fMRI	8 PD 8 HC	Off	Synchronization thumb tapping	900, 2,400 ms	No difference in behavioral performance for PD and HC. Underactivation in PD of the SMA, pre-SMA, DLPFC, caudate and putamen. Overactivation in PD of the cerebellum and primary motor cortex. This pattern was observed for both durations. Negative correlation between putamen and cerebellum in PD

*PD* Parkinson's disease, *HC* healthy control, *PET* Poistron emission tomography, *fMRI* functional magnetic resonance imaging, *S-C* synchronization-continuation, *SMC* sensorimotor cortex, *SMA* supplementary motor area

synchronization phase. Overactivation of the cerebellum in PD during motor timing has also been reported in Cerasa et al. [7] and Yu et al. [80]. Yu et al. [80] additionally reported underactivation of the striatum when 'off' medication, although Cerasa et al. [7] found overactivity in frontostriatal regions during the synchronization phase in patients tested 'off' medication. When looking at medication effects, Jahanshahi et al. [13] reported that cortical

activation was significantly more predominant 'on' medication, whereas pallidal and cerebellar activation was greater 'off' medication. Two distinct patterns of effective connectivity were found 'on' and 'off' dopaminergic medication. While there was greater task-related connectivity between the caudate and the left DLPFC and the right middle prefrontal cortex (BA 10/32) 'on' than 'off' medication, striatal-cerebellar connectivity was greater 'off' than 'on' medication.

These findings align with Yu et al. [80], who reported a negative correlation between activation of the ipsilateral cerebellum and contralateral putamen during synchronized tapping in patients with PD. Further, Elsinger et al. [10] found activation of the motor frontostriatal loop in patients with PD during the continuation phase when they were 'on' medication but not when they were 'off'.

In contrast, Husárová et al. [68] used a computerized target interception task, which requires implicit processing of time rather than the explicit engagement demanded by classic motor and perceptual tasks. A target moved at three different angles and speeds across the screen and the participants had to press a button to fire a cannonball that would intercept the moving target. The study used fMRI with 20 early stage (mean duration of illness of 2.5 years, including 8 de novo cases) patients with PD tested 'off' medication and 21 controls. Similar hit ratios were observed in the two groups, but the groups differed in the distribution of early errors relative to hits and in their trial by trial adjustment of performance. During successful trials, there was more activation in the right cerebellar lobule VI in the controls than in PD. For the controls, but not the PD patients, successful trial by trials adjustments were associated with higher activity in the right putamen and cerebellar lobule VI. Indeed, PD was characterized by hypoactivation of the striatum and cerebellum relative to the healthy controls. This study therefore implicates both the basal ganglia and the cerebellum in the adaption of motor actions to achieve optimal temporal performance. However, as a note of caution, none of the patients in this study had started levodopa medication. As levodopa responsiveness is a key criterion for distinguishing idiopathic PD from other Parkinsonian syndromes such as progressive supranuclear palsy or multiple systems atrophy, it is possible that not all participants in the patient group had idiopathic PD.

In summary, the results of these imaging studies indicate that, relative to healthy controls, perceptual and motor timing deficits in PD are

associated with underactivation of a range of frontal, temporal and parietal cortical areas as well as the striatum. Medication does not fully normalize these dysfunctional patterns of brain activation. In addition, the findings of some (e.g. [13]), but not all (e.g. [21]), studies suggest that patients with PD rely on the cerebellum for temporal processing, particularly in the 'off' medication state when task-related striatal-cerebellar connectivity is increased.

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### **Effects of Medical Treatments on Temporal Processing in Parkinson's Disease**

Pharmacological treatment and DBS are the two common medical treatment options in PD. The primary pharmacological treatment is a precursor to dopamine, levodopa. Levodopa is converted to dopamine in the central nervous system by the enzyme DOPA decarboxylase, which brings therapeutic benefit in PD. More recently, direct acting dopamine agonists have come into use. DBS involves implanting electrodes in key target areas, most commonly the sub-thalamic nucleus (STN). These electrodes are then connected to an implanted device in the chest cavity, generating electrical impulses to stimulate the STN. A recent study has shown that both STN DBS and a dopamine agonist (apomorphine) deactivate regional cerebral blood flow (rCBF) in the supplementary motor area, precentral gyrus, postcentral gyrus, putamen and cerebellum, and increase rCBF in the substantia nigra/sub-thalamic nucleus and superior parietal lobule [69]. However, the treatments also had distinct effects. Notably, STN DBS affected wider areas of the SMA, precentral gyrus and postcentral gyrus as well as uniquely affecting the globus pallidus, whilst apomorphine affected wider areas of the putamen and cerebellum and uniquely activated the superior temporal gyrus. Further, the direction of the effects on particular regions was often different between treatments. Certain areas (e.g. posterolateral cerebellum, ventrolateral thalamus) had their rCBF increased by STN DBS but decreased by apomorphine.

Thus, although both treatments have proven efficacy in ameliorating the cardinal symptoms of PD, they will not necessarily have identical effects on temporal processing. Further, it is important to recognize that both treatments do not just produce isolated effects on the basal ganglia, but rather both treatments induce changes in activation in the cortex [69]. Related to this, in addition to the targeted motor benefit, both medical treatments affect cognition, both positively and negatively, (e.g. [70, 71]).

### **The Effects of Dopaminergic Medication**

Close to half the studies reviewed in this chapter compared performance both 'on' and 'off' medication (see Table 5). For studies of motor timing, one study found that levodopa improved accuracy for short intervals [17] and one found an ameliorating effect on variability [16]. However, two studies found that medication did not improve motor timing [12, 14]; with a further two studies not reporting a direct comparison [6, 10]. A final two studies [13, 18] found no evidence that medication improved performance but interpretation is difficult as performance was also unimpaired 'off' medication. Overall, for the studies reporting a direct comparison in the context of impairment in the 'off' medication state, 3 of the 5 (60 %) reported a beneficial effect of dopamine replacement therapy. For the perceptual tasks, 6 of 12 tasks reporting a direct comparison found that medication benefits perceptual timing (50 %), while 4 (33 %) found no difference. Two studies (17 %) found better performance 'on' medication than 'off' [31, 36], which may reflect the negative effect dopamine can have on relatively preserved basal ganglia circuits, known as the 'dopamine overdose' effect. Therefore, although dopaminergic medication clearly can have a positive effect, there are many instances where it is not sufficient to impact upon performance. This may reflect a range of factors, including the different types of dopaminergic medication that patients take, as well as their effectiveness on the individual. Further, there are likely to be lingering effects of

medication in patients tested 'off' medication, which would diminish the extent of the performance difference observed 'on' vs. 'off'. Patients can also vary in their disease severity and duration of illness, which are factors that can also influence the impact of medication. Merchant et al. [6] tested the effect of dopaminergic medication across a range of perceptual and motor timing tasks. They found that while variability on their three timing tasks correlated in the 'on' medication state, the effect was not apparent when 'off' medication. They argued that the dopamine depleted state causes a major disruption to a common timing mechanism, located in the basal ganglia-thalamocortical pathway, that underpins motor and perceptual timing. It is also important to consider the wide-reaching effects that medication have on cortical structures. Thus, improvements following medication may reflect better cognitive control during the task. For example, Koch et al. [36] found that patients with PD showed greater underestimation on a time reproduction task when 'off' medication compared to 'on'. They suggested that this could reflect impulsivity or delay aversion when in the unmedicated state.

### **The Effects of Deep Brain Stimulation of the Subthalamic Nucleus**

Testing patients with STN DBS, Koch et al. [34] found that when 'off' DBS and 'off' medication the patients showed overestimation of 5 s and underestimation of 15 s intervals (i.e. the migration effect) compared to a control group. Performance was improved when the patients were either 'on' DBS (whilst 'off' medication) or 'on' medication (whilst 'off' DBS). The data are presented as evidence of the importance of thalamo-cortical projections to the prefrontal cortex in temporal processing. Similarly, Wojtecki et al. [19] found that there was improvement in time production of 15 s intervals for 130 Hz STN DBS compared to being in an untreated state. However, when they used a much lower 10 Hz DBS, time reproduction and production of 5 and 15 s intervals worsened. They

**Table 5** Effect of dopaminergic medication on motor and perceptual timing tasks

Study	Effect of dopaminergic medication
<i>Synchronization-continuation</i>	
Elsinger et al. [10] <sup>a</sup>	Off less accurate (Cont only) and more variable than Control On less accurate (Cont only) and more variable than Control
Ivry and Keele [12]	Off = On
Jahanshahi et al. [13] <sup>a</sup>	Off = On
Jones et al. [14]	Off = On
Merchant et al. [6]	Off more variability than Control On more variability than Control
O'Boyle et al. [16]	Off more variability than On
Pastor et al. [17]	Off less accurate and more variable than On for 500 and 667 ms (no statistical test)
Spencer and Ivry [18]	Off = On
<i>Duration discrimination</i>	
Guehl et al. [20]	Off = On
Harrington et al. [21] <sup>a</sup>	Off = On
Wearden et al. [25]	Short delay: Off = On Long delay: Off = On
<i>Peak interval procedure</i>	
Malapani et al. [26]	Off more error than On
<i>Temporal bisection</i>	
Merchant et al. [6]	Off more variability than Control On = Control
Wearden et al. [25]	Off = On
<i>Temporal generalization</i>	
Wearden et al. [25]	Off = On
<i>Time estimation</i>	
Lange et al. [29]	Off underestimate compared to Control On = Control
Pastor et al. [30]	Off more error than On
Wearden et al. [25]	Off = On
<i>Time production</i>	
Jones et al. [31]	On more error than Off
Lange et al. [29]	Off overestimate compared to Control On = Control
<i>Time reproduction</i>	
Jones et al. [31]	Off = On
Koch et al. [34]	Off less accurate than On
Koch et al. [35]	L hemi PD: Off less accurate than On for 15 s interval R hemi PD: Off less accurate than On for 5 s interval
Koch et al. [36]	On less accurate than Off Off = On when 1 h delay between short and long trials
Merchant et al. [6]	Off more variability than Control On more variability than Control
Torta et al. [37] <sup>b</sup>	Unfilled: Off = On Filled: Off underestimate compared to On
Pastor et al. [30]	Mixed results [Off generally worse than On for shorter intervals, and Off = On for most longer interval conditions (6 and 9 s)]

Direct comparison of 'off' vs 'on' reported where relevant. Two comparisons with Control groups reported in absence of direct comparison. *Cont* continuation phase

<sup>a</sup>Data collected during a neuroimaging (PET or fMRI) experiment

<sup>b</sup>Patients had undergone STN DBS, data reported in the table are when stimulation was turned off

interpret this as STN DBS having a frequency-dependent modulatory impact on memory representations of time, with a frequency of 10 Hz causing further disruption to an impaired temporal processing system, in contrast to the beneficial effects of 130 Hz. A further study found no effect of STN DBS on time reproduction of a seconds-range interval, albeit where performance was unimpaired without treatment, although STN DBS and medication both improved performance when the learnt interval was filled with performance of a motor task [37]. Wojtecki et al. [19] found no effect of STN DBS on millisecond-range repetitive tapping or duration discrimination, although again in patients who showed no difference from controls under any treatment state. However, a more recent study found that patients with PD who were 'on' medication had elevated variability on the synchronization-continuation task and this was improved when STN DBS was turned 'on' [15].

In summary, both medication and DBS can produce beneficial effects on temporal processing in PD. This is further evidence that the efficacy of the dopamine-rich basal ganglia is necessary for interval timing. From studies that investigated medication effects, medication is more beneficial in motor than perceptual timing, which may relate to the dominant motor demands of the former task.

### Conclusions and Future Directions

The phenotype of PD is broad, encompassing a range of motor, autonomic and cognitive symptoms (e.g. [72]). To better understand the mixed nature of some of the results reviewed above, an obvious point of exploration is to investigate heterogeneity of PD. The commonly identified clinical subtypes include those with predominantly akineto-rigid symptoms versus patients with tremor predominant symptoms [73]. Subgroups of patients can also be distinguished by age of onset, progression rate, and affected motor and non-motor domains (e.g. [74, 75]). The mixed results for motor and perceptual timing deficits in PD may be clarified through greater attention to clinically or experimentally

defined subtypes. Using an experimental approach, Merchant et al. [6] have sought to examine heterogeneity in timing in PD. They were able to divide their nineteen patients into those with 'high' variability on three diverse perceptual and motor timing tasks, and those with 'low' variability. Those with low variability did not differ in performance from a control group, which was in contrast to the group with high variability. Within the high variability group they found a further subdivision of just three individuals who did not show the scalar property, a hallmark of temporal processing. The two groups did not differ in a clinical evaluation of motor dysfunction or an experimental assessment of tapping speed, suggesting a specific difference in timing proficiency rather than a general difference in disease progression. More studies are needed that consider the effect of heterogeneity in PD. Heterogeneity may be the key to better understanding the specific clinical and biological markers of disordered motor and perceptual timing in PD.

Although the evidence on motor and perceptual timing deficits in PD is mixed, some clear conclusions can be drawn. First, there is evidence of both motor and perceptual timing dysfunction in PD. This suggests the importance of the basal ganglia in both types of timing and is compatible with the role of these subcortical nuclei as a neural clock that meters timing processes. However, this is still very much an area for debate. Although the basal ganglia may play a clock-type role in both types of timing tasks, the specific nature of this role may differ. Alternatively, they may play a timing-related role in limited types of timing task, with other findings being largely driven by cognitive or motor factors. While perceptual timing is compromised in both the milliseconds and seconds-range in PD, the deficits are confined to short (commonly 500 ms or below) intervals in motor timing. The very nature of motor timing does not lend itself to very long intervals. Long seconds-range motor timing would lose the continuous quality and become



a series of remembered, discrete intervals, much like a time reproduction task. However, studies suggest motor timing performance is preserved even at 1,000 and 2,000 ms intervals (e.g. [14]). Consistent with a critical role for the basal ganglia in temporal processing, medical treatment of PD with dopaminergic medication and STN DBS often has a positive effect on task performance. Better understanding of why some studies do not report evidence of a temporal deficit in PD, which may relate to task factors, cognitive factors or patient heterogeneity, is likely to be critical in furthering characterizing the role of the basal ganglia in interval timing.

Many researchers have considered a cognitive explanation for some of the timing deficits in PD, particularly on the perceptual timing tasks, and this alternative explanation needs to be empirically investigated in future studies. Understanding issues such as whether it is meaningful to separate memory for a timed interval from a 'clock' process would further interpretation of the data. Theoretical work on temporal processing has been limited, and has been dominated by the very influential scalar expectancy theory [76, 77]. More recently, the striatal beat frequency [78, 79] has aimed to provide a biologically plausible model of temporal processing. The field could benefit from further testable models of timing behaviour that could guide empirical investigation. This is clearly an important avenue for future progress in timing research.

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