doi:10.1093/brain/awz344 BRAIN 2020: 143; 727–750 | 727

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

Evolving concepts on bradykinesia

Matteo Bologna,[1,2] Giulia Paparella,[2] Alfonso Fasano,[3,4,5,6] Mark Hallett[7] and Alfredo Berardelli[1,2]

Bradykinesia is one of the cardinal motor symptoms of Parkinson's disease and other parkinsonisms. The various clinical aspects related to bradykinesia and the pathophysiological mechanisms underlying bradykinesia are, however, still unclear. In this article, we review clinical and experimental studies on bradykinesia performed in patients with Parkinson's disease and atypical parkinsonism. We also review studies on animal experiments dealing with pathophysiological aspects of the parkinsonian state. In Parkinson's disease, bradykinesia is characterized by slowness, the reduced amplitude of movement, and sequence effect. These features are also present in atypical parkinsonisms, but the sequence effect is not common. Levodopa therapy improves bradykinesia, but treatment variably affects the bradykinesia features and does not significantly modify the sequence effect. Findings from animal and patients demonstrate the role of the basal ganglia and other interconnected structures, such as the primary motor cortex and cerebellum, as well as the contribution of abnormal sensorimotor processing. Bradykinesia should be interpreted as arising from network dysfunction. A better understanding of bradykinesia pathophysiology will serve as the new starting point for clinical and experimental purposes.

1 Department of Human Neurosciences, Sapienza University of Rome, Italy
2 IRCCS Neuromed, Pozzilli (IS), Italy
3 Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Toronto, Ontario, Canada
4 Division of Neurology, University of Toronto, Toronto, Ontario, Canada
5 Krembil Brain Institute, Toronto, Ontario, Canada
6 Center for Advancing Neurotechnological Innovation to Application (CRANIA), Toronto, ON, Canada
7 Human Motor Control Section, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, USA

Correspondence to: Prof. Alfredo Berardelli
Department of Human Neuroscience
Sapienza University of Rome
Viale dell'Università, 30, 00185 Rome, Italy
E-mail: alfredo.berardelli@uniroma1.it

Keywords: bradykinesia; Parkinson's disease; motor control; transcranial magnetic stimulation; clinical neurophysiology

Abbreviations: DBS = deep brain stimulation; GPe/i = globus pallidus pars interna/pars externa; M1 = primary motor cortex; MDS = Movement Disorders Society; MSA = multiple system atrophy; PSP = progressive supranuclear palsy; STDT = somatosensory temporal discrimination threshold; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; TMS = transcranial magnetic stimulation; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Bradykinesia, which, as derived from the Greek, means slowness (brady-) of movement (kinesis), is one of the main motor symptoms of Parkinson's disease (Berardelli *et al.*, 2001, 2013; Postuma *et al.*, 2015; Berg *et al.*, 2018) and it is also present in atypical parkinsonisms (McFarland and Hess, 2017). Bradykinesia is the 'palsy' part of the 'shaking palsy' as originally described by James Parkinson, who referred to this aspect as 'lessened muscular power' (Parkinson, 2002; Obeso *et al.*, 2017). Although the term is apparently simple, and despite the widespread use of bradykinesia in clinical

Received July 8, 2019. Revised September 2, 2019. Accepted September 6, 2019. Advance Access publication December 13, 2019

practice and scientific literature, several issues on bradykinesia are still under debate.

In some circumstances, the term bradykinesia is used to refer to a broad range of motor disturbances, and it is often used interchangeably with the terms hypokinesia, which means low amplitude movement, and akinesia, no movement at all (Schilder *et al.*, 2017). Over the past few decades, bradykinesia in Parkinson's disease and atypical parkinsonism have been better characterized with the aid of neurophysiological measures, and a broad range of motor abnormalities have been described including the so-called sequence effect, i.e. amplitude and velocity decrement with repetitive and continuing movements. These studies indicate that the various bradykinesia features may vary considerably within and between different patients, in relation to several factors, including disease subtype and progression, dopaminergic medications and other interventions (Berardelli *et al.*, 2001; Agostino *et al.*, 2003; Espay *et al.*, 2009, 2011; Kang *et al.*, 2010; Bologna *et al.*, 2016*a*, *b*; Hasan *et al.*, 2017). Bradykinesia has been traditionally considered the consequence of a failure of basal ganglia output to the primary motor cortex (M1) (Albin *et al.*, 1989; DeLong, 1990; Berardelli *et al.*, 2001). More recent evidence based on direct basal ganglia recordings through deep brain stimulation (DBS) electrodes, as well as data from non-invasive brain stimulation and neuroimaging studies, have better defined the role of basal ganglia and indicated that other brain structures may be implicated in the pathophysiology of bradykinesia in Parkinson's disease, and these include the cerebellum. Moreover, altered mechanisms of sensorimotor integration may also play a role in the pathophysiology of bradykinesia. Insight into the pathophysiology of bradykinesia is relevant for understanding the therapeutic rationale of both pharmacological and non-pharmacological intervention in patients.

In the present paper, we will first discuss the issues of bradykinesia terminology and characterization in clinical and experimental studies in Parkinson's disease. We then focus on the pathophysiology of bradykinesia by discussing the role of basal ganglia and the possible involvement of alternative neural structures that provide further insight into a network perspective. Despite being less studied than in Parkinson's disease, clinical and experimental observations on bradykinesia in patients with atypical parkinsonisms will be also discussed. We emphasize how a better comprehension of the rationale and mechanisms of action of levodopa and other interventions (DBS) may help in understanding bradykinesia pathophysiology in Parkinson's disease and atypical parkinsonisms.

Bradykinesia: terminology and clinical aspects

Terminology

In Parkinson's disease, Barbeau *et al.* (1981) proposed the terms bradykinesia, hypokinesia and akinesia, respectively, to indicate the increasing degree of motor impairment. Others considered instead bradykinesia as synonymous of the slowness of voluntary movement and akinesia as a delay/failure of the willed movement to occur. Subsequently, the term bradykinesia has encompassed the other terms in the clinical context as well as in research (Gibb and Lees 1988; Calne *et al.*, 1992; Gelb *et al.*, 1999; Goetz *et al.*, 2008; Berardelli *et al.*, 2013; Berg *et al.*, 2013). In the first formal diagnostic criteria for Parkinson's disease, bradykinesia refers to slowness of initiation of voluntary movement with a progressive reduction in speed and amplitude of repetitive actions (Gibb and Lees, 1988). The definition was maintained by the European Federation of Neurological Societies (EFNS) criteria for Parkinson's disease diagnosis (Berardelli *et al.*, 2013) and by the current Movement Disorders Society (MDS) criteria, that define bradykinesia as slowness of movement and decrement in amplitude or speed (sequence effect) as movements are continued (Postuma *et al.*, 2015; Berg *et al.*, 2018).

In atypical parkinsonisms, the terminological use of bradykinesia is even less clear than in Parkinson's disease, because of the heterogeneity of these neurological conditions and the limited number of experimental studies. The MDS criteria for the diagnosis of progressive supranuclear palsy (PSP) (Höglinger *et al.*, 2017) indicate akinesia (and not bradykinesia) as one of the core features of the disease and as a synonymous of parkinsonism. For the clinical diagnosis of multiple system atrophy (MSA) (Gilman *et al.*, 2008), bradykinesia features are even not explicitly defined. For the diagnosis of cortical basal syndrome (CBS) (Armstrong *et al.*, 2013), the terms bradykinesia and akinesia are used interchangeably. Finally, according to the clinical criteria for dementia with Lewy bodies diagnosis (McKeith *et al.*, 2017), bradykinesia indicates slowness of movement and decrement in amplitude or speed as in Parkinson's disease, although this assumption only relies on clinical observations and there has not been a neurophysiological study of these patients.

In summary, there is still an ongoing debate on the terminology of bradykinesia in Parkinson's disease and atypical parkinsonisms. Bradykinesia terminology is nowadays based only on clinical observations; relying on neurophysiological concepts might improve the appropriateness of the terminological use of bradykinesia in Parkinson's disease and atypical parkinsonism.

The assessment of bradykinesia

The clinical assessment of bradykinesia in Parkinson's disease is currently based on the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (Goetz *et al.*, 2008), although other scales such as the Modified Bradykinesia Rating Scale (MBRS) (Kishore *et al.*, 2007) have also been proposed. In the MDS-UPDRS scale, limb bradykinesia is evaluated during different manoeuvres. The examiner is asked to rate speed, amplitude, hesitations and halts or decrement during 10 repeated movements, and all these abnormalities exert the same influence on the global

score. Similarly, spontaneous eye-blink frequency reduction, masked faces or loss of facial expression, including spontaneous smiling and the parting of lips are all considered for assessing hypomimia, i.e. facial bradykinesia. Differently from the MDS-UPDRS scale, in the MBRS the evaluator is asked to separately rate speed, amplitude and rhythm, possibly providing increased sensitivity in identifying different bradykinesia features (Kishore *et al.*, 2007; Heldman *et al.*, 2011). Nevertheless, the MBRS scale is not commonly used in clinical and experimental settings. The motor part of UPDRS is also consistently used to rate bradykinesia in atypical parkinsonisms patients. However, Golbe and Ohman-Strickland (2007) developed a disease-specific rating scale for PSP that scores several motor elements not included in the UPDRS (eye movements, bulbar function, neck extension, dystonia). This scale also allows a specific assessment of PSP staging (Golbe and Ohman-Strickland, 2007). Similarly, the European MSA Study Group developed a novel Unified MSA Rating Scale, whose motor part includes oculomotor dysfunction and ataxia evaluation (Wenning *et al.*, 2004).

Bradykinesia rating using clinical scales is significantly affected by inter- and intra-rater variability, and low reliability. To improve the reliability of bradykinesia rating, several technology-based tools have been proposed (Hasan *et al.*, 2017; Merola *et al.*, 2018). These tools provide continuous quantitative measurements and remote data collection. Some of them were approved by the Food and Drug Administration to quantify kinematics in movement disorders. Except for gait analysis systems and actigraphy, the effectiveness of technology-based tools in clinical practice has not been clearly established. Interestingly, less than 3% of ongoing clinical trials of neurodegenerative disorders have employed technology-based tools as an outcome measure (Merola *et al.*, 2018).

In summary, the clinical assessment of bradykinesia in Parkinson's disease and atypical parkinsonisms is currently based on the specific assessment of dedicated clinical rating scales. Bradykinesia rating, however, may be affected by inter- and intra-rater variability as well as by low reliability; technology-based tools can theoretically help to provide more accurate measurements. However, their role in clinical practice has not been fully established yet.

Features associated or contributing to bradykinesia

A further issue is the role of secondary contributing factors to bradykinesia, and their burden in the clinical evaluation of bradykinetic patients. It has been suggested that in Parkinson's disease weakness can contribute to bradykinesia. A correlation between muscle weakness and slowness of movement was found (Corcos *et al.*, 1996), as well as an effectiveness of strength training on UPDRS motor scores (David *et al.*, 2016; Ni *et al.*, 2016; Krumpolec *et al.*, 2017). Moreover, antiparkinson medications improved force generation (Brown *et al.*, 1997). Fatigue, defined as an overwhelming sense of tiredness and lack of energy (Krupp *et al.*, 1989), has also been described in Parkinson's disease (Friedman, 2009; Berardelli *et al.*, 2012; Fabbrini *et al.*, 2013; Friedman *et al.*, 2016; Siciliano *et al.*, 2018). However, there is no clear evidence of any relationship between fatigue, assessed by clinical rating scale, and bradykinesia tested with the Purdue pegboard test or finger tapping (Kang *et al.*, 2010; Bologna *et al.*, 2016*b*), probably in light of the several involved factors other than movement impairment (i.e. motivation, apathy, and depression). It could be that a relationship between fatigue and sequence effect is present but this has not yet been demonstrated (Berardelli *et al.*, 2012). Tinaz *et al.* (2016), for example, showed that sequence effect in Parkinson's disease cannot be explained by excessive peripheral fatigue. Additionally, there was no significant correlation between fatigue and the severity of progressive micrographia, considered a manifestation of the sequence effect (Wu *et al.*, 2016). Another possible factor contributing to bradykinesia is tremor (Berardelli *et al.*, 2001). The possible mechanisms previously suggested include the prolongation of reaction times, an incompletely fused muscle contraction caused by tremor, thus determining muscle weakness and bradykinesia (Brown *et al.*, 1997), as well the 'pacing' effect of tremor on voluntary movements (Hallett *et al.*, 1977; Logigian *et al.*, 1991). More recent data on large samples of Parkinson's disease patients, however, showed no positive correlations between action tremor and bradykinesia severity (Gigante *et al.*, 2015; Belvisi *et al.*, 2018). Finally, bradyphrenia or mental slowness is another possible contributing factor for bradykinesia. Some studies report cognitive slowing in Parkinson's disease (Wilson *et al.*, 1980; Pillon *et al.*, 1989; Cooper *et al.*, 1994; Sawamoto *et al.*, 2002; Lee *et al.*, 2003; Jokinen *et al.*, 2013; Vlagsma *et al.*, 2016). Although the relationship between cognitive abnormalities and movement execution remains poorly investigated, it has been observed that Parkinson's disease patients with cognitive impairment have prolonged reaction times compared to those with preserved cognitive capacities (Revonsuo *et al.*, 1993). Furthermore, bradykinesia score, as assessed by clinical scales, seems to be associated with mild cognitive impairment in Parkinson's disease and to deteriorate in parallel with motor disease progression (Poletti *et al.*, 2012; Domellöf *et al.*, 2013; Stojkovic *et al.*, 2018). However, other observations imply otherwise (Vlagsma *et al.*, 2016). Recently, Hanakawa *et al.* (2017) measured the agility of Parkinson's disease patients performing a series of movement, motor imagery, and calculation tasks with a progressive increase in task rate. They also performed functional MRI and diffusion tractography to test whether dysfunctions of basal-ganglia-thalamo-cortical circuits underlying motor and cognitive processing were associated with motor and cognitive slowing. The authors concluded that cognitive slowing was associated with dysfunction of different basal-ganglia-thalamo-cortical circuits from those causing motor impairments, providing a further insight in the understanding of the relation between cognitive and motor slowness.

In summary, the features associated with or contributing to bradykinesia remain poorly investigated. Weakness can contribute, at least in part, to bradykinesia. Also, cognitive abnormality may impair the movement preparation phase, thus resulting in increased reaction times. Finally, there is not enough evidence to establish a firm relationship between bradykinesia and other features like fatigue and tremor.

Neurophysiological characterization of bradykinesia

As a refinement of clinical observations, neurophysiological measures have clearly shown that bradykinesia includes a broad range of motor abnormalities, involving both the preparation and execution phases of voluntary movements, and variably affects different body segments. Many neurophysiological studies on bradykinesia have been performed in Parkinson's disease, conversely a relatively low number of studies have been performed in atypical parkinsonisms.

In Parkinson's disease, the majority of studies have consistently shown that the movement preparation is abnormally prolonged due to a delay in muscle activation, as evidenced by investigations on simple and choice reaction times (Wiesendanger *et al.*, 1969; Heilman *et al.*, 1976; Stelmach *et al.*, 1986; Dubois *et al.*, 1988; Pullman *et al.*, 1988; Rafal *et al.*, 1989; Jahanshahi *et al.*, 1992*a*, *b*, 1993; Brown *et al.*, 1993; Revonsuo *et al.*, 1993; Pascual-Leone *et al.*, 1994; Torrecillos *et al.*, 2018). Abnormalities of simple reaction times and no (or less) alterations of choice reaction times (Evarts *et al.*, 1981; Bloxham *et al.*, 1984; Sheridan *et al.*, 1987) suggested that slowness in motor execution in Parkinson's disease was not due to a global deficiency in motor preparation and that the contribution of prolonged simple reaction time in generating bradykinesia could be interpreted as a failure in programming a motor response (Berardelli *et al.*, 2001). The addition of a warning signal improved reaction times both in healthy controls and in Parkinson's disease, demonstrating that the slowness in motor preparation was not due to an 'arousal defect' (Bloxham *et al.*, 1987). Other observations also suggest that Parkinson's disease patients use different strategies for dealing with different stimulus-response relationships; for example, their performance was worse in simpler tasks with compatible stimulus-response relationship (Brown *et al.*, 1993). The effects of levodopa on reaction times have also been shown to be variable, although choice reaction times were shown to be more sensitive than simple reaction times to levodopa administration (Bloxham *et al.*, 1987; Pullman *et al.*, 1988; Jahanshahi *et al.*, 1992*b*; Brown *et al.*, 1993).

Studies on motor execution have extensively characterized bradykinesia of the upper limbs. Parkinson's disease patients performing fast single-joint movements display an inability to generate an adequate initial agonist burst so that the exerted force is insufficient to reach the desired target. The movement is completed by a series of small amplitude movements characterized by repeated agonist and antagonist EMG bursts or by a prolonged continuous discharge. Despite this, if patients aim to perform a movement of a larger amplitude, they succeed in increasing the size of the first burst. Further studies demonstrated that Parkinson's disease patients choose a smaller size than is appropriate for the motor task. This means that bradykinesia is generated from an inappropriate scaling of the dynamic muscle forces, the so-called scaling effect (Flowers, 1976; Hallett *et al.*, 1977; Hallett and Khoshbin, 1980; Baroni *et al.*, 1984; Berardelli *et al.*, 1986, 1996*a*; Pfann *et al.*, 2001; Seidler *et al.*, 2001). Complex (multi-joint) movements are also slower in Parkinson's disease (Phillips *et al.*, 1994; Bennett *et al.*, 1995; Castiello and Bennett, 1997; Majsak *et al.*, 1998; Alberts *et al.*, 2000; Castiello *et al.*, 2000; Jackson *et al.*, 2000; Farley *et al.*, 2004). The simultaneous execution of two different tasks in patients with Parkinson's disease leads to a more severe slowing in movement than that observed when each task was performed alone (Schwab *et al.*, 1954; Benecke *et al.*, 1986; Stelmach and Worringham, 1988; Brown and Marsden, 1991; Castiello and Bennett, 1997; Johnson *et al.*, 1998; Delval *et al.*, 2017). Movement slowness is even worse in the execution of sequential movements (Table 1). The slowness of sequential movements is more evident when patients rely on internal control processes (i.e. internally generated movements) in comparison to externally cued movements (Georgiou *et al.*, 1994; Currà *et al.*, 1997; Fasano and Bloem, 2013). This is particularly evident during gait, thus meaning that Parkinson's disease patients experience difficulties walking in an automatic manner and must progressively rely on a goal-directed control of their gait (Nonnekes *et al.*, 2019). External cues trigger goal-directed behaviour that is better performed, which bypasses the defective basal ganglia (Redgrave *et al.*, 2010).

One component of bradykinesia is the sequence effect, i.e. the decrement of movement speed and amplitude during movement repetition (Agostino *et al.*, 1992, 1994, 2003; Iansek *et al.*, 2006; Lee *et al.*, 2014; Postuma *et al.*, 2015; Bologna *et al.*, 2016*b*; Tinaz *et al.*, 2016) (Table 2). Patients with Parkinson's disease take progressively longer times to perform sequential segments of a geometric sequence (Agostino *et al.*, 1992, 1994; Lee *et al.*, 2014). A progressive decrease in movement speed has also been documented during finger tapping (Agostino *et al.*, 2003; Espay *et al.*, 2009, 2011; Bologna *et al.*, 2016*a*, 2018), the Purdue pegboard test (Kang *et al.*, 2010, 2011), during writing, i.e. the so-called progressive micrographia (Wu *et al.*, 2016), and walking (Iansek *et al.*, 2006; Delval *et al.*, 2017). When severe, the sequence effect can terminate with a freeze (i.e. motor block) (Giladi *et al.*, 1992). The sequence effect may indeed be a prominent feature of the early stages of Parkinson's disease (Lee *et al.*, 2014; Bologna *et al.*, 2016*a*, *b*), and it tends to be less frequent in advanced Parkinson's disease (Bologna *et al.*, 2016*a*, *b*). One possibility why the sequence effect is less frequent

Table 1 Upper limb movements

Movement type	Major findings	Effects of treatment
Single-and multi-joint movements		
Flowers *et al.*, 1976; Hallett *et al.*, 1977; Hallett and Khoshbin, 1980; Baroni *et al.*, 1984; Berardelli *et al.*, 1986; Pfann *et al.*, 2001; Seidler *et al.*, 2001.	Slowness of movement; abnormal EMG pattern in Parkinson's disease. Coactivation of muscles of different joints.	Slight improvement after levodopa.
Complex movements (reaching/grasping/drinking/drawing)		
Phillips *et al.*, 1994; Bennett *et al.*, 1995; Castiello and Bennett, 1997; Majsak *et al.*, 1998; Alberts *et al.*, 2000; Castiello *et al.*, 2000; Jackson *et al.*, 2000; Farley *et al.*, 2004.	Lower acceleration, velocity and accuracy. Underscaled grasp components. Longer pauses between sequential movements.	Improvement in velocity and regularity after levodopa. N/A on the grasp component of reaching movements. N/A on drawing.
Simultaneous movements		
Schwab *et al.*, 1954; Benecke *et al.*, 1986; Stelmach and Worringham, 1988; Brown and Marsden, 1991; Agostino *et al.*, 1992; Brown *et al.*, 1993; Castiello and Bennett, 1997; Johnson *et al.*, 1998; Delval *et al.*, 2017.	Increased slowness in simultaneous movements.	N/A

N/A = not available.

Table 2 Sequence effect

Movement type	Major findings	Effects of treatment
Sequential arm movements		
Agostino *et al.*, 1992, 1994; Lee *et al.*, 2014; Tinaz *et al.*, 2016.	Sequence effect in patients with various disease stages, including early Parkinson's disease.	N/A
Purdue pegboard test		
Kang *et al.*, 2010, 2011.	Sequence effect in patients with various disease stages, including early Parkinson's disease.	No improvement with levodopa or 1 Hz rTMS of M1.
Writing		
Wu *et al.*, 2016.	Sequence effect (progressive micrographia) in a subgroup of patients.	Levodopa improved consistent but not progressive micrographia.
Finger tapping		
Agostino *et al.*, 2003; Espay *et al.*, 2009, 2011; Ling *et al.*, 2012; Bologna, *et al.*, 2016*a*, *b*, 2018; Djuric-Jovicic *et al.*, 2016.	Sequence effect in Parkinson's disease higher in individual than in non-individual finger movements; Sequence effect in early but not in advanced Parkinson's disease. Sequence effect in Parkinson's disease and in MSA but not in PSP.	No improvement with levodopa, duodopa and selegiline administration.
Walking		
Iansek *et al.*, 2006; Delval *et al.*, 2017.	Sequence effects contribute to freezing of gait episodes.	No improvement with levodopa.

N/A = not available; rTMS = repetitive transcranial magnetic stimulation.

during arm movements in advanced patients is likely because in advanced patients the initial EMG burst is already of low amplitude (Bologna et al 2016*a*, *b*). During gait, a sequence effect is noticeable during a straight path, expressed as progressive reduction of the step length. A sequence can be terminated by a motor block (akinesia), which is clinically defined as freezing of gait (Iansek *et al.*, 2016). Alternatively, it can be transient as the patient restores the ability to generate step length, which often results in another sequence ('oscillatory variability') (Fasano and Bloem, 2013). Rarely the sequence effect does not cease, and it is not interrupted by a motor block, as seen in festination. The phenomenon of sequence effect during straight walking has been interpreted as a maladaptive motor behaviour, whereby the brain tries to compensate for gait asymmetry in the presence of defective inter-limb coordination and amplitude generation (Fasano *et al.*, 2016). In PSP, Ling *et al.* (2012) found that repetitive finger tapping, as assessed by a 3D motion analysis system, were 'hypokinetic', i.e. characterized by low amplitude movement, with no decrement in amplitude as movements continued. Djuric-Jovicic and colleagues (2016) confirmed the lack of progressive reduction in amplitude during the finger tapping in patients with PSP-Richardson syndrome compared to Parkinson's disease or MSA patients (Table 3). It has been argued that atypical

Table 3 Facial bradykinesia

Movement type	Major findings	Effects of treatment
Spontaneous blinking		
Karson *et al.*, 1984; Deuschl and Goddemeier, 1998; Kimber and Thompson, 2000; Altiparmak *et al.*, 2006; Korosec *et al.*, 2006; Agostino *et al.*, 2008; Bologna *et al.*, 2009.	Reduced rate, amplitude and velocity in Parkinson's disease, PSP and MSA.	Improvement after levodopa in Parkinson's disease.
Voluntary blinking		
Korosec *et al.*, 2006; Agostino *et al.*, 2008; Bologna *et al.*, 2009.	Normal amplitude and velocity, longer inter-phase pause in Parkinson's disease. Reduced amplitude and velocity, longer inter-phase in PSP.	Improvement after levodopa in Parkinson's disease.
Spontaneous and voluntary movements of the lower face		
Caligiuri, 1987; Katsikitis and Pilowsky, 1988; Connor *et al.*, 1989; Jacobs *et al.*, 1995; Deuschl and Goddemeier, 1998; Marsili *et al.*, 2014.	Reduced amplitude and velocity.	N/A
Facial emotion expression		
Smith *et al.*, 1996; Seidler *et al.*, 2001; Simons *et al.*, 2004; Marsili *et al.*, 2014; Bologna *et al.*, 2016*c*.	Abnormally reduced.	No improvement with levodopa.

N/A = not available.

parkinsonisms as well as advanced Parkinson's disease have a too severe impairment of amplitude generation that further decrements (i.e. the sequence effect) are not possible. Our own observation, however, is that in some cases of PSP the sequence effect can be present.

Although there are no systematic studies investigating the effect of levodopa administration in Parkinson's disease on each motor abnormality, it seems that levodopa improves but does not normalize the abnormal movement parameters. Levodopa improves the speed and amplitude of movement by modifying the amplitude and temporal scaling of the agonist and antagonist bursting pattern (Baroni *et al.*, 1984; Berardelli *et al.*, 2001; Vaillancourt *et al.*, 2004; Espay *et al.*, 2009, 2011; Suppa *et al.*, 2017). However, the improvement of kinematic measures is lower in subjects markedly hypokinetic (Espay *et al.*, 2011). Moreover, levodopa does not alleviate the sequence effect (Kang *et al.*, 2010; Lee *et al.*, 2014; Wu *et al.*, 2016; Suppa *et al.*, 2017). Further evidence of the peculiarity of the sequence effect and of its responsiveness to levodopa came from a study on micrographia in Parkinson's disease (Wu *et al.*, 2016). Patients were divided in two groups, the first showing consistent micrographia, i.e. a global reduction but without significant progressive reduction in writing size, the second presenting progressive micrographia, i.e. a gradual reduction in size during writing. While consistent micrographia can be considered a manifestation of hypokinesia (smallness of movement), progressive micrographia is a manifestation of the sequence effect. Patients underwent functional MRI, revealing different neural correlates of the two types of micrographia. Dysfunction of the basal ganglia motor circuit contributed to consistent micrographia, whereas dysfunction of the basal ganglia motor circuit plus disconnections among motor cortical areas and the cerebellum was likely involved in progressive micrographia. Consistent but not progressive micrographia improved with the treatment (Wu *et al.*, 2016). Additional characterization of the sequence effect on Parkinson's disease has been provided by Tinaz *et al.* (2016), who approached the sequence effect as a central problem of motor energy. They tested Parkinson's disease patients performing a dynamic isometric task with or without a visual feedback in two conditions (on and off therapy) and compared them with healthy subjects. They confirmed the poor effect of levodopa on the sequence effect, pointing to the possible involvement of other systems and neurotransmitters in generating the sequence effect. Second, they pointed out that energetic cost of performance in the first 15 s of the sequence was significantly higher in Parkinson's disease. Finally, visual feedback, which provided an external reference, improved the performance in both groups. The sequence effect may then reflect the difficulty in sustaining motor performance when the required effort has to be motivated and generated internally (Tinaz *et al.*, 2016).

Although limb bradykinesia must be documented to establish a diagnosis of Parkinson's disease, bradykinesia also occurs in the face, voice and axial/gait domains (Postuma *et al.*, 2015, 2018). At facial level, one of the most striking features of Parkinson's disease is hypomimia, ranging from minimal masked face and spontaneous blink rate reduction to lower face involvement and lips parted when the mouth is at rest (Goetz *et al.*, 2008). Spontaneous blink rate reduction has consistently been demonstrated in Parkinson's disease, and it has been demonstrated that it is strictly associated with low central dopaminergic activity (Karson *et al.*, 1984; Deuschl and Goddemeier, 1998; Kimber and Thompson, 2000; Altiparmak *et al.*, 2006; Korosec *et al.*, 2006; Agostino *et al.*, 2008; Bologna *et al.*, 2013). Studies based on voluntary facial movements, however, showed normal velocity and amplitude of blinking, although the duration of the inter-phase pause was longer in Parkinson's disease than in control subjects (Korosec

et al., 2006; Agostino *et al.*, 2008; Bologna *et al.*, 2012). A reduction in spontaneous lower face (perioral) movements has been observed in Parkinson's disease (Deuschl and Goddemeier, 1998). Different from upper face, reduced velocity and amplitude has been documented in the lower face during repetitive syllable productions or spontaneous and posed smile (Caligiuri, 1987; Katsikitis and Pilowsky, 1988; Connor *et al.*, 1989; Jacobs *et al.*, 1995; Smith *et al.*, 1996; Simons *et al.*, 2004; Marsili *et al.*, 2014; Bologna *et al.*, 2016*c*). Also, although levodopa improves spontaneous blinking, it seems to have negligible effects on voluntary movements of both the upper and lower face in Parkinson's disease (Bologna *et al.*, 2013; Suppa *et al.*, 2017) (Table 4). In contrast, DBS of subthalamic nucleus (STN) has been found to increase beyond normal the velocity and amplitude of voluntary blinking while prolonging the duration of the inter-phase pause (which was reduced by the concomitant administration of levodopa) (Bologna *et al.*, 2012). Recently, it has been pointed out that hypomimia is highly associated with the likelihood of striatal dopaminergic denervation more than limb bradykinesia (Mäkinen *et al.*, 2019).

Loss of spontaneous facial expression has been consistently reported in patients with PSP and MSA (Romano and Colosimo, 2001; Tison *et al.*, 2002; Fabbrini *et al.*, 2009). The spontaneous blink rate is markedly reduced in atypical parkinsonisms, particularly in PSP (Altiparmak *et al.*, 2006; Bologna *et al.*, 2009, 2013, 2014). In PSP, reduced velocity and amplitudes have been documented during voluntary movements of both the upper and lower face (Bologna *et al.*, 2013) (Table 3).

In summary, earlier neurophysiological studies in Parkinson's disease patients focused on upper limb bradykinesia and documented abnormalities of movement preparation and execution, resulting in abnormal prolongation of simple and choice reaction times and movement slowness. Subsequent studies have documented the sequence effect and its variable presence or association with other movement abnormalities in Parkinson's disease and atypical parkinsonisms. Finally, an increasing number of studies now document bradykinesia features in the face, voice, and axial/gait domains. Because some of these abnormalities (i.e. hypomimia) may be associated with a higher likelihood of striatal dopaminergic denervation compared to limb bradykinesia (Mäkinen *et al.*, 2019), the assumption that limb bradykinesia must be documented to establish a diagnosis of Parkinson's disease (Postuma *et al.*, 2015, 2018) is questionable.

Bradykinesia pathophysiology

The role of basal ganglia

According to the classical basal ganglia model the main input area of basal ganglia is the striatum, which receives afferents from many cortical areas and from the intralaminar nuclei of the thalamus (Albin *et al.*, 1989; DeLong, 1990). The major output regions of the basal ganglia are the globus pallidus pars interna (GPi) and the substantia nigra pars reticulata (SNr), which project to the thalamus modulating the activity of cortical regions and to the brainstem (Albin *et al.*, 1989; DeLong, 1990; Obeso *et al.*, 2000). The so called 'direct pathway' inhibits the GPi/

Table 4 Recordings from basal ganglia

Parameter/phenomenon	Major findings	Effects of treatment
Firing rate		
Pan and Walters, 1988; Bergman *et al.*, 1994; Hutchison *et al.*, 1994; Sterio *et al.*, 1994; Hassani *et al.*, 1996; Wichmann *et al.*, 1999; Mallet *et al.*, 2006; Kita and Kita, 2011.	Increased in STN, GPi/SNr; decreased in GPe.	Levodopa improves the firing rate abnormalities.
Firing patterns		
Bergman *et al.*, 1994; Hutchison *et al.*, 1994; Zirh *et al.*, 1998; Magnin *et al.*, 2000; Raz *et al.*, 2000; Vila *et al.*, 2000; Wichmann and Soares, 2006; Steigerwald *et al.*, 2008; Chan *et al.*, 2011	Increased bursting in GPe, STN, GPi/SNr and thalamus.	Levodopa decreases bursting activity.
Synchrony		
Nini *et al.*, 1995; Raz *et al.*, 1996; Levy *et al.*, 2000, 2002*b*; Mallet *et al.*, 2008*a*; Kühn *et al.*, 2009.	Increased in striatum, GPe, STN, GPi/SNr.	Levodopa decreases synchrony.
Oscillatory activity (single cell recordings)		
Bergman *et al.*, 1994; Raz *et al.*, 1996, 2000; Levy *et al.*, 2002*b*; Soares *et al.*, 2004; Kammermeier *et al.*, 2016; Sharott *et al.*, 2017.	Increased beta activity in striatum, GPe, STN, GPi/SNr and thalamus.	Levodopa decreases beta and increases gamma activity.
Oscillatory activity (neuronal population)		
Brown *et al.*, 2001; Priori *et al.*, 2004; Sharott *et al.*, 2005*a*; Little *et al.*, 2012; Tan *et al.*, 2013; Devergnas *et al.*, 2014; Tinkhauser *et al.*, 2017; Torrecillos *et al.*, 2018.	Increased beta activity in striatum, STN, GPi/SNr and thalamus. Decreased gamma activity in STN.	Levodopa decreases beta and increases gamma activity.

SNr, and thereby facilitates the motor centres targeted by these nuclei (Albin *et al.*, 1989; DeLong, 1990; Benarroch, 2016; Grillner and Robertson, 2016). The so-called 'indirect pathway' includes projections via the inhibitory globus pallidus pars externa (GPe) and the excitatory STN, targeting the output nuclei of the basal ganglia (GPi/SNr). The net effect of the indirect pathway is to inhibit the motor centres that are innervated by these nuclei. Regardless, studies with optogenetic techniques in mice showed a concurrent activation of striatum from both pathways in one hemisphere during the initiation of specific movements, (Cui *et al.*, 2013). A third hyperdirect cortico-subthalamic pathway is considered a inhibitory network implicated in outcome optimization (Nambu *et al.*, 2002; Aron *et al.*, 2016). As recently demonstrated, the hyperdirect and indirect pathways both projecting on the STN are differentially involved in cognitive aspects of motor preparation and control of motor performance (Neumann *et al.*, 2018). Data from rats have identified a central role of STN in generating bradykinesia, demonstrating that the delivery of negative constant current into STN dramatically ameliorates locomotor deficits in parkinsonian rats, while delivering of positive constant currents to STN induces Parkinson's disease-like locomotor deficits in normal rats (Tai *et al.*, 2012). Concerning the role of dopamine in motor control, experimental studies have shown that dopaminergic neurons are transiently and rapidly activated before spontaneous movement (Howe and Dombeck, 2016) with transient dopamine release triggering movement onset. Dopaminergic activity is likely to be critical for the modulation of movement onset and vigor of future movements (da Silva *et al.*, 2018; Yttri and Dudman 2018). Dopamine secretion is rapid, transient and has a high initial release rather than a sustained secretion (Liu *et al.*, 2018), thus explaining why chronic administration of levodopa does not restore specific motor functions, such fine motor tasks.

Bradykinesia in patients with Parkinson's disease is classically associated with a significant (around 50–60%) dopamine striatal depletion (Fearnley and Lees, 1990; Ehringer and Hornykiewicz, 1998; Kalia and Lang, 2015; Liu *et al.*, 2018), which mainly involves the vulnerable ventrolateral cell groups of the substantia nigra (nigrostriatal pathway). Loss of dopamine reduces the activity of D1 receptor direct pathway activating the striatum and increases the D2 receptor indirect pathway inhibiting the striatum (Wichmann and DeLong, 1996). While direct pathway neurons reduce their firing rate, those in the indirect pathway increase their activity. As a result, the firing in GPe neurons is reduced, which leads to disinhibition of STN neuronal activity changes and, subsequently, excessive excitation of STN targets (GPi and SNr) (Pan and Walters, 1988; Bergman *et al.*, 1994; Hutchison *et al.*, 1994; Sterio *et al.*, 1994; Hassani *et al.*, 1996; Wichmann *et al.*, 1999; Mallet *et al.*, 2006; Kita and Kita, 2011). The increased activity of GPi and SNr neurons is further reinforced by the lack of inhibition from direct pathway neurons. This leads to excessive inhibition of thalamo-cortical and brainstem motor systems, thus interfering with both preparation and execution phases of the voluntary movement (Wichmann and DeLong, 1996). Dopaminergic treatment produces its effects on converging basal ganglia pathways. Namely, it has been shown that dopamine increases the direct pathway medium spiny neurons activity, critically contributing to D1 agonism's motor stimulation in parkinsonian animals (Sagot *et al.*, 2018). The relative hyperactivity of STN and GPi has been advocated to explain the symptomatic effect of ablations or DBS of these targets (functional inhibition hypothesis) (Udupa and Chen, 2015).

The so-called 'firing model' of basal ganglia bears several limitations (Bar-Gad *et al.*, 2001). In fact, besides changes in firing rate, other complex electrophysiological phenomena occur in basal ganglia (Table 4). These include enhanced bursting, exaggerated oscillatory activity particularly in the beta frequency and coherent activity patterns between basal ganglia nuclei (Nini *et al.*, 1995; Raz *et al.*, 1996; Zirh *et al.*, 1998; Levy *et al.*, 2000, 2002*a*, *b*; Magnin *et al.*, 2000; Raz *et al.*, 2000; Vila *et al.*, 2000; Brown *et al.*, 2001; Soares *et al.*, 2004; Sharott *et al.*, 2005; Wichmann and Soares, 2006; Hammond *et al.*, 2007; Mallet *et al.*, 2008; Steigerwald *et al.*, 2008; Chan *et al.*, 2011; Tai *et al.*, 2012; Ellens and Leventhal, 2013; Devergnas *et al.*, 2014; Kammermeier *et al.*, 2016; Sharott *et al.*, 2017; Rodriguez-Sabate *et al.*, 2019). As evidenced by DBS studies basal ganglia beta activity (13–35 Hz) is increased in Parkinson's disease (Brown *et al.*, 2001; Brown, 2003) and the amplitude of this activity correlates with motor impairment. The excessive beta activity occurs more in neurons in the indirect pathway (Sharott *et al.*, 2017), and, as this pathway is inhibitory, there is some understanding as to why excessive activity might lead to bradykinesia. Pathological beta activity is characterized by prolonged bursts of activity with an excessive synchronization within bilateral basal ganglia circuits (Tinkhauser *et al.*, 2017). The abnormal synchronization is also seen between hemispheres and possibly correlates with specific signs of Parkinson's disease, such as freezing of gait; it has been argued that the longer the beta burst within the STN, the higher the chance that this synchronizes with the burst of the opposite hemisphere (Tinkhauser *et al.*, 2017). Abnormal activity patterns correlate with compromised motor performance, including various bradykinesia features (Kühn *et al.*, 2009; Jenkinson and Brown, 2011; Oswal *et al.*, 2013; Little and Brown, 2014). STN abnormal activity directly correlates with the severity of hand bradykinesia in Parkinson's disease (Little *et al.*, 2012; Tan *et al.*, 2013). Prolonged beta bursts in the STN correlates with the slowness of movement or reaction time prolongation in Parkinson's disease (Tinkhauser *et al.*, 2017; Torrecillos *et al.*, 2018). Beta bursts and beta power suppression during repeated movements progressively reduce over time and parallel progressive decrement in the frequency, velocity and amplitude of movements (Steiner *et al.*, 2017; Lofredi *et al.*, 2019). Furthermore, the lack of gamma recruitment alters the signal scaling across different

movement velocities (Lofredi *et al.*, 2018). Dopaminergic medications, or DBS, improve motor function by modifying basal ganglia circuits' dynamics from persistent synchronized activity to a more dynamic activity pattern (Priori *et al.*, 2004; Hahn *et al.*, 2008; Vitek *et al.*, 2012; Cleary *et al.*, 2013; Müller and Robinson. 2018), which correlates with clinical improvements of bradykinesia (Ray *et al.*, 2008; Kühn *et al.*, 2009; Tai *et al.*, 2012; Trager *et al.*, 2016). The effect of dopaminergic therapy on oscillatory basal ganglia activity has been studied in detail by Tinkhauser *et al.* (2017) demonstrating that in Parkinson's disease patients with externalized STN DBS electrodes levodopa administration shortens and decreases the amplitude of the prolonged bursts of beta activity; levodopa also makes the bursts of pathological activity less frequent. The reduction of burst activity induced by levodopa correlated with clinical improvement. Similar findings have been obtained with DBS, particularly when stimulating on-demand with an 'adaptive' DBS (aDBS, also known as closed-loop DBS) (Little *et al.*, 2013). The pathophysiological role of beta oscillation is confirmed, although not by all studies, by the observation that 10–20 Hz DBS can worsen bradykinesia, likely pacing or increasing these low-frequency oscillation (Timmermann *et al.*, 2004; Su *et al.*, 2018). On the other hand, studies have confirmed that levodopa induces a reduction of beta activity and synchronization within higher frequencies (70 Hz) in basal ganglia (Brown *et al.*, 2001; Williams *et al.*, 2002; Foffani *et al.*, 2003). Accordingly, DBS using frequencies within the gamma band (60–80 Hz) has been found to improve bradykinesia (reviewed in di Biase and Fasano, 2016). A recent paper found that movement regularity improved during 60-Hz DBS but not during 140-Hz DBS, while both frequencies were able to improve movement velocity, thus suggesting different but overlapping mechanisms explaining the benefit of these DBS frequencies (Blumenfeld *et al.*, 2017). In particular, 60-Hz DBS amplified oscillations in a low beta-band (11–15 Hz) and attenuated oscillations in a high beta-band (19–27 Hz) whereas 140-Hz DBS attenuated oscillations across the beta-band frequency range (Blumenfeld *et al.*, 2017). Again, these findings reinforce the hypothesis that certain low frequency oscillations (i.e. short bursts, lower end of the beta band spectrum) are indeed beneficial to the physiological function of the basal ganglia whereas others (i.e. long bursts, higher end of the beta band spectrum) are pathological underpinnings of bradykinesia. Beyond the aforementioned local effects, the beneficial effect of DBS relies on its property to decouple the excessive synchronization between cortico-subcortical regions within the same hemisphere (de Hemptinne *et al.*, 2015) and between hemispheres (Little *et al.*, 2016).

Finally, plasticity abnormalities at basal ganglia level have been recently suggested as an additional mechanism of bradykinesia (Yttri and Dudman, 2018). In mice, closed-loop stimulation of the basal ganglia induced changes in movement velocity, outlasting the end of stimulation and abolished by dopamine antagonists (Yttri and Dudman, 2016). In patients with Parkinson's disease, subthalamic and pallidal stimulation induced a long-lasting increase of the inhibitory electrophysiological phenomena recorded in GPi and SNr (Milosevic *et al.*, 2019). Notably, lower levels of plasticity were associated with higher severity of motor symptoms (Milosevic *et al.*, 2019). These data support the role of basal ganglia plasticity abnormalities in generating bradykinesia and suggest that plastic changes are influenced by dopamine depletion (Yttri and Dudman, 2018).

In summary, earlier conceptualizations emphasized their modularity property of basal ganglia and the changes in the firing rate of the various nuclei resulting from dopaminergic loss. More recent investigations demonstrate complex electrophysiological phenomena, including abnormal bursting, oscillatory and plasticity changes, and their correlation with various bradykinesia features. A better understanding of these mechanisms is required to interpret the mechanisms of action of dopaminergic medications and DBS.

The role of primary and non-primary motor cortical areas

Over time is becoming clear that besides cell death in the substantia nigra and loss of dopamine in the striatum, changes occur also in M1, playing an important role in generating voluntary movement abnormalities. First evidence came from animal studies. Dopamine depletion in parkinsonian models increases burst-firing in pyramidal tract type neurons of M1 (Goldberg *et al.*, 2002; Pasquereau and Turner, 2011), decreases the magnitude and the temporal pattern of movement-related M1 activity (Watts and Mandir 1992; Parr-Brownlie and Hyland 2005), and interferes with the specific encoding of movement parameters (Pasquereau *et al.*, 2016). Dopamine depletion in parkinsonian animals also leads to plasticity changes in M1, as evidenced by dendritic spine reduction in the lamina 5b pyramidal tract type neurons. Levodopa treatment partially rescued the enhanced spine turnover and the aberrant spine dynamics (Guo *et al.*, 2015). Thus, the dopamine system finely modulates structural plasticity of the layer V animal pyramidal neurons in M1.

Dysfunction in the M1 has long been thought to play a role in the generation of bradykinesia in patients with Parkinson's disease (Berardelli *et al.*, 2001; Wu *et al.*, 2011). It has been proposed that M1 may develop secondary changes due to the altered pattern of activity it receives from basal ganglia (Bateup *et al.*, 2010; Kravitz *et al.*, 2010; Cui *et al.*, 2013). Subsequent studies demonstrated that intrinsic M1 abnormalities contribute to parkinsonian motor signs. Electrophysiological techniques have been able to probe the activity of M1 in patients with Parkinson's disease (for a review see Burciu and Vaillancourt, 2018). Several studies revealed an abnormal synchronization in the beta rhythm between the cortex and basal ganglia that may underlie bradykinesia (de Hemptinne *et al.*, 2013).

Table 5 Primary motor cortex excitability (TMS studies)

Technique/parameters	Major findings	Effects of treatment
Paired stimulation/intracortical excitability		
Berardelli *et al.*, 1996*b*; Vacherot *et al.*, 2010.	Normal SICI.	–
Ridding *et al.*, 1995; Hanajima *et al.*, 1996; Strafella *et al.*, 2000; Bares *et al.*, 2003; MacKinnon *et al.*, 2005; Kojovic *et al.*, 2012; Zamir *et al.*, 2012; Barbin *et al.*, 2013; Kačar *et al.*, 2013; Ni *et al.*, 2013; Bologna *et al.*, 2018.	Reduced SICI.	Variable effect of levodopa.
Berardelli *et al.*, 1996*b*.	Increased LICI.	Levodopa normalized the abnormal LICI.
Cantello *et al.*, 2007; Barbin *et al.*, 2013.	Reduced LICI.	N/A
Kojovic *et al.*, 2012; Zamir *et al.*, 2012; Bologna *et al.*, 2018.	Normal ICF.	–
Ni *et al.*, 2013.	Increased ICF.	Levodopa improved ICF.
Vacherot *et al.*, 2010.	Reduced ICF of lower-limb motor area.	Levodopa improved ICF.
Paired stimulation/afferent inhibition		
Sailer *et al.*, 2003; Picillo *et al.*, 2015.	Normal SAI.	Levodopa reduced SAI.
Manganelli *et al.*, 2009; Rochester *et al.*, 2012; Nardone *et al.*, 2013; Lee *et al.*, 2015; Pelosin *et al.*, 2016; Oh *et al.*, 2017; Versace *et al.*, 2017.	Reduced SAI.	N/A
Sailer *et al.*, 2003.	Reduced LAI.	No effects of levodopa.

ICF = intracortical facilitation; LAI = long afferent inhibition; LICI = long interval intracortical inhibition; N/A = not available; SAI = short afferent inhibition; SICI = short interval intracortical inhibition.

Levodopa attenuates the abnormal synchronization and induces a clinical improvement (Brown *et al.*, 2001; Williams *et al.*, 2002; Foffani *et al.*, 2003). Magnetoencephalography data have shown that increased resting-state cortico-cortical functional connectivity in the 8–10 Hz alpha range characterizes the earliest stages of Parkinson's disease, and that, with disease progression, neighbouring frequency bands (beta and theta) become increasingly involved. These findings suggested that changes in functional intra-hemispheric and inter-hemispheric coupling over the course of Parkinson's disease may be linked to the topographical progression of pathology over the brain (Stoffers *et al.*, 2008). Moreover, phase-amplitude coupling is consistently affected by DBS (de Hemptinne *et al.*, 2015).

Transcranial magnetic stimulation (TMS) studies have provided useful information on M1 excitability and plasticity. Although some of the data are controversial overall the results indicate that Parkinson's disease patients have an increased M1 excitability, as tested with single and paired pulses stimulation (see references in Table 5). Similarly, the results overall suggest that Parkinson's disease patients have a reduced plasticity, as tested with repetitive TMS protocols (see references in Table 6). The pathophysiological roles of excitability and plasticity changes of M1 in generating bradykinesia are still debated. M1 magnetic stimulation after a go-signal has shortened reaction time, normalized the abnormal triphasic EMG pattern and increased the pre-movement cortical excitability (Pascual-Leone *et al.*, 1994). Bologna *et al.* (2018) found that excitability and plasticity TMS measures of M1 correlated with specific objective kinematic measurements of finger tapping in Parkinson's disease. Namely, excitability abnormalities correlated with motor slowness, while plasticity alterations correlated with sequence effect (Bologna *et al.*, 2018). Dopaminergic medications normalized the majority of M1 excitability and plasticity measures (Tables 5 and 6). However, the reported results are variable and there is no clear relationship between levodopa-induced changes in neurophysiological and movement measures, possibly indicating that TMS measures and movement kinematics have different sensitivity to dopaminergic tone (Monte-Silva *et al.*, 2010; Espay *et al.*, 2011; Suppa *et al.*, 2017; Bologna *et al.*, 2018). Interestingly, studies recording from chronically implanted electrodes over M1 have not consistently found specific hallmarks for bradykinesia while reporting that gamma rhythm is a biomarker for levodopa-induced dyskinesias (Swann *et al.*, 2016). More recently a study using a similar (but temporary) experimental set-up, found that pallidotomy improves bradykinesia by 'unleashing' gamma oscillations of M1 (de Hemptinne *et al.*, 2019). An alternative possibility is that some bradykinesia features are not strictly dependent on dopaminergic loss. A recent neurocomputational study suggests that bradykinesia may result from the concurrent effects of low dopaminergic levels and dysfunctional corticostriatal plasticity. The results show that training under levodopa administration improves bradykinesia. Conversely, training in unmedicated patients, has a detrimental effect on bradykinesia possibly due to dysfunctional corticostriatal plasticity induction (Ursino and Baston, 2018). Considering the role of M1 in generating bradykinesia, epidural or extradural motor cortex stimulation has been proposed as alternative to DBS in the treatment of Parkinson's disease. However, the results are controversial. Extradural motor cortex stimulation has been found to be beneficial in specific features of bradykinesia (speech and gait disorders)

Table 6 Primary motor cortex plasticity (TMS studies)

Technique/type of plasticity	Major findings	Effects of treatment
5Hz rTMS/ Short term facilitation		
Gilio *et al.*, 2002; Suppa *et al.*, 2010.	No facilitation on MEP amplitude. Normal increase in CSP.	Variable effects of levodopa.
PAS 25 ms/ LTP-like effect		
Kishore *et al.*, 2017.	Similar effect in Parkinson's disease and healthy subjects.	–
Bagnato *et al.*, 2006;	Increased LTP-like effects.	Levodopa normalized the abnormal effect.
Ueki *et al.*, 2006; Schwingenschuh *et al.*, 2010; Kačar *et al.*, 2013, 2017; Kawashima *et al.*, 2013; Kishore *et al.*, 2014; Lu *et al.*, 2016; Bologna *et al.*, 2018	Reduced LTP-like effects. Reduced LTP-like effects also in MSA patients. Correlation with sequence effect.	Variable effects of levodopa. No effect in MSA.
Kojovic *et al.*, 2012.	Reduced LTP-like effects on the more affected hemisphere. Increased LTP-like effects on the less affected hemisphere.	N/A
PAS 21.5 ms/LTP-like effect		
Morgante *et al.*, 2006.	Reduced LTP-like effects.	Levodopa improved the effects only in non-dyskinetic patients.
iTBS/ LTP-like effect		
Zamir *et al.*, 2012.	Normal LTP-like effects	–
Suppa *et al.*, 2011; Kishore *et al.*, 2012*a*, *b*, 2014.	Reduced LTP-like effects. No correlations with bradykinesia (UPDRS scores).	No effect of levodopa.
cTBSc0/ LTP-like effect		
Huang *et al.*, 2011.	Reduced LTP-like effects	Levodopa improved the effects.
cTBS/ LTD-like effect		
Eggers *et al.*, 2010; Kishore *et al.*, 2012*a*, *b*.	No LTD-like effects. No correlations with bradykinesia (UPDRS scores).	No effect of levodopa.
cTBS150/ Depotentiation protocol		
Huang *et al.*, 2011; Lago-Rodrigz *et al.*, 2016.	Reduced depotentation.	Levodopa improved the effects.

CSP = cortical silent period; cTBS = continuous theta burst stimulation; cTBSc0 = continuous theta burst stimulation followed by 1-min contraction; iTBS = intermittent theta burst stimulation; LTD = long term depression; LTP = long term potentiation; MEP = motor evoked potential; N/A = not available; PAS = paired associative stimulation; rTMS = repetitive TMS.

in few studies involving Parkinson's disease (Cilia *et al.*, 2007; Bentivoglio *et al.*, 2012) and PSP patients (Piano *et al.*, 2018). Other studies have, however, only reported a transient benefit (Fasano *et al.*, 2008) or no benefit at all (Moro *et al.*, 2011).

Non-invasive brain stimulation techniques can be also used for the study of altered connectivity between primary and non-primary motor areas (Hallett *et al.*, 2017). For example, a conditioning single-pulse TMS can influence the effect of a test TMS given over M1 (Koch *et al.*, 2007; Karabanov *et al.*, 2013). Effects on M1 can be also tested after repetitive TMS (rTMS) of non-primary motor areas. RTMS delivered over non-primary motor areas have shown that dorsal premotor cortex-to-M1 functional connectivity is abnormal in patients with Parkinson's disease and it is promptly normalized by levodopa administration (Buhmann *et al.*, 2004; Mir *et al.*, 2005; Suppa *et al.*, 2010). Premotor rTMS, however, has no effect on clinical parkinsonian symptoms or motor performance of ballistic wrist movements, regardless of whether patients were ON or OFF dopaminergic medications (Mir *et al.*, 2005).

Abnormal M1 excitability and plasticity have been investigated less extensively in atypical parkinsonisms. PSP and MSA patients showed an increase M1 excitability and a reduction in short intracortical inhibition (Marchese *et al.*, 2000; Kühn *et al.*, 2004). CBS patients exhibit a pattern similar to Parkinson's disease, with a reduced short intracortical inhibition and a normal intracortical facilitation (Frasson *et al.*, 2003; Murgai and Jog, 2018). MSA patients showed a reduction in long term potentiation (LTP)-like effects after paired associative stimulation, not restored after dopaminergic therapy (Kawashima *et al.*, 2013).

The role of primary and non-primary motor cortical areas abnormalities in Parkinson's disease have also been investigated by neuroimaging, showing either grey matter atrophy (Jankovic *et al.*, 1990; Rosenberg-Katz *et al.*, 2013; Shao *et al.*, 2014) or cortical thinning (Wilson *et al.*, 2019). Early studies also showed a reduced activation of the putamen and the medial frontal cortex (Playford *et al.*, 1992). Variable functional M1 changes, ranging from movement related hypo- (Rascol *et al.*, 1992; Catalan *et al.*, 1999; Turner *et al.*, 2003; Tessa *et al.*, 2010; Hanakawa *et al.*, 2017) to hyperactivation (Sabatini *et al.*, 2000; Thobois *et al.*, 2000; Haslinger *et al.*, 2001) have been also described. The two different patterns of functional M1 changes may be due to several technical differences in the experiments performed and also in the clinical features of the patients studied. Overall functional neuroimaging studies performed, controlling several confounding features that might had affected the results, showed a consistent

pattern of reduced activation of M1 (Burciu and Vaillancourt, 2018). Likewise, neuroimaging studies consistently revealed abnormalities of non-primary motor cortical areas regions such as the hypoactivation of the supplementary motor area and hyperactivation of the lateral premotor cortex (Playford *et al.*, 1992; Rascol *et al.*, 1992; Jahanshahi *et al.*, 1995; Samuel *et al.*, 1997; Catalan *et al.*, 1999; Sabatini *et al.*, 2000; Haslinger *et al.*, 2001; Rowe *et al.*, 2002; Buhmann *et al.*, 2003; Wu and Hallett, 2005; Eckert *et al.*, 2006; Ukmar *et al.*, 2006; Yu *et al.*, 2007; Tessa *et al.*, 2010; Wu *et al.*, 2010, 2011; Zhang *et al.*, 2015; Criaud *et al.*, 2016; Karunanayaka *et al.*, 2016; Hanakawa *et al.*, 2017; Hu *et al.*, 2017). Neuroimaging is also a suitable tool for investigating altered connectivity between prefrontal cortex or premotor areas and M1 as well as basal ganglia-cortical interactions (Wu *et al.*, 2011, 2016; Esposito *et al.*, 2013; Spay *et al.*, 2019). Studies investigating network analysis showed an abnormal connectivity between motor regions (Rowe *et al.*, 2002) and abnormal connectivity between the cortico-striatal circuit (Helmich *et al.*, 2010). Levodopa administration (Haslinger *et al.*, 2001; Buhmann *et al.*, 2003; Poston and Eidelberg, 2012; Esposito *et al.*, 2013), as well as STN stimulation (Grafton *et al.*, 2006; Akram *et al.*, 2017, Horn *et al.*, 2017) enhanced the sensorimotor network functional connectivity in the supplementary motor area improving the activation responses. Resting state functional MRI studies also showed that there is an increased interaction between cerebral networks with a loss of segregation between functional networks (Kim *et al.*, 2017). Although patients with loss of segregation had more severe motor symptoms it is unclear whether the loss of segregation correlates with any specific symptom including bradykinesia.

In summary, the demonstration that intrinsic abnormalities of the M1 play an essential role in generating bradykinesia is one of the most important pathophysiological advances in the last decade. The most compelling evidence came from animal studies. Electrophysiological techniques and neuroimaging have provided *in vivo* confirmation of the M1 abnormalities in human Parkinson's disease patients. Some of these studies also found a correlation between M1 abnormalities and with various bradykinesia features. The role of non-primary motor cortical area abnormalities in Parkinson's disease, although less compelling, have also been suggested.

The role of cerebellum

The hypothesis that cerebellum contributes to bradykinesia in Parkinson's disease is based on the anatomical evidence of reciprocal connections between the cerebellum and basal ganglia (Ichinohe *et al.*, 2000; Bostan and Strick, 2018). Namely, the cerebellum receives a disynaptic glutamatergic projection from the STN. The hypothesis that abnormal signals from the STN in Parkinson's disease results in abnormal cerebellar activation is supported by the observation that STN high-frequency stimulation through DBS electrodes in rats leads to a reduction in the activity of cerebellar Purkinje cells and, as a consequence, disinhibition of cerebellar nuclei as also evidenced by increased cFOS expression in the cerebellar nuclei (Moers-Hornikx *et al.*, 2011). In keeping with these notions, a recent connectivity study in Parkinson's disease patients found that bradykinesia is improved when DBS affects the ascending ipsilateral cerebellar-thalamo-cortical pathway (Strotzer *et al.*, 2019). Moreover, it has been reported that dopaminergic loss is associated with loss of Nissl-stained Purkinje cells, reported in parkinsonian animals (Rolland *et al.*, 2007; Heman *et al.*, 2012).

Neurophysiological studies investigating cerebellar function demonstrate that Parkinson's disease patients, with prominent bradykinetic-rigid symptoms, have deficient short-latency and long-lasting cerebellar-thalamo-cortical inhibitory interactions that cannot be restored by dopaminergic medication (Carrillo *et al.*, 2013). Functional or metabolic neuroimaging studies demonstrated abnormal cerebellar activation in patients with Parkinson's disease while performing various upper limb movements (Rascol *et al.*, 1997; Catalan *et al.*, 1999; Wu and Hallett, 2005; Yu *et al.*, 2007; Wu *et al.*, 2010), including finger movements (Rascol *et al.*, 1997; Cerasa *et al.*, 2006; Yu *et al.*, 2007), motor timing tasks (Jahanshahi *et al.*, 2010), complex sequential movements (Catalan *et al.*, 1999), bimanual two-hand coordinated tasks (Wu *et al.*, 2010) or simultaneous movements (Wu and Hallett, 2008). In addition to abnormal activity in the cerebellum, a series of neuroimaging studies showed an abnormal connectivity pattern of the cerebellum in Parkinson's disease (Wu *et al.*, 2009, 2011, 2016; Jahanshahi *et al.*, 2010). The relationship between cerebellar hyperactivation or abnormal cerebellar connectivity and bradykinesia remains unclear. Interestingly, in patients with progressive micrographia, a manifestation of the sequence effect, a decreased connectivity between the posterior putamen and cerebellum was found (Wu *et al.*, 2016), but this abnormality did not correlate with the severity of progressive micrographia, and normalization of connectivity with levodopa did not improve progressive micrographia. A disconnection among the cerebellum, the pre-supplementary motor area and the rostral cingulate motor area, in addition to the dysfunction of the basal ganglia motor circuit, was demonstrated in Parkinson's disease presenting progressive micrographia. i.e. the sequence effect (Wu *et al.*, 2016). Also relevant in this regard, a recent neuroimaging study of freezing of gait cases induced by discrete brain lesions found that a variety of different involved networks all localize to a dysfunction of the cerebellar locomotor centre (Fasano *et al.*, 2017). The cerebellar involvement in Parkinson's disease is finally supported by the evidence of abnormal visuomotor learning in patients, restored through DBS (de Almeida *et al.*, 2019).

In summary, cerebellar dysfunction is now undoubtedly considered one of the factors involved in the pathophysiology of bradykinesia. This is supported by the evidence of

anatomical reciprocal connections between cerebellum and basal ganglia and by neurophysiological and neuroimaging studies in Parkinson's disease patients. A relationship between cerebellar involvement, micrographia, and some bradykinesia features of the upper limb is present. Cerebellar involvement in Parkinson's disease supports the view of bradykinesia as a network disorder.

The sensorimotor function

Converging evidence indicates that defective integration of sensory information at various levels of a complex cortico-subcortical network, including the primary somatosensory cortex (S1) and basal ganglia, may be involved in the pathophysiology of bradykinesia. Several studies on Parkinson's disease patients have indicated abnormalities in sensory processing, including abnormalities of sensory discrimination, proprioceptive integration, kinaesthetic sense of joint displacement (Demirci *et al.*, 1997; Seiss *et al.*, 2003; Konczak *et al.*, 2007; Wright *et al.*, 2010; Patel *et al.*, 2014) and mechanisms of sensorimotor integration (Georgiev *et al.*, 2016). Demirci *et al.* (1997) also provided evidence of a mismatch between kinaesthetic and visual perception in Parkinson's disease, linking the sensory disturbances to a scaling abnormality. Recent information on the altered sensorimotor integration in Parkinson's disease has been provided by studies assessing the somatosensory temporal discrimination threshold (STDT), (Lacruz *et al.*, 1991; Artieda *et al.*, 1992; Rocchi *et al.*, 2016; Conte *et al.*, 2017*a*; Lee *et al.*, 2017). The STDT abnormalities in Parkinson's disease reflect disease severity and duration (Conte *et al.*, 2016, 2018). Some studies have reported that higher values of STDT correlate with higher UPDRS part III score (Artieda *et al.*, 1992) while other studies found no correlations (Conte *et al.*, 2010; Lee *et al.*, 2010, 2017; Lyoo *et al.*, 2012; Rocchi *et al.*, 2013). Quantitative measurement of bradykinesia throughout inertial sensors showed a correlation between higher STDT values and increased variability in amplitude and speed, which may reflect the prolonged temporal processing of tactile information and altered sensorimotor integration (Lee *et al.*, 2017). Accordingly, recent findings from studies on movement-related changes of STDT in Parkinson's disease patients further support a link between an altered STDT and finger movement abnormalities in Parkinson's disease patients (Conte *et al.*, 2017*b*). Levodopa treatment influences STDT values in Parkinson's disease (Artieda *et al.*, 1992; Lee *et al.*, 2005; Conte *et al.*, 2010; Rocchi *et al.*, 2013). In a dopamine transporter PET study, Lyoo *et al.* (2012) reported that increased STDT values correlated with ligand uptake in both the caudate and putamen. Finally, little is known about STDT and atypical parkinsonisms. One study found higher values of STDT in patients with MSA compared to healthy subjects (Lyoo *et al.*, 2007) and to Parkinson's disease patients (Rocchi *et al.*, 2013).

In summary, a defective integration of sensory information at the cortico-subcortical network is another essential component involved in the pathophysiology of bradykinesia. Evidence comes from the study of sensorimotor integration and STDT. Despite some of these studies reporting correlations between altered sensory processing and bradykinesia, this issue deserves further experimental confirmation.

Discussion

The term bradykinesia has historically been used to indicate slowness in the execution of voluntary movement in patients affected by Parkinson's disease. Clinical and experimental studies, however, have suggested the use of the term bradykinesia to encompass other motor abnormalities, including low amplitude movement (hypokinesia), absence of movement (akinesia) and amplitude reduction during movement repetition (sequence effect) (Berardelli *et al.*, 2013; Postuma *et al.*, 2015; Schilder *et al.*, 2017). Neurophysiological investigations indicated that slowness of movement and reduced movement amplitude rely on different mechanisms than those underlying the sequence effect (Espay *et al.*, 2009, 2011; Wu *et al.*, 2016; Bologna *et al.*, 2018). The various neurophysiological abnormalities are not always present together in the same patient (Kang *et al.*, 2011; Lee *et al.*, 2014; Bologna *et al.*, 2016*a*; Wu *et al.*, 2016) and they not necessarily involve all the body segments. Bradykinesia features also vary according to the disease stage (less frequent sequence effect in advanced Parkinson's disease) (Bologna *et al.*, 2016*a*) and the different types of parkinsonism. Some evidence suggests that the lack of sequence effect may help distinguishing PSP from Parkinson's disease and MSA (Ling *et al.*, 2012; Djurić-Jovičić *et al.*, 2016). Further compelling evidence for lack of unity is the differential effects that levodopa exerts on the various bradykinesia features. Levodopa improves slowed and reduced amplitude movements (Hallett *et al.*, 1977; Berardelli *et al.*, 1986; Castiello and Bennett, 1997; Alberts *et al.*, 2000; Castiello *et al.*, 2000; Espay *et al.*, 2009, 2011) but not the sequence effect (Agostino *et al.*, 2003; Kang *et al.*, 2010, 2011; Bologna *et al.*, 2016*a*, 2018; Wu *et al.*, 2016). Levodopa may exert different modulation on basal ganglia circuits and on their interaction with cortical and cerebellar areas underlying the various motor abnormalities. DBS also improves bradykinesia, but its effect is more complex as it depends on exact electrode location, specific adopted frequency and volume of tissue activated (Fasano and Lozano, 2014; di Biase and Fasano, 2016; Strotzer *et al.*, 2019).

In Parkinson's disease, earlier studies have demonstrated abnormalities in basal ganglia firing rate (Wichmann and DeLong, 1996), firing pattern (Ellens and Leventhal, 2013) and oscillatory activity, with an increase of beta band power in the GPi and STN nuclei (Brown *et al.*, 2001; Little *et al.*, 2012; Torrecillos *et al.*, 2018), suggesting a

key role of basal ganglia. Disrupted basal ganglia plasticity has been also pointed out as a possible mechanism of bradykinesia (Yttri and Dudman, 2018; Milosevic *et al.*, 2019). More recent experimental studies now indicate that mechanisms other than basal ganglia may be involved in the pathophysiology of bradykinesia in Parkinson's disease. These include excitability and plasticity changes of M1 and other non-primary motor areas (Ridding *et al.*, 1995; Berardelli *et al.*, 1996*b*; Sabatini *et al.*, 2000; Buhmann *et al.*, 2004; Mir *et al.*, 2005; Wu and Hallett, 2005; Lyoo *et al.*, 2007; Suppa *et al.*, 2010, 2011; Bologna *et al.*, 2016*d*, 2018; Hu *et al.*, 2017). Recent evidence has demonstrated a correlation between M1 excitability changes and motor slowness, and between M1 plasticity abnormalities and the sequence effect (Bologna *et al.*, 2018). Whether M1 abnormalities are primary mechanisms or, alternatively, compensatory adaptations to the disease still need to be clarified (Ni *et al.*, 2013; Blesa *et al.*, 2017). Hyperactivity of cortical motor areas has been also described and interpreted as a possible compensatory mechanism for the defective basal ganglia function (Rascol *et al.*, 1997; Sabatini *et al.*, 2000; Thobois *et al.*, 2000; Ceballos-Baumann 2003; Wu and Hallett, 2005), although it has been argued that hyperactivation could be related to other motor abnormalities, such as rigidity and levodopa-induced dyskinesias (Ridding *et al.*, 1995; Kleine *et al.*, 2001; Pierantozzi *et al.*, 2001; Yu *et al.*, 2007). Noteworthy, part of the beneficial effects of DBS resides within its decoupling property within these hyperactivated networks (de Hemptinne *et al.*, 2015, Tinkhauser *et al.*, 2017). The cerebellum may also be involved in the pathophysiology of bradykinesia. As the activation of the cerebello-thalamo-cortical circuit increases with Parkinson's disease progression severity (Wu *et al.*, 2009, 2010; Sen *et al.*, 2010), the cerebellum probably compensates for the defective activity in basal ganglia and M1 activation

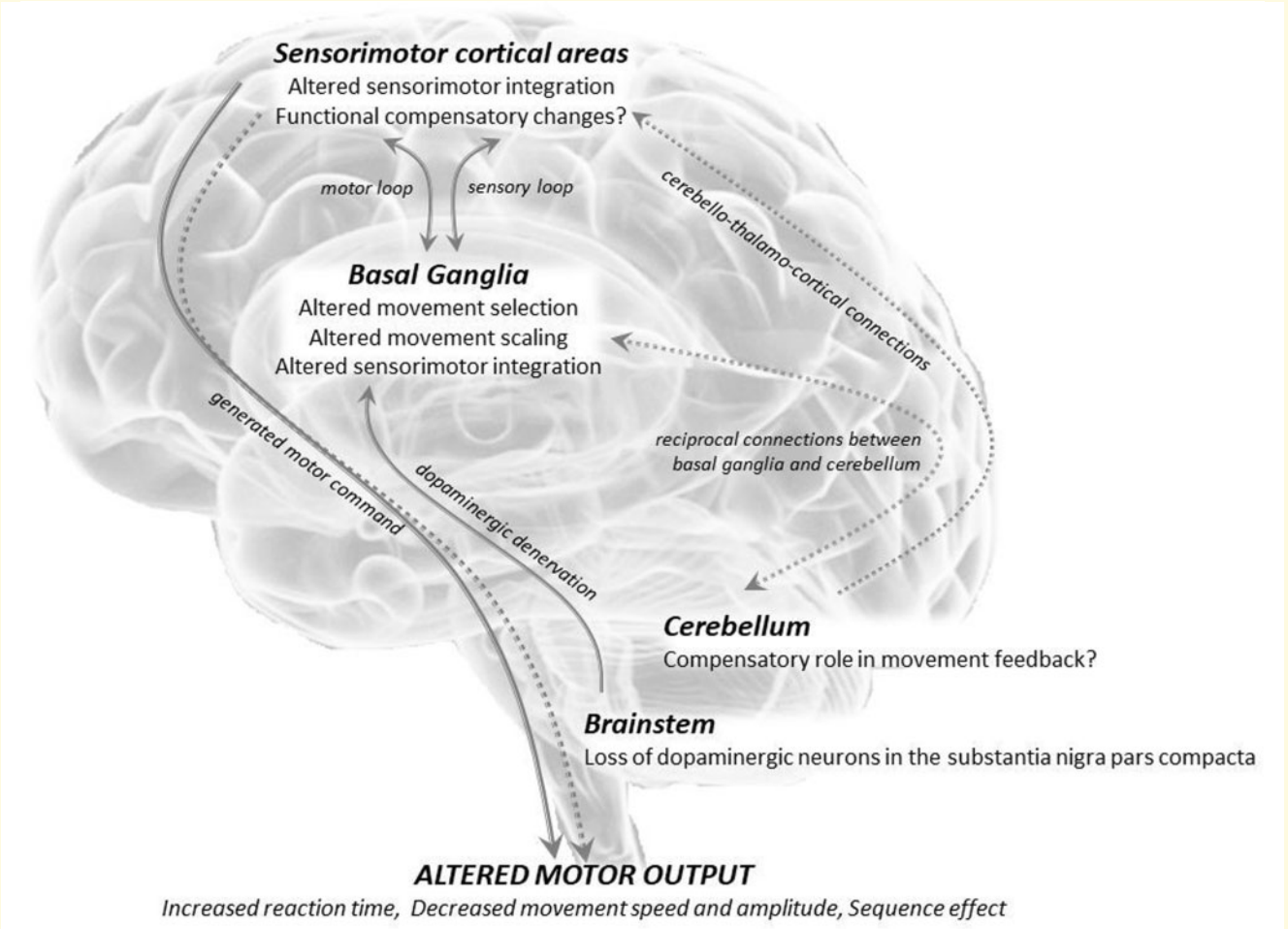

Figure 1 The Network hypothesis for bradykinesia pathophysiology. Basal ganglia dysfunction is responsible for altered movement selection. The altered movement scaling at basal ganglia level may also arise from a fault in the sensory loop, responsible for sensorimotor integration. Other mechanisms involve sensorimotor areas. Cerebellar structures likely play a role in movement feedback, particularly important for continued and repetitive movements. The energy for all basal ganglia, sensorimotor areas, and the cerebellar functions appear to come from dopamine. With dopamine loss, the system slows down, reaction times increase, movement speed and amplitude decrease, and the sequence effect develops. Dotted lines indicate possible compensatory mechanisms.

(Cerasa *et al.*, 2006; Yu *et al.*, 2007; Wu and Hallett, 2013; Fasano *et al.*, 2017). An alternative possibility is that the increased cerebellar activity in Parkinson's disease reflects a primary pathophysiological change, i.e. failure to inhibit inappropriate basal ganglia outflow (Turner *et al.*, 2003; Grafton *et al.*, 2006). Changes at the level of sensory cortical areas are also involved in generating bradykinesia. The abnormal sensorimotor processing, as demonstrated by tactile sensory discrimination studies (Rocchi *et al.*, 2013; Conte *et al.*, 2018), suggested that the normal filtering of sensory information exerted by basal ganglia is lost. How this translates to bradykinesia is unknown, but it is likely that an abnormal sensory integration is also present at the level of sensory cortical area.

All these data indicate that bradykinesia should be interpreted as the result of a network dysfunction, including basal ganglia, sensorimotor cortical areas, and the cerebellum, rather than a consequence of one single system default. The role of each structure in determining bradykinesia is still unclear. One hypothesis is that basal ganglia are responsible for aiding the joint processes of movement selection and inhibition, through the direct and indirect pathways. Recent evidence suggests that the basal ganglia-cortical loops in a parallel fashion contribute to different functions, including speed within the motor loop. The energy for these functions appears to come from dopamine. With dopamine loss, the system slows down, reaction times increase, movement speed and amplitude decrease. A signature of this loss is the increase of beta oscillation in the indirect pathway. The scaling problems observed in patients with bradykinesia may arise at least in part from a fault in the sensory loop, responsible of sensorimotor integration. This function involves cerebellar structures, which may play a role in movement feedback, particularly important for continued and repetitive movements. Other cerebellar components, involved in motor loops, try then to compensate. If they cannot fully compensate, then the sequence effect develops. Other compensatory mechanisms could finally involve primary and non-primary motor cortex functional changes. When interpreted in a network perspective, distinct bradykinesia features are likely to be mediated by a variable involvement of the various nodes in the network (Fig. 1).

Neurophysiological insight is relevant to improve the appropriateness of the terminological use of bradykinesia in Parkinson's disease and atypical parkinsonism. Features of bradykinesia are slowness of voluntary movements together with a decrement in amplitude or speed during repetitive or continued movements (sequence effect), small (i.e. underscaled, low amplitude) movements (hypokinesia), and loss of spontaneous/automatic movements or absence of movement or difficulty initiating a movement such as in freezing, motor blocks, or hesitations (akinesia). In this perspective, we suggest that the terms bradykinesia (slowness of movement), hypokinesia (reduced amplitude of movement), akinesia (lack of movement), and sequence effect (progressive decrement of amplitude and velocity of movement) should be defined separately in the description of clinical phenotypes, saving the Greek origin of the words, rather than encompass them in one word. This is supported by the evidence that each single abnormality has a specific pathophysiological mechanism and can occur in isolation in one given patient.

Understanding the features of bradykinesia has very important implications when it comes to enrolment criteria for research studies and, more importantly, diagnostic criteria of parkinsonism, e.g. in the differential diagnosis with pyramidal slowness or functional hypokinesia (Thenganatt and Jankovic, 2016), Huntington disease (Berardelli *et al.*, 1999), cerebellar disorders (Manto *et al.*, 2012), and other neurological conditions in which a slowness of movement is present. Specific pathophysiological mechanisms likely explain the pathophysiology of bradykinesia which is present in the various pathological conditions. Increasing insight into bradykinesia pathophysiology in Parkinson's disease, atypical parkinsonisms and other movement disorders, will serve as a new starting point for clinical and experimental purposes.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. M.H. is supported by the NINDS Intramural Program (grant number: Z01 NS003031).

Competing interests

The authors report no competing interests.

References

Agostino R, Berardelli A, Formica A, Accornero N, Manfredi M. Sequential arm movements in patients with Parkinson's disease, Huntington's disease and dystonia. Brain 1992; 115: 1481–95.

Agostino R, Berardelli A, Formica A, Stocchi F, Accornero N, Manfredi M. Analysis of repetitive and nonrepetitive sequential arm movements in patients with Parkinson's disease. Mov Disord 1994; 9: 311–4.

Agostino R, Bologna M, Dinapoli L, Gregori B, Fabbrini G, Accornero N, et al. Voluntary, spontaneous, and reflex blinking in Parkinson's disease. Mov Disord 2008; 23: 669–75.

Agostino R, Currà A, Giovannelli M, Modugno N, Manfredi M, Berardelli A. Impairment of individual finger movements in Parkinson's disease. Mov Disord 2003; 18: 560–5.

Alberts JL, Saling M, Adler CH, Stelmach GE. Disruptions in the reach-to-grasp actions of Parkinson's patients. Exp Brain Res 2000; 134: 353–62.

Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989; 12: 366–75.

Altiparmak UE, Eggenberger E, Coleman A, Condon K. The ratio of square wave jerk rates to blink rates distinguishes progressive supranuclear palsy from Parkinson disease. J Neuroophthalmol 2006; 26: 257–9.

Anidi C, O'Day JJ, Anderson RW, Afzal MF, Syrkin-Nikolau J, Velisar A, et al. Neuromodulation targets pathological not physiological beta bursts during gait in Parkinson's disease. Neurobiol Dis 2018; 120: 107–17.

Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013; 80: 496–503.

Aron AR, Herz DM, Brown P, Forstmann BU, Zaghloul K. Frontosubthalamic circuits for control of action and cognition. J Neurosci 2016; 36: 11489–95.

Artieda J, Pastor MA, Lacruz F, Obeso JA. Temporal discrimination is abnormal in Parkinson's disease. Brain 1992; 115: 199–210.

Bagnato S, Agostino R, Modugno N, Quartarone A, Berardelli A. Plasticity of the motor cortex in Parkinson's disease patients on and off therapy. Mov Disord 2006; 21: 639–45.

Barbeau A, Duvoisin RC, Gerstenbrand F, Lakke JP, Marsden CD, Stern G. Classification of extrapyramidal disorders. Proposal for an international classification and glossary of terms. J Neurol Sci 1981; 51: 311–27.

Barbin L, Leux C, Sauleau P, Meyniel C, Nguyen J-M, Pereon Y, et al. Non-homogeneous effect of levodopa on inhibitory circuits in Parkinson's disease and dyskinesia. Parkinsonism Relat Disord 2013; 19: 165–70.

Bares M, Kanovský P, Klajblová H, Rektor I. Intracortical inhibition and facilitation are impaired in patients with early Parkinson's disease: a paired TMS study. Eur J Neurol 2003; 10: 385–9.

Bar-Gad I, Bergman H. Stepping out of the box: information processing in the neural networks of the basal ganglia. Curr Opin Neurobiol 2001; 11: 689–95.

Baroni A, Benvenuti F, Fantini L, Pantaleo T, Urbani F. Human ballistic arm abduction movements: effects of L-dopa treatment in Parkinson's disease. Neurology 1984; 34: 868–76.

Bateup HS, Santini E, Shen W, Birnbaum S, Valjent E, Surmeier DJ et al. Distinct subclasses of medium spiny neurons differentially regulate striatal motor behaviors. Proc Natl Acad Sci USA 2010; 107: 14845–50.

Belvisi D, Conte A, Cutrona C, Costanzo M, Ferrazzano G, Fabbrini G, et al. Re-emergent tremor in Parkinson's disease: the effect of dopaminergic treatment. Eur J Neurol 2018; 25: 799–804.

Benarroch EE. Intrinsic circuits of the striatum: complexity and clinical correlations. Neurology 2016; 86: 1531–42.

Benecke R, Rothwell JC, Dick JP, Day BL, Marsden CD. Performance of simultaneous movements in patients with Parkinson's disease. Brain 1986; 109: 739–57.

Bennett KM, Marchetti M, Iovine R, Castiello U. The drinking action of Parkinson's disease subjects. Brain 1995; 118: 959–70.

Bentivoglio AR, Fasano A, Piano C, Soleti F, Daniele A, Zinno M, et al. Unilateral extradural motor cortex stimulation is safe and improves Parkinson disease at 1 year. Neurosurgery 2012; 71: 815–25.

Berardelli A, Conte A, Fabbrini G, Bologna M, Latorre A, Rocchi L, et al. Pathophysiology of pain and fatigue in Parkinson's disease. Parkinsonism Relat Disord 2012; 18 Suppl 1: S226–8.

Berardelli A, Dick JP, Rothwell JC, Day BL, Marsden CD. Scaling of the size of the first agonist EMG burst during rapid wrist movements in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1986; 49: 1273–9.

Berardelli A, Hallett M, Rothwell JC, Agostino R, Manfredi M, Thompson PD, et al. Single-joint rapid arm movements in normal subjects and in patients with motor disorders. Brain 1996a; 119: 661–74.

Berardelli A, Noth J, Thompson PD, Bollen EL, Currà A, Deuschl G, et al. Pathophysiology of chorea and bradykinesia in Huntington's disease. Mov Disord 1999; 14: 398–403.

Berardelli A, Rona S, Inghilleri M, Manfredi M. Cortical inhibition in Parkinson's disease. A study with paired magnetic stimulation. Brain 1996b; 119: 71–7.

Berardelli A, Rothwell JC, Thompson PD, Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. Brain 2001; 124: 2131–46.

Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, et al. EFNS/MDS-ES/ENS [corrected] recommendations for the diagnosis of Parkinson's disease. Eur J Neurol 2013; 20: 16–34.

Berg D, Adler CH, Bloem BR, Chan P, Gasser T, Goetz CG, et al. Movement disorder society criteria for clinically established early Parkinson's disease. Mov Disord 2018; 33: 1643–6.

Berg D, Lang AE, Postuma RB, Maetzler W, Deuschl G, Gasser T, et al. Changing the research criteria for the diagnosis of Parkinson's disease: obstacles and opportunities. Lancet Neurol 2013; 12: 514–24.

Bergman H, Wichmann T, Karmon B, DeLong MR. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. J Neurophysiol 1994; 72: 507–20.

Blesa J, Trigo-Damas I, Dileone M, Del Rey NL, Hernandez LF, Obeso JA. Compensatory mechanisms in Parkinson's disease: Circuits adaptations and role in disease modification. Exp Neurol 2017; 298: 148–61.

Bloxham CA, Dick DJ, Moore M. Reaction times and attention in Parkinson's disease. J Neurol Neurosurg Psychiatry 1987; 50: 1178–83.

Bloxham CA, Mindel TA, Frith CD. Initiation and execution of predictable and unpredictable movements in Parkinson's disease. Brain 1984; 107: 371–84.

Blumenfeld Z, Koop MM, Prieto TE, Shreve LA, Velisar A, Quinn EJ, et al. Sixty-hertz stimulation improves bradykinesia and amplifies subthalamic low-frequency oscillations. Mov Disord 2017; 32: 80–8.

Bologna M, Agostino R, Gregori B, Belvisi D, Ottaviani D, Colosimo C, et al. Voluntary, spontaneous and reflex blinking in patients with clinically probable progressive supranuclear palsy. Brain 2009; 132: 502–10.

Bologna M, Berardelli I, Paparella G, Marsili L, Ricciardi L, Fabbrini G, et al. Altered kinematics of facial emotion expression and emotion recognition deficits are unrelated in Parkinson's disease. Front Neurol 2016c; 7: 230.

Bologna M, Fabbrini G, Marsili L, Defazio G, Thompson PD, Berardelli A. Facial bradykinesia. J Neurol Neurosurg Psychiatry 2013; 84: 681–5.

Bologna M, Fasano A, Modugno N, Fabbrini G, Berardelli A. Effects of subthalamic nucleus deep brain stimulation and L-DOPA on blinking in Parkinson's disease. Exp Neurol 2012; 235: 265–72.

Bologna M, Guerra A, Paparella G, Giordo L, Alunni Fegatelli D, Vestri AR, et al. Neurophysiological correlates of bradykinesia in Parkinson's disease. Brain 2018.

Bologna M, Latorre A, Di Biasio F, Conte A, Belvisi D, Modugno N, et al. The effect of L-dopa/carbidopa intestinal gel in Parkinson Disease assessed using neurophysiologic techniques. Clin Neuropharmacol 2016a; 39: 302–5.

Bologna M, Leodori G, Stirpe P, Paparella G, Colella D, Belvisi D, et al. Bradykinesia in early and advanced Parkinson's disease. J Neurol Sci 2016b; 369: 286–91.

Bologna M, Marsili L, Khan N, Parvez AK, Paparella G, Modugno N, et al. Blinking in patients with clinically probable multiple system atrophy. Mov Disord 2014; 29: 415–20.

Bologna M, Suppa A, Conte A, Latorre A, Rothwell JC, Berardelli A. Are studies of motor cortex plasticity relevant in human patients with Parkinson's disease? Clin Neurophysiol 2016d; 127: 50–9.

Bostan AC, Strick PL. The basal ganglia and the cerebellum: nodes in an integrated network. Nat Rev Neurosci 2018; 19: 338–50.

Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord 2003; 18: 357–63.

Brown P, Corcos DM, Rothwell JC. Does parkinsonian action tremor contribute to muscle weakness in Parkinson's disease? Brain 1997; 120: 401–8.

Brown P, Oliviero A, Mazzone P, Insola A, Tonali P, Di Lazzaro V. Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. J Neurosci 2001; 21: 1033–8.

Brown RG, Marsden CD. Dual task performance and processing resources in normal subjects and patients with Parkinson's disease. Brain 1991; 114: 215–31.
Brown VJ, Schwarz U, Bowman EM, Fuhr P, Robinson DL, Hallett M. Dopamine dependent reaction time deficits in patients with Parkinson's disease are task specific. Neuropsychologia 1993; 31: 459–69.
Buhmann C, Glauche V, Stürenburg HJ, Oechsner M, Weiller C, Büchel C. Pharmacologically modulated fMRI–cortical responsiveness to levodopa in drug-naive hemiparkinsonian patients. Brain 2003; 126: 451–61.
Buhmann C, Gorsler A, Bäumer T, Hidding U, Demiralay C, Hinkelmann K, et al. Abnormal excitability of premotor-motor connections in de novo Parkinson's disease. Brain 2004; 127: 2732–46.
Burciu RG, Vaillancourt DE. Imaging of motor cortex physiology in Parkinson's disease. Mov Disord 2018; 33: 1688–99.
Caligiuri MP. Labial kinematics during speech in patients with parkinsonian rigidity. Brain 1987; 110: 1033–44.
Calne DB, Snow BJ, Lee C. Criteria for diagnosing Parkinson's disease. Ann Neurol 1992; 32: S125–7.
Cantello R, Tarletti R, Varrasi C, Cecchin M, Monaco F. Cortical inhibition in Parkinson's disease: new insights from early, untreated patients. Neuroscience 2007; 150: 64–71.
Carrillo F, Palomar FJ, Conde V, Diaz-Corrales FJ, Porcacchia P, Fernández-Del-Olmo M, et al. Study of cerebello-thalamocortical pathway by transcranial magnetic stimulation in Parkinson's disease. Brain Stimul 2013; 6: 582–9.
Castiello U, Bennett KM. The bilateral reach-to-grasp movement of Parkinson's disease subjects. Brain 1997; 120: 593–604.
Castiello U, Bennett KM, Bonfiglioli C, Peppard RF. The reach-to-grasp movement in Parkinson's disease before and after dopaminergic medication. Neuropsychologia 2000; 38: 46–59.
Catalan MJ, Ishii K, Honda M, Samii A, Hallett M. A PET study of sequential finger movements of varying length in patients with Parkinson's disease. Brain 1999; 122: 483–95.
Ceballos-Baumann AO. Functional imaging in Parkinson's disease: activation studies with PET, fMRI and SPECT. J Neurol 2003; 250: I15–23.
Cerasa A, Hagberg GE, Peppe A, Bianciardi M, Gioia MC, Costa A, et al. Functional changes in the activity of cerebellum and frontostriatal regions during externally and internally timed movement in Parkinson's disease. Brain Res Bull 2006; 71: 259–69.
Chan V, Starr PA, Turner RS. Bursts and oscillations as independent properties of neural activity in the parkinsonian globus pallidus internus. Neurobiol Dis 2011; 41: 2–10.
Cilia R, Landi A, Vergani F, Sganzerla E, Pezzoli G, Antonini A. Extradural motor cortex stimulation in Parkinson's disease. Mov Disord 2007; 22: 111–4.
Cleary DR, Raslan AM, Rubin JE, Bahgat D, Viswanathan A, Heinricher MM, et al. Deep brain stimulation entrains local neuronal firing in human globus pallidus internus. J Neurophysiol 2013; 109: 978–87.
Connor NP, Abbs JH, Cole KJ, Gracco VL. Parkinsonian deficits in serial multiarticulate movements for speech. Brain 1989; 112: 997–1009.
Conte A, Belvisi D, Tartaglia M, Cortese FN, Baione V, Battista E, et al. Abnormal temporal coupling of tactile perception and motor action in Parkinson's Disease. Front Neurol 2017b; 8: 249.
Conte A, Ferrazzano G, Belvisi D, Manzo N, Battista E, Li Voti P, et al. Somatosensory temporal discrimination in Parkinson's disease, dystonia and essential tremor: pathophysiological and clinical implications. Clin Neurophysiol 2018; 129: 1849–53.
Conte A, Leodori G, Ferrazzano G, De Bartolo MI, Manzo N, Fabbrini G, et al. Somatosensory temporal discrimination threshold in Parkinson's disease parallels disease severity and duration. Clin Neurophysiol 2016; 127: 2985–9.
Conte A, McGovern EM, Narasimham S, Beck R, Killian O, O'Riordan S, et al. Temporal discrimination: mechanisms and relevance to adult-onset dystonia. Front Neurol 2017a; 8: 625. doi: 10.3389/fneur.2017.00625.
Conte A, Modugno N, Lena F, Dispenza S, Gandolfi B, Iezzi E, et al. Subthalamic nucleus stimulation and somatosensory temporal discrimination in Parkinson's disease. Brain 2010; 133: 2656–63.
Cooper JA, Sagar HJ, Tidswell P, Jordan N. Slowed central processing in simple and go/no-go reaction time tasks in Parkinson's disease. Brain 1994; 117: 517–29.
Corcos DM, Chen CM, Quinn NP, McAuley J, Rothwell JC. Strength in Parkinson's disease: relationship to rate of force generation and clinical status. Ann Neurol 1996; 39: 79–88.
Criaud M, Poisson A, Thobois S, Metereau E, Redouté J, Ibarrola D, et al. Slowness in movement initiation is associated with proactive inhibitory network dysfunction in Parkinson's disease. J Parkinsons Dis 2016; 6: 433–40.
Cui G, Jun SB, Jin X, Pham MD, Vogel SS, Lovinger DM, et al. Concurrent activation of striatal direct and indirect pathways during action initiation. Nature 2013; 494: 238–42.
Currà A, Berardelli A, Agostino R, Modugno N, Puorger CC, Accornero N, et al. Performance of sequential arm movements with and without advance knowledge of motor pathways in Parkinson's disease. Mov Disord 1997; 12: 646–54.
da Silva JA, Tecuapetla F, Paixão V, Costa RM. Dopamine neuron activity before action initiation gates and invigorates future movements. Nature 2018; 554: 244–8.
David FJ, Robichaud JA, Vaillancourt DE, Poon C, Kohrt WM, Comella CL, et al. Progressive resistance exercise restores some properties of the triphasic EMG pattern and improves bradykinesia: the PRET-PD randomized clinical trial. J Neurophysiol 2016; 116: 2298–311.
de Almeida Marcelino AL, Horn A, Krause P, Kühn AA, Neumann WJ. Subthalamic neuromodulation improves short-term motor learning in Parkinson's disease. Brain 2019; 142: 2198–206.
de Hemptinne C, Ryapolova-Webb ES, Air EL, Garcia PA, Miller KJ, Ojemann JG, et al. Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. Proc Natl Acad Sci USA 2013; 110: 4780–5.
de Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB, et al. Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. Nat Neurosci 2015; 18: 779–86.
de Hemptinne C, Wang DD, Miocinovic S, Chen W, Ostrem JL, Starr PA. Pallidal thermolesion unleashes gamma oscillations in the motor cortex in Parkinson's disease. Mov Disord 2019; 34: 903–11.
DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990; 13: 281–5.
Delval A, Defebvre L, Tard C. Freezing during tapping tasks in patients with advanced Parkinson's disease and freezing of gait. PLoS ONE 2017; 12: e0181973.
Demirci M, Grill S, McShane L, Hallett M. A mismatch between kinesthetic and visual perception in Parkinson's disease. Ann Neurol 1997; 41: 781–8.
Deuschl G, Goddemeier C. Spontaneous and reflex activity of facial muscles in dystonia, Parkinson's disease, and in normal subjects. J Neurol Neurosurg Psychiatry 1998; 64: 320–4.
Devergnas A, Pittard D, Bliwise D, Wichmann T. Relationship between oscillatory activity in the cortico-basal ganglia network and parkinsonism in MPTP-treated monkeys. Neurobiol Dis 2014; 68: 156–66.
di Biase L, Fasano A. Low-frequency deep brain stimulation for Parkinson's disease: great expectation or false hope? Mov Disord 2016; 31: 962–7.
Djurić-Jovičić M, Petrović I, Ječmenica-Lukić M, Radovanović S, Dragašević-Mišković N, Belić M, et al. Finger tapping analysis in patients with Parkinson's disease and atypical parkinsonism. J Clin Neurosci 2016; 30: 49–55.
Domellöf ME, Forsgren L, Elgh E. Persistence of associations between cognitive impairment and motor dysfunction in the early phase of Parkinson's disease. J Neurol 2013; 260: 2228–36.

Dubois B, Pillon B, Legault F, Agid Y, Lhermitte F. Slowing of cognitive processing in progressive supranuclear palsy. A comparison with Parkinson's disease. Arch Neurol 1988; 45: 1194–9.
Eckert T, Peschel T, Heinze H-J, Rotte M. Increased pre-SMA activation in early PD patients during simple self-initiated hand movements. J Neurol 2006; 253: 199–207.
Eggers C, Fink GR, Nowak DA. Theta burst stimulation over the primary motor cortex does not induce cortical plasticity in Parkinson's disease. J Neurol 2010; 257: 1669–74.
Ehringer H, Hornykiewicz O. Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. Parkinsonism Relat Disord 1998; 4: 53–7.
Ellens DJ, Leventhal DK. Review: electrophysiology of basal ganglia and cortex in models of Parkinson disease. J Parkinsons Dis 2013; 3: 241–54.
Espay AJ, Beaton DE, Morgante F, Gunraj CA, Lang AE, Chen R. Impairments of speed and amplitude of movement in Parkinson's disease: a pilot study. Mov Disord 2009; 24: 1001–8.
Espay AJ, Giuffrida JP, Chen R, Payne M, Mazzella F, Dunn E. Differential response of speed, amplitude, and rhythm to dopaminergic medications in Parkinson's disease. Mov Disord 2011; 26: 2504–8.
Esposito F, Tessitore A, Giordano A, De Micco R, Paccone A, Conforti R, et al. Rhythm-specific modulation of the sensorimotor network in drug-naive patients with Parkinson's disease by levodopa. Brain 2013; 136: 710–25.
Evarts EV, Teräväinen H, Calne DB. Reaction time in Parkinson's disease. Brain 1981; 104: 167–86.
Fabbrini G, Defazio G, Colosimo C, Thompson PD, Berardelli A. Cranial movement disorders: clinical features, pathophysiology, differential diagnosis and treatment. Nat Clin Pract Neurol 2009; 5: 93–105.
Fabbrini G, Latorre A, Suppa A, Bloise M, Frontoni M, Berardelli A. Fatigue in Parkinson's disease: motor or non-motor symptom? Parkinsonism Relat Disord 2013; 19: 148–52.
Farley BG, Sherman S, Koshland GF. Shoulder muscle activity in Parkinson's disease during multijoint arm movements across a range of speeds. Exp Brain Res 2004; 154: 160–75.
Fasano A, Bloem BR. Gait disorders. Continuum (Minneap Minn) 19; 2013: 1344–82.
Fasano A, Laganiere SE, Lam S, Fox MD. Lesions causing freezing of gait localize to a cerebellar functional network. Ann Neurol 2017; 81: 129–41.
Fasano A, Lozano AM. The FM/AM world is shaping the future of deep brain stimulation. Mov Disord. 2014; 29: 161–3.
Fasano A, Piano C, De Simone C, Cioni B, Di Giuda D, Zinno M, et al. High frequency extradural motor cortex stimulation transiently improves axial symptoms in a patient with Parkinson's disease. Mov Disord 2008; 23: 1916–19.
Fasano A, Schlenstedt C, Herzog J, Plotnik M, Rose FEM, Volkmann J, et al. Split-belt locomotion in Parkinson's disease links asymmetry, dyscoordination and sequence effect. Gait Posture 2016; 48: 6–12.
Fearnley JM, Lees AJ. Striatonigral degeneration. A clinicopathological study. Brain 1990; 113: 1823–42.
Flowers KA. Visual "closed-loop" and "open-loop" characteristics of voluntary movement in patients with Parkinsonism and intention tremor. Brain 1976; 99: 269–310.
Foffani G, Priori A, Egidi M, Rampini P, Tamma F, Caputo E, et al. 300-Hz subthalamic oscillations in Parkinson's disease. Brain 2003; 126: 2153–63.
Frasson E, Bertolasi L, Bertasi V, Fusina S, Bartolomei L, Vicentini S, et al. Paired transcranial magnetic stimulation for the early diagnosis of corticobasal degeneration. Clin Neurophysiol 2003; 114: 272–8.
Friedman JH. Fatigue in Parkinson's disease patients. Curr Treat Options Neurol 2009; 11: 186–90.
Friedman JH, Beck JC, Chou KL, Clark G, Fagundes CP, Goetz CG, et al. Fatigue in Parkinson's disease: report from a mutidisciplinary symposium. NPJ Parkinsons Dis 2016; 2: 15025.
Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol 1999; 56: 33–9.
Georgiev D, Lange F, Seer C, Kopp B, Jahanshahi M. Movement-related potentials in Parkinson's disease. Clin Neurophysiol 2016; 127: 2509–19.
Georgiou N, Bradshaw JL, Iansek R, Phillips JG, Mattingley JB, Bradshaw JA. Reduction in external cues and movement sequencing in Parkinson's disease. J Neurol Neurosurg Psychiatry 1994; 57: 368–70.
Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 745–52.
Gigante AF, Bruno G, Iliceto G, Guido M, Liuzzi D, Mancino PV, et al. Action tremor in Parkinson's disease: frequency and relationship to motor and non-motor signs. Eur J Neurol 2015; 22: 223–8.
Giladi N, McMahon D, Przedborski S, Flaster E, Guillory S, Kostic V, et al. Motor blocks in Parkinson's disease. Neurology 1992; 42: 333–9.
Gilio F, Currà A, Inghilleri M, Lorenzano C, Manfredi M, Berardelli A. Repetitive magnetic stimulation of cortical motor areas in Parkinson's disease: implications for the pathophysiology of cortical function. Mov Disord 2002; 17: 467–73.
Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008; 71: 670–76.
Glickstein M, Stein J. Paradoxical movement in Parkinson's disease. Trends Neurosci 1991; 14: 480–2.
Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008; 23: 2129–70.
Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain 2007; 130: 1552–65.
Goldberg JA, Boraud T, Maraton S, Haber SN, Vaadia E, Bergman H. Enhanced synchrony among primary motor cortex neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of Parkinson's disease. J Neurosci 2002; 22: 4639–53.
Grafton ST, Turner RS, Desmurget M, Bakay R, Delong M, Vitek J, et al. Normalizing motor-related brain activity: subthalamic nucleus stimulation in Parkinson disease. Neurology 2006; 66: 1192–9.
Grillner S, Robertson B. The basal ganglia over 500 million years. Curr Biol 2016; 26: R1088–100.
Guo L, Xiong H, Kim J-I, Wu Y-W, Lalchandani RR, Cui Y, et al. Dynamic rewiring of neural circuits in the motor cortex in mouse models of Parkinson's disease. Nat Neurosci 2015; 18: 1299–309.
Hahn PJ, Russo GS, Hashimoto T, Miocinovic S, Xu W, McIntyre CC, et al. Pallidal burst activity during therapeutic deep brain stimulation. Exp Neurol 2008; 211: 243–51.
Hallett M. Clinical neurophysiology of akinesia. Rev Neurol (Paris) 1990; 146: 585–90.
Hallett M, Di Iorio R, Rossini PM, Park JE, Chen R, Celnik P, et al. Contribution of transcranial magnetic stimulation to assessment of brain connectivity and networks. Clin Neurophysiol 2017; 128: 2125–39.
Hallett M, Khoshbin S. A physiological mechanism of bradykinesia. Brain 1980; 103: 301–14.
Hallett M, Shahani BT, Young RR. Analysis of stereotyped voluntary movements at the elbow in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1977; 40: 1129–35.
Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci 2007; 30: 357–64.
Hanajima R, Ugawa Y, Terao Y, Ogata K, Kanazawa I. Ipsilateral cortico-cortical inhibition of the motor cortex in various neurological disorders. J Neurol Sci 1996; 140: 109–16.
Hanakawa T, Goldfine AM, Hallett M. A common function of basal ganglia-cortical circuits subserving speed in both motor and cognitive domains. eNeuro 2017; 4.

Hasan H, Athauda DS, Foltynie T, Noyce AJ. Technologies assessing limb bradykinesia in Parkinson's Disease. J Parkinsons Dis 2017; 7: 65–77.

Haslinger B, Erhard P, Kämpfe N, Boecker H, Rummeny E, Schwaiger M, et al. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. Brain 2001; 124: 558–70.

Hassani OK, Mouroux M, Féger J. Increased subthalamic neuronal activity after nigral dopaminergic lesion independent of disinhibition via the globus pallidus. Neuroscience 1996; 72: 105–15.

Heilman KM, Bowers D, Watson RT, Greer M. Reaction times in Parkinson disease. Arch Neurol 1976; 33: 139–40.

Heldman DA, Giuffrida JP, Chen R, Payne M, Mazzella F, Duker AP, et al. The modified bradykinesia rating scale for Parkinson's disease: reliability and comparison with kinematic measures. Mov Disord 2011; 26: 1859–63.

Helmich RC, Derikx LC, Bakker M, Scheeringa R, Bloem BR, Toni I. Spatial remapping of cortico-striatal connectivity in Parkinson's disease. Cereb Cortex 2010; 20: 1175–86.

Heman P, Barcia C, Gómez A, Ros CM, Ros-Bernal F, Yuste JE, et al. Nigral degeneration correlates with persistent activation of cerebellar Purkinje cells in MPTP-treated monkeys. Histol Histopathol 2012; 27: 89–94.

Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Mov Disord 2017; 32: 853–64.

Howe MW, Dombeck DA. Rapid signalling in distinct dopaminergic axons during locomotion and reward. Nature 2016; 535: 505–10.

Hu X, Jiang Y, Jiang X, Zhang J, Liang M, Li J, et al. Altered functional connectivity density in subtypes of Parkinson's disease. Front Hum Neurosci 2017; 11: 458.

Huang Y-Z, Rothwell JC, Lu C-S, Chuang W-L, Chen R-S. Abnormal bidirectional plasticity-like effects in Parkinson's disease. Brain 2011; 134: 2312–20.

Hutchison WD, Lozano AM, Davis KD, Saint-Cyr JA, Lang AE, Dostrovsky JO. Differential neuronal activity in segments of globus pallidus in Parkinson's disease patients. Neuroreport 1994; 5: 1533–7.

Iansek R, Danoudis M. Freezing of Gait in Parkinson's Disease: its pathophysiology and pragmatic approaches to management. Mov Disord Clin Pract 2016; 4: 290–7.

Iansek R, Huxham F, McGinley J. The sequence effect and gait festination in Parkinson disease: contributors to freezing of gait? Mov Disord 2006; 21: 1419–24.

Ichinohe N, Mori F, Shoumura K. A di-synaptic projection from the lateral cerebellar nucleus to the laterodorsal part of the striatum via the central lateral nucleus of the thalamus in the rat. Brain Res 2000; 880: 191–7.

Jackson GM, Jackson SR, Hindle JV. The control of bimanual reach-to-grasp movements in hemiparkinsonian patients. Exp Brain Res 2000; 132: 390–8.

Jacobs DH, Shuren J, Bowers D, Heilman KM. Emotional facial imagery, perception, and expression in Parkinson's disease. Neurology 1995; 45: 1696–702.

Jahanshahi M, Brown RG, Marsden CD. Simple and choice reaction time and the use of advance information for motor preparation in Parkinson's disease. Brain 1992a; 115: 539–64.

Jahanshahi M, Brown RG, Marsden CD. The effect of withdrawal of dopaminergic medication on simple and choice reaction time and the use of advance information in Parkinson's disease. J Neurol Neurosurg Psychiatry 1992b; 55: 1168–76.

Jahanshahi M, Brown RG, Marsden CD. A comparative study of simple and choice reaction time in Parkinson's, Huntington's and cerebellar disease. J Neurol Neurosurg Psychiatry 1993; 56: 1169–77.

Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 1995; 118: 913–33.

Jahanshahi M, Jones CRG, Zijlmans J, Katzenschlager R, Lee L, Quinn N, et al. Dopaminergic modulation of striato-frontal connectivity during motor timing in Parkinson's disease. Brain 2010; 133: 727–45.

Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 1990; 40: 1529–34.

Jenkinson N, Brown P. New insights into the relationship between dopamine, beta oscillations and motor function. Trends Neurosci 2011; 34: 611–8.

Ji G-J, Hu P, Liu T-T, Li Y, Chen X, Zhu C, et al. Functional connectivity of the corticobasal ganglia-thalamocortical network in Parkinson disease: a systematic review and meta-analysis with cross-validation. Radiology 2018; 287: 973–82.

Johnson KA, Cunnington R, Bradshaw JL, Phillips JG, Iansek R, Rogers MA. Bimanual co-ordination in Parkinson's disease. Brain 1998; 121: 743–53.

Jokinen P, Karrasch M, Brück A, Johansson J, Bergman J, Rinne JO. Cognitive slowing in Parkinson's disease is related to frontostriatal dopaminergic dysfunction. J Neurol Sci 2013; 329: 23–8.

Kačar A, Filipović SR, Kresojević N, Milanović SD, Ljubisavljević M, Kostić VS, et al. History of exposure to dopaminergic medication does not affect motor cortex plasticity and excitability in Parkinson's disease. Clin Neurophysiol 2013; 124: 697–707.

Kačar A, Milanović SD, Filipović SR, Ljubisavljević MR. Changes in cortical excitability during paired associative stimulation in Parkinson's disease patients and healthy subjects. Neurosci Res 2017; 124: 51–6.

Kalia LV, Lang AE. Parkinson's disease. Lancet 2015; 386: 896–912.

Kammermeier S, Pittard D, Hamada I, Wichmann T. Effects of high-frequency stimulation of the internal pallidal segment on neuronal activity in the thalamus in parkinsonian monkeys. J Neurophysiol 2016; 116: 2869–81.

Kang SY, Wasaka T, Shamim EA, Auh S, Ueki Y, Dang N, et al. The sequence effect in de novo Parkinson's disease. J Mov Disord 2011; 4: 38–40.

Kang SY, Wasaka T, Shamim EA, Auh S, Ueki Y, Lopez GJ, et al. Characteristics of the sequence effect in Parkinson's disease. Mov Disord 2010; 25: 2148–55.

Karabanov AN, Chao C-C, Paine R, Hallett M. Mapping different intra-hemispheric parietal-motor networks using twin Coil TMS. Brain Stimul 2013; 6: 384–9.

Karson CN, Burns RS, LeWitt PA, Foster NL, Newman RP. Blink rates and disorders of movement. Neurology 1984; 34: 677–8.

Karunanayaka PR, Lee E-Y, Lewis MM, Sen S, Eslinger PJ, Yang QX, et al. Default mode network differences between rigidity- and tremor-predominant Parkinson's disease. Cortex 2016; 81: 239–50.

Katsikitis M, Pilowsky I. A study of facial expression in Parkinson's disease using a novel microcomputer-based method. J Neurol Neurosurg Psychiatry 1988; 51: 362–6.

Kawashima S, Ueki Y, Mima T, Fukuyama H, Ojika K, Matsukawa N. Differences in dopaminergic modulation to motor cortical plasticity between Parkinson's disease and multiple system atrophy. PLoS ONE 2013; 8: e62515.

Kim J, Criaud M, Cho SS, Díez-Cirarda M, Mihaescu A, Coakeley S, et al. Abnormal intrinsic brain functional network dynamics in Parkinson's disease. Brain 2017; 140: 2955–67.

Kimber TE, Thompson PD. Increased blink rate in advanced Parkinson's disease: a form of 'off'-period dystonia? Mov Disord 2000; 15: 982–5.

Kishore A, Espay AJ, Marras C, Al-Khairalla T, Arenovich T, Asante A, et al. Unilateral versus bilateral tasks in early asymmetric Parkinson's disease: differential effects on bradykinesia. Mov Disord 2007; 22: 328–33.

Kishore A, James P, Krishnan S, Yahia-Cherif L, Meunier S, Popa T. Motor cortex plasticity can indicate vulnerability to motor fluctuation and high L-DOPA need in drug-naïve Parkinson's disease. Parkinsonism Relat Disord 2017; 35: 55–62.

Kishore A, Joseph T, Velayudhan B, Popa T, Meunier S. Early, severe and bilateral loss of LTP and LTD-like plasticity in motor cortex (M1) in de novo Parkinson's disease. Clin Neurophysiol 2012a; 123: 822–8.

Kishore A, Popa T, Balachandran A, Chandran S, Pradeep S, Backer F, et al. Cerebellar sensory processing alterations impact motor cortical plasticity in Parkinson's disease: clues from dyskinetic patients. Cereb Cortex 2014; 24: 2055–67.

Kishore A, Popa T, Velayudhan B, Joseph T, Balachandran A, Meunier S. Acute dopamine boost has a negative effect on plasticity of the primary motor cortex in advanced Parkinson's disease. Brain 2012b; 135: 2074–88.

Kita H, Kita T. Role of striatum in the pause and burst generation in the globus pallidus of 6-OHDA-treated rats. Front Syst Neurosci 2011; 5: 42.

Kleine BU, Praamstra P, Stegeman DF, Zwarts MJ. Impaired motor cortical inhibition in Parkinson's disease: motor unit responses to transcranial magnetic stimulation. Exp Brain Res 2001; 138: 477–83.

Koch G, Fernandez Del Olmo M, Cheeran B, Ruge D, Schippling S, Caltagirone C, Rothwell JC. Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. J Neurosci 2007; 27: 6815–22.

Kojovic M, Bologna M, Kassavetis P, Murase N, Palomar FJ, Berardelli A, et al. Functional reorganization of sensorimotor cortex in early Parkinson disease. Neurology 2012; 78: 1441–8.

Kojovic M, Kassavetis P, Bologna M, Pareés I, Rubio-Agusti I, Berardelli A, et al. Transcranial magnetic stimulation follow-up study in early Parkinson's disease: a decline in compensation with disease progression? Mov Disord 2015; 30: 1098–106.

Konczak J, Krawczewski K, Tuite P, Maschke M. The perception of passive motion in Parkinson's disease. J Neurol 2007; 254: 655–63.

Korosec M, Zidar I, Reits D, Evinger C, Vanderwerf F. Eyelid movements during blinking in patients with Parkinson's disease. Mov Disord 2006; 21: 1248–51.

Kravitz AV, Freeze BS, Parker PRL, Kay K, Thwin MT, Deisseroth K, et al. Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature 2010; 466: 622–6.

Krumpolec P, Vallova S, Slobodova L, Tirpakova V, Vajda M, Schon M, et al. Aerobic-strength exercise improves metabolism and clinical state in Parkinson's disease patients. Front Neurol 2017; 8: 698.

Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989; 46: 1121–3.

Kühn AA, Grosse P, Holtz K, Brown P, Meyer B-U, Kupsch A. Patterns of abnormal motor cortex excitability in atypical parkinsonian syndromes. Clin Neurophysiol 2004; 115: 1786–95.

Kühn AA, Tsui A, Aziz T, Ray N, Brücke C, Kupsch A, et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Exp Neurol 2009; 215: 380–7.

Lacruz F, Artieda J, Pastor MA, Obeso JA. The anatomical basis of somaesthetic temporal discrimination in humans. J Neurol Neurosurg Psychiatry 1991; 54: 1077–81.

Lago-Rodriguez A, Ponzo V, Jenkinson N, Benitez-Rivero S, Del-Olmo MF, Hu M, et al. Paradoxical facilitation after depotentiation protocol can precede dyskinesia onset in early Parkinson's disease. Exp Brain Res 2016; 234: 3659–67.

Lee C, Grossman M, Morris J, Stern MB, Hurtig HI. Attentional resource and processing speed limitations during sentence processing in Parkinson's disease. Brain Lang 2003; 85: 347–56.

Lee M-S, Kim H-S, Lyoo C-H. "Off" gait freezing and temporal discrimination threshold in patients with Parkinson disease. Neurology 2005; 64: 670–4.

Lee KD, Koo JH, Song SH, Jo KD, Lee MK, Jang W. Central cholinergic dysfunction could be associated with oropharyngeal dysphagia in early Parkinson's disease. J Neural Transm (Vienna) 2015; 122: 1553–61.

Lee E, Lee JE, Yoo K, Hong JY, Oh J, Sunwoo MK, et al. Neural correlates of progressive reduction of bradykinesia in de novo Parkinson's disease. Parkinsonism Relat Disord 2014; 20: 1376–81.

Lee MS, Lee MJ, Conte A, Berardelli A. Abnormal somatosensory temporal discrimination in Parkinson's disease: pathophysiological correlates and role in motor control deficits. Clin Neurophysiol 2017; 129: 442–7.

Lee MS, Lyoo CH, Lee MJ, Sim J, Cho H, Choi YH. Impaired finger dexterity in patients with Parkinson's disease correlates with discriminative cutaneous sensory dysfunction. Mov Disord 2010; 25: 2531–5.

Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. Brain 2002a; 125: 1196–209.

Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. J Neurosci 2000; 20: 7766–75.

Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. J Neurosci 2002b; 22: 2855–61.

Ling H, Massey LA, Lees AJ, Brown P, Day BL. Hypokinesia without decrement distinguishes progressive supranuclear palsy from Parkinson's disease. Brain 2012; 135: 1141–53.

Little S, Beudel M, Zrinzo L, Foltynie T, Limousin P, Hariz M, et al. Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. J Neurol Neurosurg Psychiatry 2016; 87: 717–21.

Little S, Brown P. The functional role of beta oscillations in Parkinson's disease. Parkinsonism Relat Disord 2014; 20: S44–8.

Little S, Pogosyan A, Kuhn AA, Brown P. β band stability over time correlates with Parkinsonian rigidity and bradykinesia. Exp Neurol 2012; 236: 383–8.

Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, et al. Adaptive deep brain stimulation in advanced Parkinson disease. Ann Neurol 2013; 74: 449–57.

Liu C, Kershberg L, Wang J, Schneeberger S, Kaeser PS. Dopamine secretion is mediated by sparse active zone-like release sites. Cell 2018; 172: 706–18.

Lofredi R, Neumann WJ, Bock A, Horn A, Huebl J, Siegert S, et al. Dopamine-dependent scaling of subthalamic gamma bursts with movement velocity in patients with Parkinson's disease. Elife 2018; 1: 7.

Lofredi R, Tan H, Neumann WJ, Yeh CH, Schneider GH, Kühn AA, Brown P. Beta bursts during continuous movements accompany the velocity decrement in Parkinson's disease patients. Neurobiol Dis 2019; 127: 462–71.

Logigian E, Hefter H, Reiners K, Freund HJ. Does tremor pace repetitive voluntary motor behavior in Parkinson's disease? Ann Neurol 1991; 30: 172–9.

Lu M-K, Chen C-M, Duann J-R, Ziemann U, Chen J-C, Chiou S-M, et al. Investigation of motor cortical plasticity and corticospinal tract diffusion tensor imaging in patients with Parkinsons disease and essential tremor. PLoS ONE 2016; 11: e0162265.

Lyoo CH, Lee SY, Song TJ, Lee MS. Abnormal temporal discrimination threshold in patients with multiple system atrophy. Mov Disord 2007; 22: 556–9.

Lyoo CH, Ryu YH, Lee MJ, Lee MS. Striatal dopamine loss and discriminative sensory dysfunction in Parkinson's disease. Acta Neurol Scand 2012; 126: 344–9.

MacKinnon CD, Gilley EA, Weis-McNulty A, Simuni T. Pathways mediating abnormal intracortical inhibition in Parkinson's disease. Ann Neurol 2005; 58: 516–24.

Magnin M, Morel A, Jeanmonod D. Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. Neuroscience 2000; 96: 549–64.

Majsak MJ, Kaminski T, Gentile AM, Flanagan JR. The reaching movements of patients with Parkinson's disease under self-determined maximal speed and visually cued conditions. Brain 1998; 121: 755–66.

Mäkinen E, Joutsa J, Jaakkola E, Noponen T, Johansson J, Pitkonen M, et al. Individual parkinsonian motor signs and striatal dopamine transporter deficiency: a study with [I-123]FP-CIT SPECT. J Neurol 2019; 266: 826–34.

Mallet N, Ballion B, Le Moine C, Gonon F. Cortical inputs and GABA interneurons imbalance projection neurons in the striatum of parkinsonian rats. J Neurosci 2006; 26: 3875–84.

Mallet N, Pogosyan A, Márton LF, Bolam JP, Brown P, Magill PJ. Parkinsonian beta oscillations in the external globus pallidus and their relationship with subthalamic nucleus activity. J Neurosci 2008; 28: 14245–58.

Manganelli F, Vitale C, Santangelo G, Pisciotta C, Iodice R, Cozzolino A, et al. Functional involvement of central cholinergic circuits and visual hallucinations in Parkinson's disease. Brain 2009; 132: 2350–5.

Manto M, Bower JM, Conforto AB, Delgado-García JM, da Guarda SN, Gerwig M, et al. Consensus paper: roles of the cerebellum in motor control–the diversity of ideas on cerebellar involvement in movement. Cerebellum 2012; 11: 457–87.

Marchese R, Trompetto C, Buccolieri A, Abbruzzese G. Abnormalities of motor cortical excitability are not correlated with clinical features in atypical parkinsonism. Mov Disord 2000; 15: 1210–4.

Marsili L, Agostino R, Bologna M, Belvisi D, Palma A, Fabbrini G, et al. Bradykinesia of posed smiling and voluntary movement of the lower face in Parkinson's disease. Parkinsonism Relat Disord 2014; 20: 370–75.

McFarland NR, Hess CW. Recognizing atypical Parkinsonisms: "red flags" and therapeutic approaches. Semin Neurol 2017; 37: 215–27.

McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology 2017; 89: 88–100.

Merola A, Sturchio A, Hacker S, Serna S, Vizcarra JA, Marsili L, et al. Technology-based assessment of motor and nonmotor phenomena in Parkinson disease. Expert Rev Neurother 2018; 8: 825–45.

Milosevic L, Gramer R, Kim TH, Algarni M, Fasano A, Kalia SK, et al. Modulation of inhibitory plasticity in basal ganglia output nuclei of patients with Parkinson's disease. Neurobiol Dis 2019; 124: 46–56.

Mir P, Matsunaga K, Gilio F, Quinn NP, Siebner HR, Rothwell JC. Dopaminergic drugs restore facilitatory premotor-motor interactions in Parkinson disease. Neurology 2005; 64: 1906–12.

Moers-Hornikx VMP, Vles JSH, Tan SKH, Cox K, Hoogland G, Steinbusch WMH, et al. Cerebellar nuclei are activated by high-frequency stimulation of the subthalamic nucleus. Neurosci Lett 2011; 496: 111–5.

Monte-Silva K, Liebetanz D, Grundey J, Paulus W, Nitsche MA. Dosage-dependent non-linear effect of L-dopa on human motor cortex plasticity. J Physiol (Lond) 2010; 588: 3415–24.

Morgante F, Espay AJ, Gunraj C, Lang AE, Chen R. Motor cortex plasticity in Parkinson's disease and levodopa-induced dyskinesias. Brain 2006; 129: 1059–69.

Moro E, Schwalb JM, Piboolnurak P, Poon Y-YW, Hamani C, Hung SW, et al. Unilateral subdural motor cortex stimulation improves essential tremor but not Parkinson's disease. Brain 2011; 134: 2096–105.

Müller EJ, Robinson PA. Suppression of Parkinsonian beta oscillations by deep brain stimulation: determination of effective protocols. Front Comput Neurosci 2018; 12: 98.

Murgai AA, Jog MS. Neurophysiology and neurochemistry of corticobasal syndrome. J Neurol 2018; 265: 991–8.

Nambu A, Tokuno H, Takada M. Functional significance of the cortico-subthalamo-pallidal "hyperdirect" pathway. Neurosci Res 2002; 43: 111–7.

Nardone R, Bergmann J, Brigo F, Christova M, Kunz A, Seidl M, et al. Functional evaluation of central cholinergic circuits in patients with Parkinson's disease and REM sleep behavior disorder: a TMS study. J Neural Transm (Vienna) 2013; 120: 413–22.

Neumann W-J, Schroll H, de Almeida Marcelino AL, Horn A, Ewert S, Irmen F, et al. Functional segregation of basal ganglia pathways in Parkinson's disease. Brain 2018; 141: 2655–69.

Ni Z, Bahl N, Gunraj CA, Mazzella F, Chen R. Increased motor cortical facilitation and decreased inhibition in Parkinson disease. Neurology 2013; 80: 1746–53.

Ni M, Signorile JF, Balachandran A, Potiaumpai M. Power training induced change in bradykinesia and muscle power in Parkinson's disease. Parkinsonism Relat Disord 2016; 23: 37–44.

Nini A, Feingold A, Slovin H, Bergman H. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. J Neurophysiol 1995; 74: 1800–5.

Nonnekes J, Ružicka E, Nieuwboer A, Hallett M, Fasano A, Bloem BR. Compensation strategies for gait impairments in Parkinson disease: a review. JAMA Neurol 2019; 76: 718–25.

Obeso JA, Rodríguez-Oroz MC, Rodríguez M, Lanciego JL, Artieda J, Gonzalo N, et al. Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci 2000; 23: S8–19.

Obeso JA, Stamelou M, Goetz CG, Poewe W, Lang AE, Weintraub D, et al. Past, present, and future of Parkinson's disease: a special essay on the 200th anniversary of the Shaking Palsy. Mov Disord 2017; 32: 1264–310.

Oh E, Park J, Youn J, Kim JS, Park S, Jang W. Olfactory dysfunction in early Parkinson's disease is associated with short latency afferent inhibition reflecting central cholinergic dysfunction. Clin Neurophysiol 2017; 128: 1061–8.

Oswal A, Brown P, Litvak V. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr Opin Neurol 2013; 26: 662–70.

Pan HS, Walters JR. Unilateral lesion of the nigrostriatal pathway decreases the firing rate and alters the firing pattern of globus pallidus neurons in the rat. Synapse 1988; 2: 650–56.

Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci 2002; 14: 223–36; discussion 222.

Parr-Brownlie LC, Hyland BI. Bradykinesia induced by dopamine D2 receptor blockade is associated with reduced motor cortex activity in the rat. J Neurosci 2005; 25: 5700–9.

Pascual-Leone A, Valls-Solé J, Brasil-Neto JP, Cohen LG, Hallett M. Akinesia in Parkinson's disease. I. Shortening of simple reaction time with focal, single-pulse transcranial magnetic stimulation. Neurology 1994; 44: 884–91.

Pasquereau B, DeLong MR, Turner RS. Primary motor cortex of the parkinsonian monkey: altered encoding of active movement. Brain 2016; 139: 127–43.

Pasquereau B, Turner RS. Primary motor cortex of the parkinsonian monkey: differential effects on the spontaneous activity of pyramidal tract-type neurons. Cereb Cortex 2011; 21: 1362–78.

Patel N, Jankovic J, Hallett M. Sensory aspects of movement disorders. Lancet Neurol 2014; 13: 100–12.

Pelosin E, Ogliastro C, Lagravinese G, Bonassi G, Mirelman A, Hausdorff JM, et al. Attentional control of gait and falls: is cholinergic dysfunction a common substrate in the elderly and Parkinson's disease? Front Aging Neurosci 2016; 8: 104.

Pfann KD, Buchman AS, Comella CL, Corcos DM. Control of movement distance in Parkinson's disease. Mov Disord 2001; 16: 1048–65.

Phillips JG, Martin KE, Bradshaw JL, Iansek R. Could bradykinesia in Parkinson's disease simply be compensation? J Neurol 1994; 241: 439–47.

Piano C, Fasano A, Daniele A, Di Giuda D, Ciavarro M, Tufo T, et al. Extradural motor cortex stimulation improves gait, speech, and language in a patient with pure akinesia. Brain Stimul 2018; 11: 1192–4.

Picillo M, Dubbioso R, Iodice R, Iavarone A, Pisciotta C, Spina E, et al. Short-latency afferent inhibition in patients with Parkinson's disease and freezing of gait. J Neural Transm (Vienna) 2015; 122: 1533–40.

Pierantozzi M, Palmieri MG, Marciani MG, Bernardi G, Giacomini P, Stanzione P. Effect of apomorphine on cortical inhibition in Parkinson's disease patients: a transcranial magnetic stimulation study. Exp Brain Res 2001; 141: 52–62.

Pillon B, Dubois B, Cusimano G, Bonnet AM, Lhermitte F, Agid Y. Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? J Neurol Neurosurg Psychiatry 1989; 52: 201–6.

Playford ED, Jenkins IH, Passingham RE, Nutt J, Frackowiak RS, Brooks DJ. Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. Ann Neurol 1992; 32: 151–61.

Poletti M, Frosini D, Pagni C, Baldacci F, Nicoletti V, Tognoni G, et al. Mild cognitive impairment and cognitive-motor relationships in newly diagnosed drug-naive patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2012; 83: 601–6.

Poston KL, Eidelberg D. Functional brain networks and abnormal connectivity in the movement disorders. Neuroimage 2012; 62: 2261–70.

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015; 30: 1591–601.

Postuma RB, Poewe W, Litvan I, Lewis S, Lang AE, Halliday G, et al. Validation of the MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2018; 33: 1601–8.

Priori A, Berardelli A, Inghilleri M, Accornero N, Manfredi M. Motor cortical inhibition and the dopaminergic system. Pharmacological changes in the silent period after transcranial brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. Brain 1994; 117: 317–23.

Priori A, Foffani G, Pesenti A, Tamma F, Bianchi AM, Pellegrini M, et al. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. Exp Neurol 2004; 189: 369–79.

Pullman SL, Watts RL, Juncos JL, Chase TN, Sanes JN. Dopaminergic effects on simple and choice reaction time performance in Parkinson's disease. Neurology 1988; 38: 249–54.

Rafal RD, Friedman JH, Lannon MC. Preparation of manual movements in hemiparkinsonism. J Neurol Neurosurg Psychiatry 1989; 52: 399–402.

Rascol O, Sabatini U, Chollet F, Celsis P, Montastruc JL, Marc-Vergnes JP, et al. Supplementary and primary sensory motor area activity in Parkinson's disease. Regional cerebral blood flow changes during finger movements and effects of apomorphine. Arch Neurol 1992; 49: 144–8.

Rascol O, Sabatini U, Fabre N, Brefel C, Loubinoux I, Celsis P, et al. The ipsilateral cerebellar hemisphere is overactive during hand movements in akinetic parkinsonian patients. Brain 1997; 120: 103–10.

Ray NJ, Jenkinson N, Wang S, Holland P, Brittain JS, Joint C, et al. Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. Exp Neurol 2008; 213: 108–13.

Raz A, Feingold A, Zelanskaya V, Vaadia E, Bergman H. Neuronal synchronization of tonically active neurons in the striatum of normal and parkinsonian primates. J Neurophysiol 1996; 76: 2083–8.

Raz A, Vaadia E, Bergman H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. J Neurosci 2000; 20: 8559–71.

Redgrave P, Rodriguez M, Smith Y, Rodriguez-Oroz MC, Lehericy S, Bergman H, et al. Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. Nat Rev Neurosci 2010; 11: 760–72.

Revonsuo A, Portin R, Koivikko L, Rinne JO, Rinne UK. Slowing of information processing in Parkinson's disease. Brain Cogn 1993; 21: 87–110.

Ridding MC, Inzelberg R, Rothwell JC. Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. Ann Neurol 1995; 37: 181–8.

Rocchi L, Casula E, Tocco P, Berardelli A, Rothwell J. Somatosensory temporal discrimination threshold involves inhibitory mechanisms in the primary somatosensory area. J Neurosci 2016; 36: 325–35.

Rocchi L, Conte A, Nardella A, Li Voti P, Di Biasio F, Leodori G, et al. Somatosensory temporal discrimination threshold may help to differentiate patients with multiple system atrophy from patients with Parkinson's disease. Eur J Neurol 2013; 20: 714–9.

Rochester L, Yarnall AJ, Baker MR, David RV, Lord S, Galna B, et al. Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease. Brain 2012; 135: 2779–88.

Rodriguez-Sabate C, Morales I, Monton F, Rodriguez M. The influence of Parkinson's disease on the functional connectivity of the motor loop of human basal ganglia. Parkinsonism Relat Disord 2019; 63: 100–05.

Rolland A-S, Herrero M-T, Garcia-Martinez V, Ruberg M, Hirsch EC, François C. Metabolic activity of cerebellar and basal ganglia-thalamic neurons is reduced in parkinsonism. Brain 2007; 130: 265–75.

Romano S, Colosimo C. Procerus sign in progressive supranuclear palsy. Neurology 2001; 57: 1928.

Rosenberg-Katz K, Herman T, Jacob Y, Giladi N, Hendler T, Hausdorff JM. Gray matter atrophy distinguishes between Parkinson disease motor subtypes. Neurology 2013; 80: 1476–84.

Rowe J, Stephan KE, Friston K, Frackowiak R, Lees A, Passingham R. Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. Brain 2002; 125: 276–89.

Sabatini U, Boulanouar K, Fabre N, Martin F, Carel C, Colonnese C, et al. Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. Brain 2000; 123: 394–403.

Sacks O. Awakenings. London: Picador; 1991.

Sagot B, Li L, Zhou F-M. Hyperactive response of direct pathway striatal projection neurons to L-dopa and D1 Agonism in freely moving Parkinsonian mice. Front Neural Circuits 2018; 12: 57.

Sailer A, Molnar GF, Paradiso G, Gunraj CA, Lang AE, Chen R. Short and long latency afferent inhibition in Parkinson's disease. Brain 2003; 126: 1883–94.

Samuel M, Ceballos-Baumann AO, Blin J, Uema T, Boecker H, Passingham RE, et al. Evidence for lateral premotor and parietal overactivity in Parkinson's disease during sequential and bimanual movements. A PET study. Brain 1997; 120: 963–76.

Sawamoto N, Honda M, Hanakawa T, Fukuyama H, Shibasaki H. Cognitive slowing in Parkinson's disease: a behavioral evaluation independent of motor slowing. J Neurosci 2002; 22: 5198–203.

Schilder JCM, Overmars SS, Marinus J, van Hilten JJ, Koehler PJ. The terminology of akinesia, bradykinesia and hypokinesia: past, present and future. Parkinsonism Relat Disord 2017; 37: 27–35.

Schwab RS, Chafetz ME, Walker S. Control of two simultaneous voluntary motor acts in normals and in parkinsonism. AMA Arch Neurol Psychiatry 1954; 72: 591–8.

Schwingenschuh P, Ruge D, Edwards MJ, Terranova C, Katschnig P, Carrillo F, et al. Distinguishing SWEDDs patients with asymmetric resting tremor from Parkinson's disease: a clinical and electrophysiological study. Mov Disord 2010; 25: 560–9.

Seidler RD, Alberts JL, Stelmach GE. Multijoint movement control in Parkinson's disease. Exp Brain Res 2001; 140: 335–44.

Seiss E, Praamstra P, Hesse CW, Rickards H. Proprioceptive sensory function in Parkinson's disease and Huntington's disease: evidence from proprioception-related EEG potentials. Exp Brain Res 2003; 148: 308–19.

Sen S, Kawaguchi A, Truong Y, Lewis MM, Huang X. Dynamic changes in cerebello-thalamo-cortical motor circuitry during progression of Parkinson's disease. Neuroscience 2010; 166: 712–9.

Shao N, Yang J, Li J, Shang H-F. Voxelwise meta-analysis of gray matter anomalies in progressive supranuclear palsy and Parkinson's disease using anatomic likelihood estimation. Front Hum Neurosci 2014; 8: 63.

Sharott A, Magill PJ, Bolam JP, Brown P. Directional analysis of coherent oscillatory field potentials in the cerebral cortex and basal ganglia of the rat. J Physiol (Lond) 2005; 562: 951–63.

Sharott A, Vinciati F, Nakamura KC, Magill PJ. A population of indirect pathway striatal projection neurons is selectively entrained to parkinsonian beta oscillations. J Neurosci 2017; 37: 9977–98.

Sheridan MR, Flowers KA, Hurrell J. Programming and execution of movement in Parkinson's disease. Brain 1987; 110: 1247–71.

Siciliano M, Trojano L, Santangelo G, De Micco R, Tedeschi G, Tessitore A. Fatigue in Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2018; 33: 1712–23.

Simons G, Pasqualini MCS, Reddy V, Wood J. Emotional and nonemotional facial expressions in people with Parkinson's disease. J Int Neuropsychol Soc 2004; 10: 521–35.

Smith MC, Smith MK, Ellgring H. Spontaneous and posed facial expression in Parkinson's disease. J Int Neuropsychol Soc 1996; 2: 383–91.

Snijders AH, Bloem BR. Images in clinical medicine. Cycling for freezing of gait. N Engl J Med 2010; 362: e46.

Soares J, Kliem MA, Betarbet R, Greenamyre JT, Yamamoto B, Wichmann T. Role of external pallidal segment in primate parkinsonism: comparison of the effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism and lesions of the external pallidal segment. J Neurosci 2004; 24: 6417–26.

Spay C, Meyer G, Welter M-L, Lau B, Boulinguez P, Ballanger B. Functional imaging correlates of akinesia in Parkinson's disease: still open issues. Neuroimage Clin 2019; 21: 101644.

Steigerwald F, Pötter M, Herzog J, Pinsker M, Kopper F, Mehdorn H, et al. Neuronal activity of the human subthalamic nucleus in the parkinsonian and nonparkinsonian state. J Neurophysiol 2008; 100: 2515–24.

Steiner LA, Neumann W-J, Staub-Bartelt F, Herz DM, Tan H, Pogosyan A, et al. Subthalamic beta dynamics mirror Parkinsonian bradykinesia months after neurostimulator implantation. Mov Disord 2017; 32: 1183–90.

Stelmach GE, Worringham CJ. The control of bimanual aiming movements in Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 223–31.

Stelmach GE, Worringham CJ, Strand EA. Movement preparation in Parkinson's disease. The use of advance information. Brain 1986; 109: 1179–94.

Sterio D, Berić A, Dogali M, Fazzini E, Alfaro G, Devinsky O. Neurophysiological properties of pallidal neurons in Parkinson's disease. Ann Neurol 1994; 35: 586–91.

Stoffers D, Bosboom JLW, Deijen JB, Wolters EC, Stam CJ, Berendse HW. Increased cortico-cortical functional connectivity in early-stage Parkinson's disease: an MEG study. Neuroimage 2008; 41: 212–22.

Stojkovic T, Stefanova E, Soldatovic I, Markovic V, Stankovic I, Petrovic I, et al. Exploring the relationship between motor impairment, vascular burden and cognition in Parkinson's disease. J Neurol 2018; 265: 1320–7.

Strafella AP, Valzania F, Nassetti SA, Tropeani A, Bisulli A, Santangelo M, et al. Effects of chronic levodopa and pergolide treatment on cortical excitability in patients with Parkinson's disease: a transcranial magnetic stimulation study. Clin Neurophysiol 2000; 111: 1198–202.

Strotzer QD, Anthofer JM, Faltermeier R, Brawanski AT, Torka E, Waldthaler JA, et al. Deep brain stimulation: Connectivity profile for bradykinesia alleviation. Ann Neurol 2019; 85: 852–64.

Su D, Chen H, Hu W, Liu Y, Wang Z, Wang X, et al. Frequency-dependent effects of subthalamic deep brain stimulation on motor symptoms in Parkinson's disease: a meta-analysis of controlled trials. Sci Rep 2018; 8: 14456.

Suppa A, Bologna M, Conte A, Berardelli A, Fabbrini G. The effect of L-dopa in Parkinson's disease as revealed by neurophysiological studies of motor and sensory functions. Expert Rev Neurother 2017; 17: 181–92.

Suppa A, Iezzi E, Conte A, Belvisi D, Marsili L, Modugno N, et al. Dopamine influences primary motor cortex plasticity and dorsal premotor-to-motor connectivity in Parkinson's disease. Cereb Cortex 2010; 20: 2224–33.

Suppa A, Marsili L, Belvisi D, Conte A, Iezzi E, Modugno N, et al. Lack of LTP like plasticity in primary motor cortex in Parkinson's disease. Exp Neurol 2011; 227: 296–301.

Swann NC, de Hemptinne C, Miocinovic S, Qasim S, Wang SS, Ziman N, et al. Gamma oscillations in the hyperkinetic state detected with chronic human brain recordings in Parkinson's disease. J Neurosci 2016; 36: 6445–58.

Tai C-H, Pan M-K, Lin JJ, Huang C-S, Yang Y-C, Kuo C-C. Subthalamic discharges as a causal determinant of parkinsonian motor deficits. Ann Neurol 2012; 72: 464–76.

Tan H, Pogosyan A, Anzak A, Foltynie T, Limousin P, Zrinzo L, et al. Frequency specific activity in subthalamic nucleus correlates with hand bradykinesia in Parkinson's disease. Exp Neurol 2013; 240: 122–9.

Thenganatt MA, Jankovic J. Psychogenic (functional) parkinsonism. Handb Clin Neurol 2016; 139: 259–62.

Tessa C, Lucetti C, Diciotti S, Baldacci F, Paoli L, Cecchi P, et al. Decreased and increased cortical activation coexist in de novo Parkinson's disease. Exp Neurol 2010; 224: 299–306.

Thobois S, Dominey P, Decety J, Pollak P, Gregoire MC, Broussolle E. Overactivation of primary motor cortex is asymmetrical in hemiparkinsonian patients. Neuroreport 2000; 11: 785–9.

Timmermann L, Wojtecki L, Gross J, Lehrke R, Voges J, Maarouf M, et al. Ten-Hertz stimulation of subthalamic nucleus deteriorates motor symptoms in Parkinson's disease. Mov Disord 2004; 19: 1328–33.

Tinaz S, Pillai AS, Hallett M. Sequence effect in Parkinson's disease is related to motor energetic cost. Front Neurol 2016; 7: 83.

Tinkhauser G, Pogosyan A, Tan H, Herz DM, Kühn AA, Brown P. Beta burst dynamics in Parkinson's disease OFF and ON dopaminergic medication. Brain 2017; 140: 2968–81.

Tison F, Yekhlef F, Chrysostome V, Balestre E, Quinn NP, Poewe W, et al. Parkinsonism in multiple system atrophy: natural history, severity (UPDRS-III), and disability assessment compared with Parkinson's disease. Mov Disord 2002; 17: 701–9.

Torrecillos F, Tinkhauser G, Fischer P, Green AL, Aziz TZ, Foltynie T, et al. Modulation of beta bursts in the subthalamic nucleus predicts motor performance. J Neurosci 2018; 38: 8905–17.

Trager MH, Koop MM, Velisar A, Blumenfeld Z, Nikolau JS, Quinn EJ, et al. Subthalamic beta oscillations are attenuated after withdrawal of chronic high frequency neurostimulation in Parkinson's disease. Neurobiol Dis 2016; 96: 22–30.

Turner RS, Grafton ST, McIntosh AR, DeLong MR, Hoffman JM. The functional anatomy of parkinsonian bradykinesia. Neuroimage 2003; 19: 163–79.

Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. Prog Neurobiol 2015; 133: 27–49.

Ueki Y, Mima T, Kotb MA, Sawada H, Saiki H, Ikeda A, et al. Altered plasticity of the human motor cortex in Parkinson's disease. Ann Neurol 2006; 59: 60–71.

Ukmar M, Furlan C, Moretti R, Garbin G, Torre P, Longo R, et al. Functional MRI in the assessment of cortical activation in subjects with Parkinson's disease. Radiol Med 2006; 111: 104–15.

Ursino M, Baston C. Aberrant learning in Parkinson's disease: a neurocomputational study on bradykinesia. Eur J Neurosci 2018; 47: 1563–82.

Vacherot F, Attarian S, Eusebio A, Azulay J-P. Excitability of the lower-limb area of the motor cortex in Parkinson's disease. Neurophysiol Clin 2010; 40: 201–8.

Vaillancourt DE, Prodoehl J, Verhagen Metman L, Bakay RA, Corcos DM. Effects of deep brain stimulation and medication on bradykinesia and muscle activation in Parkinson's disease. Brain 2004; 127: 491–504.

Valls-Solé J, Pascual-Leone A, Brasil-Neto JP, Cammarota A, McShane L, Hallett M. Abnormal facilitation of the response to transcranial magnetic stimulation in patients with Parkinson's disease. Neurology 1994; 44: 735–41.

Versace V, Langthaler PB, Sebastianelli L, Höller Y, Brigo F, Orioli A, et al. Impaired cholinergic transmission in patients with Parkinson's disease and olfactory dysfunction. J Neurol Sci 2017; 377: 55–61.

Vila M, Périer C, Féger J, Yelnik J, Faucheux B, Ruberg M, et al. Evolution of changes in neuronal activity in the subthalamic nucleus of rats with unilateral lesion of the substantia nigra assessed by metabolic and electrophysiological measurements. Eur J Neurosci 2000; 12: 337–44.

Vitek JL, Zhang J, Hashimoto T, Russo GS, Baker KB. External pallidal stimulation improves parkinsonian motor signs and modulates neuronal activity throughout the basal ganglia thalamic network. Exp Neurol 2012; 233: 581–6.

Vlagsma TT, Koerts J, Tucha O, Dijkstra HT, Duits AA, van Laar T, et al. Mental slowness in patients with Parkinson's disease: Associations with cognitive functions? J Clin Exp Neuropsychol 2016; 38: 844–52.

Watts RL, Mandir AS. The role of motor cortex in the pathophysiology of voluntary movement deficits associated with parkinsonism. Neurol Clin 1992; 10: 451–69.

Wenning GK, Tison F, Seppi K, Sampaio C, Diem A, Yekhlef F, et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord 2004; 19: 1391–402.

Wichmann T, Bergman H, Starr PA, Subramanian T, Watts RL, DeLong MR. Comparison of MPTP-induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia nigra pars reticulata in primates. Exp Brain Res 1999; 125: 397–409.

Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol 1996; 6: 751–8.

Wichmann T, Soares J. Neuronal firing before and after burst discharges in the monkey basal ganglia is predictably patterned in the normal state and altered in parkinsonism. J Neurophysiol 2006; 95: 2120–33.

Wiesendanger M, Schneider P, Villoz JP. Electromyographic analysis of a rapid volitional movement. Am J Phys Med 1969; 48: 17–24.

Williams D, Tijssen M, Van Bruggen G, Bosch A, Insola A, Di Lazzaro V, et al. Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. Brain 2002; 125: 1558–69.

Wilson H, Niccolini F, Pellicano C, Politis M. Cortical thinning across Parkinson's disease stages and clinical correlates. J Neurol Sci 2019; 398: 31–8.

Wilson RS, Kaszniak AW, Klawans HL, Garron DC. High speed memory scanning in parkinsonism. Cortex 1980; 16: 67–72.

Wright WG, Gurfinkel VS, King LA, Nutt JG, Cordo PJ, Horak FB. Axial kinesthesia is impaired in Parkinson's disease: effects of levodopa. Exp Neurol 2010; 225: 202–9.

Wu T, Hallett M. A functional MRI study of automatic movements in patients with Parkinson's disease. Brain 2005; 128: 2250–9.

Wu T, Hallett M. Neural correlates of dual task performance in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2008; 79: 760–6.

Wu T, Hallett M. The cerebellum in Parkinson's disease. Brain 2013; 136: 696–709.

Wu T, Long X, Zang Y, Wang L, Hallett M, Li K, Chan P. Regional homogeneity changes in patients with Parkinson's disease. Hum Brain Mapp 2009; 30: 1502–10.

Wu T, Wang L, Hallett M, Chen Y, Li K, Chan P. Effective connectivity of brain networks during self-initiated movement in Parkinson's disease. Neuroimage 2011; 55: 204–15.

Wu T, Wang L, Hallett M, Li K, Chan P. Neural correlates of bimanual anti-phase and in-phase movements in Parkinson's disease. Brain 2010; 133: 2394–409.

Wu T, Zhang J, Hallett M, Feng T, Hou Y, Chan P. Neural correlates underlying micrographia in Parkinson's disease. Brain 2016; 139: 144–60.

Yttri EA, Dudman JT. Opponent and bidirectional control of movement velocity in the basal ganglia. Nature 2016; 533: 402–6.

Yttri EA, Dudman JT. A proposed circuit computation in basal ganglia: history-dependent gain. Mov Disord 2018; 33: 704–16.

Yu H, Sternad D, Corcos DM, Vaillancourt DE. Role of hyperactive cerebellum and motor cortex in Parkinson's disease. Neuroimage 2007; 35: 222–33.

Zamir O, Gunraj C, Ni Z, Mazzella F, Chen R. Effects of theta burst stimulation on motor cortex excitability in Parkinson's disease. Clin Neurophysiol 2012; 123: 815–21.

Zhang J, Wei L, Hu X, Xie B, Zhang Y, Wu G-R, et al. Akinetic-rigid and tremor-dominant Parkinson's disease patients show different patterns of intrinsic brain activity. Parkinsonism Relat Disord 2015; 21: 23–30.

Ziemann U, Paulus W, Nitsche MA, Pascual-Leone A, Byblow WD, Berardelli A, et al. Consensus: Motor cortex plasticity protocols. Brain Stimul 2008; 1: 164–82.

Zirh TA, Lenz FA, Reich SG, Dougherty PM. Patterns of bursting occurring in thalamic cells during parkinsonian tremor. Neuroscience 1998; 83: 107–21.