UNIVERSITY OF MODENA AND REGGIO EMILIA

PhD Programme of Clinical and Experimental Medicine

Curriculum: Translational Medicine

XXXIV Doctorate Cycle

Director of the PhD Programme: Prof. Giuseppe Biagini

STUDY ON THE ASSOCIATION BETWEEN AXIAL SYMPTOMS, COGNITIVE IMPAIRMENT, CLINICAL-INSTRUMENTAL VARIABLES OF MOTOR FUNCTION AND BRAIN AMYLOID BETA-PEPTIDE DEPOSITION IN PARKINSON'S DISEASE PATIENTS WITH BILATERAL SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION

Supervisor:

Dr. Franco Valzania

PhD Candidate

Francesco Cavallieri

a.a. 2020/2021

This Thesis is Dedicated in Loving Memory of Eng. Marcello Fiorentini

TABLE OF CONTENTS

ABBREVIATIONS

10MWT: 10 Meter Walk Test

ADL: activities of daily living

Aβ: Amyloid-β

CNS: Central Nervous System

CoM: Center of Mass

COMT: catechol-O-methyltransferase

CoP: center of pressure

CSF: cerebrospinal fluid

dB: decibels

FCSRT: Free and Cued Selective Reminding Test

FOG: freezing of gait

GBA: glucocerebrosidase

HIIFRM: Hendrich Fall Risk Model II

ICDs: impulse control disorders

IPG: impulse control generator

iTUG: Instrumented Timed Up and go

LAM: Movement Analysis Laboratory

LEDD: Levodopa Equivalent Daily Dose

LID: Levodopa-induced dyskinesia

LSVT-BIG®: Lee Silverman Voice Therapy – BIG

MCD: minimal detectable change

MCID: minimally clinical important difference

MDS: Movement Disorders Society

MRI: magnetic resonance imaging

MSA: multiple system atrophy

NHR: noise to harmonic ratio

PD: Parkinson's disease

PET: positron emission tomography

PIGD: Postural Instability Gait Disorders phenotype

PSP: progressive supranuclear palsy

RBD: Rapid eye movement sleep behaviour disorder

RLS: Restless Legs Syndrome

RMS: Root Mean Square

SD: standard deviation

Sit2St: Elevation

SN: Substantia Nigra

St2Sit: Sitting

STN-DBS: Subthalamic nucleus deep brain stimulation

TUG test: Timed up and go test

UPDRS: Unified Parkinson's Disease Scale

WMH: white matter hyperintensities of vascular origin

ABSTRACT ENGLISH VERSION

Background

Subthalamic nucleus deep brain stimulation (STN-DBS) represents a long-term effective treatment in advanced Parkinson's disease (PD). STN-DBS allows a stable improvement of motor complications, tremor and rigidity with a less relevant effect on axial symptoms (i.e. gait and balance symptoms, speech and swallowing troubles) and cognitive decline, which are the main causes of long-term disability. Many studies have analysed axial symptoms in PD patients with an instrumental approach focusing only on gait and postural alterations or speech disturbances. The very few studies that have instrumentally assessed the whole spectrum of axial symptoms in PD have showed the presence of similarities between spatial-temporal gait and speech parameters. Anatomopathological data have confirmed that the neurodegeneration of central dopaminergic pathways, considered the hallmark of PD, is accompanied by a contemporary involvement of other neurotransmitter pathways (i.e., cholinergic, serotoninergic). Prevalent involvement of cholinergic system is associated with a clinical "cholinergic" phenotype dominated by axial symptoms, early cognitive deterioration and cerebral Amyloid-β (Aβ) deposition.

Objectives

- To evaluate the effects of STN-DBS and dopaminergic treatment on motor, gait and speech variables through a standardized instrumental approach in the long-term after surgery.
- To evaluate the possible correlation between speech and gait parameters in the different medications and stimulation conditions.
- To evaluate the possible correlation between speech and gait parameters with clinical scales.

Methods

At first, retrospective preoperative clinical and instrumental data from 30 PD patients operated on with bilateral STN-DBS from January 2012 to December 2018 were collected. Furthermore, in the prospective phase of the study, each patient has been reevaluated three to seven years after surgery: axial symptoms have been studied applying a standardized clinical-instrumental approach with the contemporary analysis of speech, gait and postural parameters. Disease severity was assessed using the Unified Parkinson's Disease Scale (UPDRS). Each patient has been studied in different stimulation and drug conditions: preoperative off-medication and on-medication conditions; postoperative on-stimulation/off-medication, off-stimulation/off-medication and on-

stimulation/on-medication conditions (single and dual task). Patients also underwent complete neuropsychological assessment and [18F] flutemetamol positron emission tomography (PET).

Results

25 PD patients, previously treated with bilateral STN-DBS, were recruited from September 2019 to October 2021. Comparing the three postoperative conditions, both stimulation alone and the combination of stimulation and medications led to an improvement of motor score and gait parameters. Both stimulation and levodopa had an heterogenous effect on speech. Ten patients undergone [18F] flutemetamol PET and in four of them brain Aβ deposition was detected. The complete neuropsychological assessment showed a significant worsening of cognitive function compared to preoperative values.

Conclusions

Even if in a preliminary analysis, our data highlights that STN-DBS and levodopa could improve motor scores and gait parameters in the long-term after surgery, with mixed effect on speech parameters. Cognitive function deteriorates in the long-term after surgery. More data are needed to evaluate the possible correlation between brain Aβ deposition and axial and cognitive alterations.

ABSTRACT VERSIONE IN ITALIANO

Introduzione

La stimolazione cerebrale profonda del nucleo subtalamico (STN-DBS) rappresenta un trattamento efficace a lungo termine nella malattia di Parkinson (MP) in fase avanzata. La STN-DBS consente un miglioramento duraturo di complicanze motorie, tremore e rigidità tuttavia con un effetto ridotto sui sintomi assiali (disturbi del cammino, dell'equilibrio, dell'eloquio e della deglutizione) e declino cognitivo, che rappresentano le principali cause di disabilità a lungo termine. Molti studi hanno analizzato i sintomi assiali nella MP con un approccio strumentale focalizzato unicamente su alterazioni del cammino o dell'eloquio. Dati anatomopatologici hanno confermato che la neurodegenerazione delle vie dopaminergiche centrali, considerata il segno distintivo del MP, è accompagnata da un coinvolgimento di altre vie neurotrasmettitoriali (colinergiche, serotoninergiche). Il coinvolgimento prevalente del sistema colinergico si assocerebbe ad un fenotipo clinico "colinergico" dominato da sintomi assiali, alterazioni cognitive e deposizione di amiloide-β (Aβ) cerebrale.

Obiettivi

- Confrontare l'efficacia della STN-DBS e della levodopa sui sintomi assiali in una coorte di pazienti affetti da MP sottoposti a STN-DBS bilaterale.

- Valutare le possibili correlazioni tra i differenti sintomi assiali nelle differenti condizioni farmacologiche e di stimolazione.

- Valutare le possibili correlazioni tra i differenti sintomi assiali e le scale cliniche.

Metodi

Lo studio si compone di una iniziale fase retrospettiva a cui è seguita una fase prospettica. Inizialmente sono stati raccolti retrospettivamente dati preoperatori clinici e strumentali di 30

pazienti con MP sottoposti a STN-DBS bilaterale da gennaio 2012 a dicembre 2018. Ogni paziente è stato rivalutato da tre a sette anni dopo l'intervento: i sintomi assiali sono stati studiati con un approccio clinico-strumentale standardizzato analizzando contemporaneamente i parametri di eloquio, cammino e posturali. La gravità di malattia è stata valutata con la Unified Parkinson's Disease Rating Scale (UPDRS). Ogni paziente è stato studiato in diverse condizioni di stimolazione e farmaco: condizioni preoperatorie off-farmaco e on-farmaco; condizioni postoperatorie on-stimolazione/off-farmaco, off-stimolazione/off-farmaco e on-stimolazione/on-farmaco (single e dual-task). I pazienti sono stati inoltre sottoposti ad una valutazione neuropsicologica e una tomografia a emissione di positroni (PET) con [18F] flutemetamolo.

Risultati

25 pazienti sono stati reclutati da settembre 2019 a ottobre 2021. Confrontando le tre condizioni postoperatorie, sia la sola stimolazione che la combinazione di stimolazione e levodopa hanno portato a un miglioramento dei punteggi motori e del cammino. Sia la stimolazione che la levodopa hanno avuto un effetto eterogeneo sull'eloquio. Dieci pazienti sono stati sottoposti a PET con [18F] flutemetamolo e in quattro di essi è stata rilevata la deposizione di Aβ cerebrale. La valutazione neuropsicologica eseguita a distanza dall'intervento ha mostrato un significativo peggioramento delle differenti funzioni cognitive rispetto al preoperatorio.

Conclusioni

Anche se parte di un'analisi preliminare, i dati raccolti evidenziano come la STN-DBS e la terapia dopaminergica possano migliorare i punteggi motori ed i parametri del cammino a lungo termine dopo l'intervento, con effetti eterogenei sui parametri dell'eloquio. Il peggioramento cognitivo è risultato significativo nel lungo-termine. Sono necessari ulteriori dati per la valutazione della possibile correlazione tra deposizione di Aβ cerebrale e alterazioni assiali e cognitive.

INTRODUCTION

Subthalamic nucleus deep brain stimulation (STN-DBS) represents a short and long-term effective treatment in advanced Parkinson's disease (PD) patients. Several randomized controlled trials have confirmed the superiority of STN-DBS compared to the best medical treatment in complicated PD patients, improving motor disability and global quality of life (Deuschl et al. 2006; Limousin et al. 2019; Rodriguez-Oroz et al. 2012; Weaver et al. 2009). In the long-term STN-DBS allows a stable improvement of motor complications, tremor, and rigidity with a less relevant effect on axial symptoms (i.e., gait and balance symptoms, speech and swallowing troubles) and cognitive decline, which are the main causes of long-term impairment and disability (Limousin et al. 2019). Many studies have analysed axial symptoms in PD patients with an instrumental approach focusing only on gait and postural alterations or speech disturbances. The very few studies that have instrumentally assessed the whole spectrum of axial symptoms in PD have showed the presence of some similarities between spatial-temporal gait and speech parameters (Ricciardi et al. 2016; Cantinaux et al., 2010). Anatomopathological data have confirmed that the neurodegeneration of central dopaminergic pathways, considered the hallmark of PD, is accompanied by a contemporary involvement of other neurotransmitter pathways (i.e., cholinergic, serotoninergic) (Titova et al., 2017). Prevalent involvement of cholinergic system (pedunculopontine nucleus and nucleus basalis of Meynert) is associated with a clinical “cholinergic” phenotype dominated by axial symptoms, early cognitive deterioration and cerebral Amyloid-β (Aβ) deposition (Titova et al., 2017; Titova et al. 2017). However, so far there are no studies that have analysed the correlation between axial symptoms, Aβ deposition and cognitive alterations in PD patients who have undergone STN-DBS.

Epidemiology of Parkinson's Disease (PD)

PD is the second most common neurodegenerative disorder after Alzheimer's disease and is the most common type of parkinsonism, a group of progressive neurological disorders which includes progressive supranuclear palsy (PSP), multiple system atrophy (MSA), vascular and drug-induced parkinsonism (Armstrong et al., 2020). The incidence of PD varies from 5/100,000 to over 35/100,000 new cases per year (Twelves et al., 2003; Poewe et. Al, 2017) and increases from 5 to 10 times between the sixth and ninth decade of life (Simon et. al, 2020). Excluding genetic forms of PD, which begin earlier, the average onset of the disease is comprised between the ages of 50 and 60 (Calabrese et al., 2007; Wirdefeldt et al., 2011; Armstrong et al., 2020). In addition, PD is more common in men with a male-female ratio of 1.4: 1.0 (Calabrese et al., 2007; Wirdefeldt et al., 2011; Armstrong et al., 2020). The prevalence in general population also increases with age: indeed, a recent meta-analysis highlights an increase in prevalence ranging from less than 1% in men and women aged 45-54 to 4% in men and 2% in women aged 85 or older (Marras et al., 2018; Simon et al., 2020). As the world population ages, the prevalence of PD is expected to double over the next two decades (Dorsey et al., 2018). Mortality does not increase in the first decade of disease diagnosis compared to unaffected individuals, but increases thereafter (Pinter et al., 2015).

Clinical manifestations of PD

Tremor

Tremor represents the most socially disabling motor symptom of the disease and has specific characteristics that allow to distinguish it from different types of tremors associated with other neurological disorders. First, parkinsonian tremor is observed at rest, as opposed to essential tremor, mainly present during the maintenance of a posture, and from intentional tremor of

cerebellar origin. PD rest tremor has a frequency of 4-7 Hz and is prevalent in the hands ("pill-rolling" tremor), lower limbs, feet, jaw and tongue. Although the frequency of 4-7 Hz is characteristic, cases with a higher frequency have been reported (Bhatia, et al., 2018). In addition, other forms of tremor (postural or kinetic) can also coexist in patients with PD with the same frequency as the typical tremor at rest (Bhatia, et al., 2018). In the recent classification of tremors proposed by Bhatia et al., parkinsonian tremor has been classified in the "Tremor Syndromes with Prominent Additional Signs" category (Bhatia, et al., 2018).

Bradykinesia

The term bradykinesia refers to the slowdown in the execution of voluntary movements accompanied by a reduction in amplitude and/or the presence of hesitations and interruptions (Postuma, et al., 2015). Although bradykinesia may also involve the voice, face, or gait; limb bradykinesia must be documented to establish a diagnosis of PD (Postuma, et al., 2015). This definition of bradykinesia, stated within the new diagnostic criteria of PD formulated by the Task force of the Movement Disorders Society (MDS), differs from the previous definition of bradykinesia, considered solely as a slowing of movement. In fact, the new definition also includes the reduction of amplitude and the presence of hesitations and interruptions (formerly included in the definition of akinesia) (Postuma, et al., 2015). Bradykinesia can be clinically highlighted through the execution of repeated motor gestures such as finger tapping or the alternating opening and closing of the hands. Due to bradykinesia, the patients may be unable to express their emotions through facial expressions leading to the characteristic "facial hypomimia" one of the typical PD manifestations (Poewe et. al, 2017). The writing is uncertain, slow and the words are very small in size (micrography) (Poewe et. al, 2017). Bradykinesia is also indirectly responsible for the onset of sialorrhea caused by a reduction of swallowing acts (Chou et al., 2007).

Rigidity

Rigidity is the third cardinal symptom of PD. The increase in muscle tone leads to a slowdown and hindrance in the execution of the movements of the major joints. Rigidity does not vary even when the speed of passive mobilization of the examined joint varies, configuring the classic plastic-type rigidity (Postuma, et al., 2015). Through the Froment maneuver, rigidity can be elicited, and during passive mobilization it can take on the appearance of a cogwheel, especially in the wrist. This is due to the alternated contraction of pairs of agonist and antagonist muscles in the limb examined (Powell et al. 2011).

Axial symptoms

Axial symptoms include dysarthria, dysphagia, gait disorders, and postural instability, and represent one of the main causes of long-term impairment and disability in PD patients (Cavallieri et al. 2021). Axial symptoms are considered resulting from non-dopaminergic (i.e., cholinergic) lesions affecting brain areas resulting resistant to dopaminergic treatment (Brabenec et al. 2017). The different axial symptoms will be discussed in detail in the next paragraphs.

Motor Phenotypes

The intensity of the different cardinal (i.e., tremor, rigidity, bradykinesia) and axial symptoms may vary in each patient leading to the identification of three main motor phenotypes (Marras et al., 2015):

- Postural Instability Gait Disorders phenotype (PIGD)
- Tremor-dominant phenotype
- Indeterminate phenotype

The progression and prognosis of PD vary between these different motor phenotypes. Indeed, the PIGD phenotype is characterized by a faster progression, greater disability over time and more cognitive alterations than the tremor and indeterminate phenotypes (Marras et al. 2015; Kalia & Lang, 2015).

Non-motor symptoms

In addition to motor features, PD patients may present a number of non-motor manifestations, including neuropsychiatric symptoms (i.e., depression and apathy), cognitive dysfunction (discussed in detail in the next paragraph), sweating and sexual disorders, sleep disturbances and autonomic disorders (urinary incontinence and constipation) (Chaudhuri & Schapira, 2009). Non-motor symptoms may appear many years before motor manifestations representing the first prodromic symptom of the disease (Poewe et al., 2017; Muzerengi et al., 2006). Moreover, in the advanced stages, they represent one of the main causes of disability and reduced quality of life (Poewe et al., 2017; Muzerengi et al., 2006). Unfortunately, dopaminergic therapy has little effect on non-motor symptoms often causing their worsening (Schaeffer & Berg, 2017).

The prevalence of orthostatic hypotension in PD patients varies from 9.6% to 58% and correlates with disease duration (Low, 2008). Orthostatic hypotension can increase postural instability and risk of falls and negatively impacts on cognitive performance (Fereshtehnejad & Lökk, 2014). In addition, dopaminergic drugs can contribute to the development, or worsening, of orthostatic hypotension (Fereshtehnejad & Lökk, 2014).

Sexual disturbances are very common in PD (68% in males, 36% in females) (Bronner et al., 2015). In male patients, erectile dysfunction, difficulty in reaching orgasm and premature ejaculation are the most typical manifestations. Meanwhile, in female patients decreased sexual desire and difficulty in reaching orgasm represent the main manifestations (Bronner et al., 2015). Age, female

sex, low education, high scores on the "Beck Depression Inventory scale" and history of depression are associated with a decrease in sexual desire (Bronner et al., 2015; Kummer et al., 2009).

Hyperhidrosis is a frequent non-motor symptom in PD and occurs primarily in the off-phases or during on-phases associated with severe dyskinesias (Swinn, Schrag, Viswanathan, Bloem, Lees, & Quinn, 2003). Hyperhidrosis does not correlate with the severity of the disease but with the presence of other dysautonomic disorders (Swinn et al., 2003).

Constipation is the main gastrointestinal symptom in PD, being reported in 80-90% of patients (Fasano et al., 2015). Furthermore, constipation represents one of the so-called “pre-motor symptoms” of the disease, often appearing many years before the onset of motor features (Fasano et al., 2015). Indeed, constipation represents one of the earliest autonomic dysfunctions in PD, developing approximately 15 years before motor symptoms (Postuma et al., 2013). Constipation has a multifactorial origin and can be negatively influenced by dopaminergic drugs (Jost, 2010).

Sleep disorders are very common in parkinsonian patients (prevalence: 60-70%) and have a negative impact on quality of life (Oerlemans et al., 2002; Scaravilli et al., 2003). Most patients have a variable pattern of nocturnal insomnia associated with daytime sleepiness and occasionally sleep attacks (Schrempf et al., 2014). Daytime sleepiness is greater in the advanced stages of the disease and could be related to the intake of high doses of dopaminergic drugs (Kumar et al., 2002). Restless Legs Syndrome (RLS) is characterized by a need or urgency to move the lower limbs to stop unpleasant sensations or paraesthesia in the same region typically occurring in the evening or during the night (Wijemanne & Jankovic, 2015). The diagnosis of RLS is based on the "Restless Legs Syndrome Study Group" diagnostic criteria revised in 2012 (Allen, et al., 2014). RLS presents a good response to dopamine agonists (pramipexole, ropinirole, rotigotine) treatment at least in the short term. However, only 50% of patients have a sustained response to dopamine agonist treatment in the long-term (Scholz et al., 2011).

Rapid eye movement sleep behaviour disorder (RBD) is characterized by a loss of muscle atony during the REM phase that leads the patients to "act" their dreams (Schrempf et al., 2014). They can speak, scream, and reproduce dream-related movements. However, these movements are potentially harmful for both the patient and his/her partner. About 30-50% of PD patients suffer from RBD (Schrempf et al., 2014). RBD could also be one of the first manifestations of alpha-synucleopathies (multisystem atrophy, PD, Lewy Body dementia) before the onset of motor symptoms (premotor phase) (Schrempf et al., 2014). Longitudinal studies have shown that 38% of subjects with RBD develop a neurodegenerative disease within 4 years, while after 20 years of follow-up the percentage rises to 81% (Schenck et al., 2013). RBD is therefore a good clinical predictor of the development of a neurodegenerative disease with a high sensibility (conversion rate of 80%) but low specificity (only 30-50 % of parkinsonian patients are affected by RBD) (Schenck et al., 2013). Meanwhile, other pre-motor symptoms such as hyposmia or constipation have a lower specificity (Schrempf et al., 2014). Clonazepam is considered the first-choice drug in the treatment of RBD with response rates of 80-90%. Melatonin, pramipexole and levodopa can be also used as a second line treatment in case of clonazepam failure (Boeve et al., 2003; Fantini et al., 2003).

Different behavioural and psychiatric disorders (depression, anxiety, apathy, anhedonia) may be related to PD. Dopaminergic drugs may cause or exacerbate these symptoms including delusions, hallucinations, paranoid phenomena, psychosis, compulsive behaviours, and impulse control disorders (ICDs), a condition characterized by an irresistible and uncontrollable urge or temptation to perform an action although it may be harmful to oneself or to others (Weiss & Marsh, 2012). Compulsive behaviours such as punding (stereotypical behaviours, characterized by unproductively handling, rearranging, and cataloguing objects) and hobbyism, represent further behavioural disorders related to dopamine replacement therapy (Weiss & Marsh, 2012). About 13% of PD patients develop one or more ICDs during the disease (Weintraub, et al., 2010). However, patients

on dopaminergic therapy (particularly if treated with dopamine agonists) can develop an addictive attitude towards the therapy by self-managing its intake and taking doses that are incongruous and excessive compared to the dose required to control the symptoms of the disease. This condition has been defined as "dopaminergic dysregulation syndrome" (DDS) and is characterized by the patient's need to increase dopaminergic therapy even in the presence of significant dyskinesias and absence of fluctuations (Weintraub et al., 2015; Giovannoni et al., 2000). The presence of depressive or anxious symptoms is very common in PD patients with a higher prevalence than in healthy population. However, data regarding the prevalence of depressive symptoms in PD are heterogeneous with a prevalence ranging from 7 to 70% (Yamamoto, 2001). Depression and anxiety are associated with a faster cognitive and motor decline as well as reduction in quality of life (Jacob et al., 2010). Furthermore, the presence of depressive and anxious symptoms may represent the first pre-motor manifestation of the disease (Jacob et al., 2010).

Cognitive alterations in PD

The presence of cognitive disorders and dementia is reported in 75–90% of PD patients from 15 to 20 years after the diagnosis (Aarsland & Kurz, 2010; Biundo et al., 2016; Aarsland et al., 2003; Buter et al., 2008). Compared to healthy subjects, PD patients have a six times higher risk than age-matched healthy controls to develop dementia (Jankovic, 2008). The clinical phenotype of dementia associated with PD extends from the characteristic dysexecutive syndrome of the early stage of the disease to more complex phenotypes associated with the presence of multiple deficits in memory, attentional processes, and visual perception as well as the presence of visual hallucinations and cognitive fluctuations (Gratwicke et al., 2015). The following factors are related to the development of dementia in PD patients: age, disease duration, PIGD phenotype, presence of RBD (Aarsland et al., 2010). Indeed, the presence of RBD is associated with PIGD phenotype and cognitive alterations

(i.e., attentional performance, executive functions, visual-constructive abilities, verbal episodic memory) (Postuma, et al., 2012; Vendette, et al., 2007).

Gait and balance alterations in PD

Gait alterations

Walking is a unique and complex motor behavior controlled by multiple cortico-subcortical and brainstem areas (Navratilova et al., 2020). Physiological gait requires a proper interaction between different neuronal circuits and consists of three main components: locomotion, including the initiation and maintenance of the rhythm of the step, balance, and the ability to adapt to the environment (Snijders et al., 2007). The success of locomotion depends on the integration of sensory inputs to ensure an appropriate postural orientation of the body segments with respect to each other and with respect to the surrounding environment (Earhart et al., 2013). Gait disturbances are one of the main manifestations of PD and are characterized by slowness, difficulty in starting the movement, camptocormia, axial rigidity, reduction or asymmetry of arm swing, gait festination, and freezing of gait (FOG) (Cambier, Masson, 2013; Mirelman et al., 2019). As disease progresses, patients may develop camptocormia (from the Greek kamptos: bend and kormos: trunk) characterized by an anteflexion of the trunk and head associated with a flexion of the hips and knees with adducted upper limbs, anteposition of the shoulders and internal rotation of the forearms (Doherty, et al., 2011; Moreau et al., 2010). Gait is characterized by reduction of speed, stride length and oscillation phase (Kemoun & Defebvre, 2001). On the contrary, the cadence of the steps may increase as a compensatory mechanism for the aforementioned alterations (Kemoun & Defebvre, 2001). The decrease in stride length is considered a manifestation of parkinsonian hypokinesia (Kemoun & Defebvre, 2001). As happens in other sequential and repetitive motor tasks, PD patients do not show changes in joint kinematics but only in amplitude and speed of movement (Keus et al.,

2006). Mirelman et al. (Mirelman et al., 2019) have identified and divided the characteristic gait alterations in PD according to the stage of the disease:

- Initial phase: patients' walking slows down, and the stride length is reduced, as also happens in healthy subjects with advancing age. However, more specific changes may occur, including a reduced amplitude of the pendular movements of the upper limbs and increased asymmetry. These alterations are exacerbated by the dual task condition.
- Mild to moderate phase: noticeable increase in the cadence of the step and reduction in axial rotations. The motor automatisms become more and more fragmented and problems in initiating the movement increase. FOG and festination also become more apparent, and patients face an increased risk of falling.
- Advanced phase: motor blocks during walking become frequent, in association with motor fluctuations and dyskinesias (late motor complications linked to the therapeutic response to levodopa).

Gait festination is characterized by a progressive acceleration of the walk with shortening of the stride length and represents a typical PD motor manifestation. During gait festination, the patient seems to be constantly chasing the center of gravity of his own body (Moreau et al., 2010).

FOG is characterized by the inability either to start walking or to continue walking in certain situations. In particular, the patient is unable to take his feet off the ground and start walking. In 2010, the Washington DC workshop defined FOG as "a brief and episodic absence or marked reduction in the forward progression of the foot despite the intention to walk" (Nutt et al., 2011).

Three different clinical phenotypes of FOG have been distinguished:

- Tremor in place with rapid and alternating movements of the knees (knee trembling)
- Shuffling forward with very short, grounded steps

- Complete akinesia with no movement

Different conditions may favor the appearance of FOG: the turning phase during the walking, the beginning of walking, the overcoming of obstacles or the crossing of narrow paths (Yasuyuki, 2014). Turning is the phase of walking in which the subject changes direction of movement with a greater involvement of some anatomical structures: the lower limbs, the trunk, the head, and the vestibular system. Turning is more compromised especially in the advanced phase of the disease and is characterized by an increase in the duration of the turn, a greater number of steps to make the change of direction and difficulties in changing the motor pattern from straight walking to the action of turning around (Earhart 2013). FOG led to a marked increase in the risk of falling and a worsening of the overall postural stability. Moreover, FOG represents an independent factor of worsening of quality of life in PD patients (Boonstra et al., 2008). Although always considered part of the advanced stages of the disease, FOG can also occur in the early stages of PD. Approximately 16% of patients present episodes of freezing even before the start of dopaminergic therapy (Lamberti, et al., 1997). The prevalence of FOG in the advanced stage is approximately 50% (Giladi, et al., 2001). The FOG appears more frequently in the "off" pharmacological state and less frequently during the "on" phase. Furthermore, in patients with strongly asymmetrical disease, unilateral FOG has been reported (Bloem et al., 2004). The execution of other activities during walking (dual task condition) carries a greater risk of developing FOG or falling (Bloem et al., 2004). The severity of the disease correlates, at least initially, with the severity of FOG and there is a strong association between the FOG and the presence of alterations in balance and speech (Giladi et al., 2001; Bloem et al., 2004) Unlike cardinal symptoms, postural instability, FOG, and gait festination poorly respond to dopaminergic therapy, thus representing an important cause of disability in PD patients (Moreau et al, 2010). Many prospective cohort studies have assessed the occurrence of falls in PD showing an incidence up to 70% during the first year of follow-up (Wood et al., 2002). In addition,

compared to healthy subjects, parkinsonian patients had a 9.0 higher relative risk of falls in a 6-month follow-up (Bloem et al., 2001). In the early stages of PD, postural control is normally preserved, and falls are rare, distinguish it from atypical parkinsonism in which falls occur earlier (Wenning, et al., 1999). The risk of falling correlates with the severity of the disease calculated with the Unified Parkinson's Disease Rating Scale (UPDRS) part III score, with a probability of falling of 60% for UPDRS values between 25 and 35 (Wenning, et al., 1999). With higher UPDRS values, the risk remains stable and indeed tends to progressively decrease, indicating that the curve of the relationship between fall risk and disease severity had a U-shaped trend (Pickering, et al., 2007). The presence of one or more falls in the previous year represents the best predictor of falling risk with 68% sensitivity and 81% specificity. On the contrary, the duration of the disease does not represent a good predictor of falling risk (Pickering, et al., 2007).

Balance alterations

Balance can be classified into (O'Sullivan et al., 2013):

- Static balance: the ability to maintain stability and postural orientation with the Center of Mass (CoM) above the support base and the body stationary.
- Dynamic balance: the ability to transfer the vertical projection of the center of gravity around the support base, thus, maintaining stability and postural orientation while the body is in motion.

Maintaining postural stability in both static and dynamic conditions require a balance between stabilizing and destabilizing forces and sensory information that derives mainly from the visual, vestibular, and proprioceptive systems (Earhart et al., 2013). Schoneburg and colleagues (Schoneburg et al., 2013) have described balance alterations in PD proposing a framework for

understanding it. They assumed that balance disorders in PD may result from the alteration of four different domains (Schoneburg et al., 2013):

- Balance at rest altered by: postural misalignment (probably due to greater rigidity of the flexor muscles); an increase in the speed and frequency of the body's oscillations (especially in the mid-lateral direction); a reduced perception of stability limits within which is possible to move the CoM without falling or having to take a step.
- Automatic postural reactions to external perturbations: altered by postural strategies and adaptations with high latency times due to bradykinesia. In healthy subjects, the recovery of balance is guaranteed by different combinations of arm, hip and ankle movements. PD patients have difficulties in switching from one recovery strategy to another and are unable to adequately adapt the size of their postural responses to the size of the perturbations.
- Anticipatory postural adjustments: in PD patients these kinds of postural adjustments have a reduced amplitude especially in the lower limbs, causing difficulties and prolonged times in starting the walk.
- Dynamic balance during movement: characterized by a reduced walking speed and a high variability in the length and duration of the step between one stride and the next.

Overall, postural instability in PD can lead to changes in both anticipatory postural adjustments (feedforward control mechanisms) and automatic postural reactions (feedback control mechanisms) (Smania et al. 2010). In addition, it has been reported that parkinsonian patients have difficulties in detecting or determining the positions of the limbs due to an altered elaboration of proprioceptive sensory inputs. Therefore, the perception of the position of the body in space is impaired, at least partially explaining the difficulty in reaching the upright and stable position (Vaugoyeau et al., 2020).

Clinical and instrumental assessment of gait and balance in PD

The objective assessment of walking and balance and the quantification of parameters related to kinematics, dynamics, and musculoskeletal function, play a fundamental role in diagnosis and rehabilitation (Bouça-Machado et al., 2020). Numerous tests and rating scales allow to measure balance and gait in PD patients. However, there is no clarity on which screening tools are preferable depending on the patient's condition and which outcome measures are preferable to monitor patient changes over time (Bloem et al., 2016). Scientific evidence on the efficacy of rehabilitation treatment in PD is still limited due to the difficulty of objective clinical assessments (Keus et al., 2006). PD symptoms changes considerably depending on the stage of the disease, making it difficult to generalize along the course of the disease or to identify subgroups of patients who could benefit from a particular rehabilitation approach (Mirelman et al., 2019).

Outcome measures for gait alterations in PD

The most reported outcome measures for PD gait alterations are walking speed and the Timed up and go test (TUG test) (Brognara et al., 2019; Tomlinson et al., 2014). Walking speed is usually measured through the 10 Meter Walk Test (10MWT) (Tomlinson et al., 2014), a short test that has good clinimetric properties in PD patients. Furthermore, walking speed accurately predicts the risk of falling in PD patients (Bloem et al., 2016). The TUG is a very simple and widely used exam in both elderly and parkinsonian patients, allowing to evaluate different parameters: static-dynamic balance, functional mobility, and risk of falls (Palmerini et al., 2013). The most used tests for the assessment of balance in PD are the Berg Balance Scale (BBS), TUG, Tinetti test, tandem walking, and balance test on one leg (Kamieniarz et al., 2018). Other validated clinical scales for PD lack of threshold or cut-off values able to define the limit between positive and negative test results and to identify patients at higher risk with respect to the parameter or domain analyzed (Mirelman et

al., 2019). With respect to the choice of clinical scales to use, psychometric properties play an important role. According to the work of Bloem et al. (Bloem et al., 2016) no clinical test fully evaluates the specific characteristics of the Parkinsonian walk with good clinometric properties, and none provides scores with adequate content validity regarding balance and walking. The minimal clinical important difference (MCID) is an essential information to understand which changes can be considered clinically significant and, consequently, to describe the longitudinal characteristic variations of a patient over time (Steffen et al., 2008).

Instrumental measurements

The use of instrumental systems allows to obtain direct performance measures both in quantitative and qualitative terms (Brognara et al., 2019). The balance analysis performed through posturography is considered a useful technique for the early recognition and evaluation of balance dysfunctions in PD. The use of force platforms allows to obtain more objective and sensitive measures of postural instability (Kamieniarz et al., 2018). Posturography in static conditions records the displacements of the center of pressure (CoP) of the feet in an upright position, both with eyes closed and open or even with the use of unstable surfaces. It allows to appreciate the time response of the subjects to sudden perturbations or to highlight anticipated control mechanisms in case of voluntary changes of posture. In dynamic conditions it allows to describe the morphological and mechanical characteristics of the foot, to identify gait alterations in all phases of the gait cycle (Rocco et al., 2011). In recent years, instrumental evaluation with inertial sensors has allowed to obtain more ecological and efficient performances, with a reduced margin of error (Bouça-Machado et al., 2020). These systems provide a series of space-time parameters useful for investigating the progression of gait deficits in PD, even without the need for specialized laboratories (Brognara et al., 2019). Accelerometers represent the most frequent type of sensors used, usually positioned in

the back, between the second and fifth lumbar vertebrae. Although this area is not considered the most comfortable and discreet, to date it has been shown that a single sensor in this position is able to accurately detect physical activity and walking parameters in a laboratory and daily life context (Bouça-Machado et al., 2020). The quantification of these parameters may allow to support the clinical evaluation to make a personalized therapeutic exercise program (Bloem et al., 2016).

iTUG

The TUG is widely used as a clinical measure of balance and mobility in the elderly and PD patients (Zampieri et al., 2010). However, it has some limitations: it focuses only on the time covered ignoring any other movement deficits and measures the total time to carry out a sequence of complex actions without separating the different performances (Salarian A et al., 2010). The traditional TUG is not appropriate for assessing the distinctive gait alterations of the disease, especially in the initial phase when the locomotor function is not yet very compromised (Palmerini et al., 2013; Zampieri et al., 2010). For this reason, an instrumental version of the test has been proposed (Instrumented Timed Up and go, iTUG) through the application of inertial sensors (Palmerini et al., 2013) (Figure 1). If with the first sensor models only the duration of each phase was measured, the current sensors seem to have overcome this problem, allowing to obtain qualitative and quantitative information on the execution modalities of the different functions (Salarian A et al., 2010).

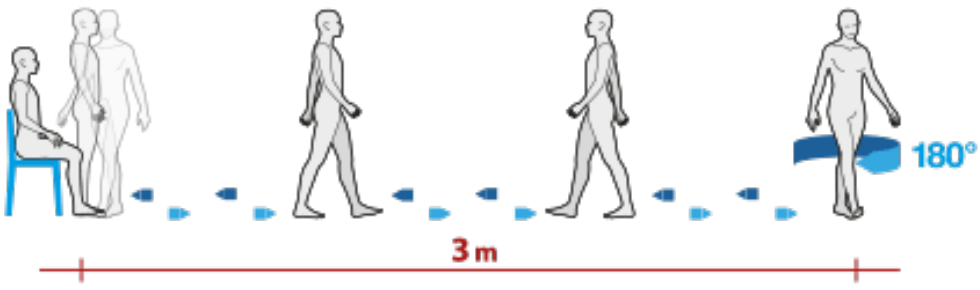


Fig. 1 Instrumented Timed up and go test

The iTUG is divided into four main components: sit-to-stand, stead-state gait, turning and turn-to-sit (Salarian et al., 2010). It allows the analysis of turning which, unlike the linear path, puts postural stability to the test more, as it requires a complex sequence of reorienting the body towards a new direction with reduced stability margins (Curtze et al., 2016). Circular walking and functional mobility more generally, are related to the increase in postural tone, particularly in the neck. The difficulty of turning in PD can also be related to the inherently asymmetrical nature of rotation, which requires different stride lengths and leg speeds (Earhart et al., 2013).

Speech disorders in PD

About 90% of people with PD develop speech impairment during the course of the disease (Ho et al., 1998), causing a reduction in quality of life and social isolation. Dysarthric speech may appear at any stage of PD even in the first years after the diagnosis (Klawans, 1986). James Parkinson firstly described in his essay "An Essay on Shaking Palsy" (Parkinson, 1817) characteristics speech alterations of PD patients and how it became poorly intelligible over time. 150 years later Darley, Aronson and Brown firstly defined the term “dysarthria” in 1969, describing it as:

"... a collective name to indicate a group of speech disorders, due to disorders of muscle control of oral verbal expression, resulting from damage to the central or peripheral nervous system ..." (Darley et al., 1969).

PD is associated with hypokinetic dysarthria, one of the subtypes of dysarthria (Tjaden, 2008). Hypokinetic dysarthria is defined as “a perceptually identifiable motor language disorder that results from a pathological involvement of basal ganglia circuits”. It can be evident in all the levels of speech - breathing, phonation, resonance, articulation, but it particularly concerns the voice, articulation, and prosody. These abnormalities are the consequence of stiffness of the speech

muscles, insufficient strength, and amplitude of excursion as well as the abnormal speed (slowness or rapidity) of the movements. " (Freed, 2015)

A recent systematic review published in 2017 reports the main clinical-instrumental characteristics of hypokinetic dysarthria (Brabenec et al., 2017):

- Increased acoustic noise
- Reduced intensity of voice
- Harsh and breathy voice quality
- Increased voice nasality
- Monoloudness and monopitch (monotony and monotonous tonal pitch)
- Speech rate disturbances (perturbations in the speed of speech)
- Imprecise consonants articulation (imprecise articulation of consonants)
- Involuntary introduction of pauses
- Sudden acceleration or deceleration in speech (sudden acceleration or deceleration)

The alterations of prosody, very common in hypokinetic dysarthria, leads to monotony, acoustically characterized by the presence of reductions in the variations of the fundamental frequency and intensity during spontaneous speech (Freed, 2015). Speech rhythm alterations are also frequent, including sudden accelerations of speed (tachyphemia), linear increase in speed (more rarely) and inappropriate pauses. The increase in speech rate can contribute to the worsening of speech intelligibility due to the lower precision in the articulation of phonemes. It is assumed that tachyphemia represents the oral correlation of gait festination, being precisely defined as "oral festination" (Moreau et al., 2007). Two types of dysfluencies have also been found in patients with PD: repetition of phonemes and palilalia which is the increasingly rapid repetition of a word or a phrase. Some studies in the literature have shown that the repetition of phones and palilalia can be

related to walking disorders, assuming that disfluencies represent the vocal equivalent of FOG being defined as "freezing of speech" (Benke et al., 2000). In 2016, Ricciardi and colleagues conducted a study with the aim to verify the relationship between speech disorder and FOG in PD (Ricciardi et al., 2016). Speech was evaluated solely through a perceptual approach and compared with motor data derived from the UPDRS scale. The results showed that patients with FOG had major changes in articulation, intelligibility, and prosodic aspects (rhythm, speed and adequate maintenance of the speed of speech) (Ricciardi et al., 2016). In conclusion, the study confirmed that the rhythmic components of speech were significantly more impaired in patients with FOG than in patients without FOG (Ricciardi et al., 2016). The abovementioned findings confirmed the presence of a relationship between walking alterations and speech disorders in PD. Speech alterations in PD substantially reflect the changes in basal ganglia circuits caused by the loss of dopaminergic cells in the Central Nervous System (CNS). It is well known that the loss of dopaminergic input at striatal level and the consequent dysregulation of the basal ganglia lead to the cardinal motor symptoms of PD such as tremor at rest, muscle rigidity, bradykinesia and postural alterations (Harel et al., 2004). These alterations negatively affect the three main systems underlying language production, namely the respiratory, phonatory and articulatory systems (Harel et al., 2004). However, the poor response to dopaminergic therapy and STN-DBS led to the hypothesis that other neural pathways insensitive to dopaminergic therapy (i.e., cholinergic and serotonergic) are also involved in speech production, as well as in the other axial symptoms (Brabenec et al., 2017). Dopaminergic therapy has been shown to have beneficial effects on the main motor manifestations of PD, however its effect on different speech parameters and overall speech intelligibility remains debated. Some studies have reported a positive effect of Levodopa on language strength and duration of sustained phonation with a contemporary improvement in speech intelligibility evaluated through perceptual analysis (De Letter et al., 2003; De Letter et al., 2005; De Letter et al., 2007). However, most of the studies

found no relevant effect of dopaminergic therapy on speech frequency (De Letter et al., 2006), speech prosody (Gamboa et al., 1997; Goberman et al., 2002) and on overall intelligibility (Baker et al., 1997; Kompoliti et al., 2000; Skodda et al. 2010). Instrumental speech analysis data have shown that dopaminergic therapy can slightly improve the articulation of the vowels, increase the loudness and the speech rate (with variable effects as regards the final quality of the speech), the global voice quality and the articulation of consonants (Benke et al., 2000; Goberman et al., 2003; Rusz et al., 2013; Cavallieri et al. 2021). Two recent systematic reviews with meta-analysis found that levodopa therapy only changed fundamental frequency, jitter, and shimmer (indicative of voice quality) with little or no effect on the vocal intensity in PD patients (Pinho et al., 2018; Lechien et al., 2018). However, other acoustic instrumental studies have found no improvement in dopaminergic therapy at phonatory level, intonation, articulation, and speech rate (Cavallieri et al., 2021). Furthermore, it has been reported that chronic levodopa treatment is associated with more disfluent speech after 3-6 years of treatment (Tykalová et al., 2015). This inconsistency in results may depend at least in part on the different pathophysiological mechanisms underlying speech disorders in PD. Finally, it has recently emerged that axial dyskinesias can negatively affect the quality of speech after taking levodopa (Cavallieri et al., 2021). This could explain why the 10-20% of PD patients may develop a mixed dysarthria with hyperkinetic components (Tjaden, 2008).

Cholinergic phenotype in PD

In recent years, the study of non-motor symptoms associated with PD has been increasingly growing. This was also supported by numerous clinical and anatomopathological data which highlighted that the neurodegeneration of nigro-striatal dopaminergic pathways is accompanied by a contemporary involvement of multiple central and peripheral non-dopaminergic circuits. (Sauerbier et al., 2016). According to recent studies, the neuropathological processes spread

through the peripheral and central nervous system, through different propagation pathways, according to a multistage profile that follows a caudo-cranial progression (Braak et al., 2003; Marras & Chaudhuri, 2016).

It is also assumed that the different cardinal motor signs of the disease may underlie alterations of different neurotransmitter circuits. Dopaminergic deficiency would correlate with bradykinesia and rigidity, serotonin deficiency with tremor, while alterations of cholinergic circuits would correlate with axial symptoms (Thenganatt & Jankovic, 2014). The dysfunction of the cholinergic circuits due to the diffusion of the neurodegenerative process at the level of the peduncolo-pontine nucleus, thalamus, basal nucleus of Meynert and associated cortical cholinergic projections, would therefore represent one of the main neuropathological substrates of axial disorders in PD (Bohnen et al., 2013; Lim et al., 2019). Further studies have confirmed the link between motor and non-motor symptoms: in fact, while the tremor phenotype presents a relative sparing of the non-motor component, the PIGD phenotype is associated with greater cognitive and humoral alterations (Titova et al., 2017).

Cluster analysis studies in de-novo PD patients not yet on dopaminergic replacement therapy allowed to identify four different phenotypic clusters: benign motor, benign mixed motor and non-motor, non-motor dominant and motor dominant. In the mixed benign phenotype, the most affected non-motor domain was represented by sexual dysfunctions, while in the dominant non-motor group urinary symptoms prevailed (Erro et al., 2013). The different motor and non-motor phenotypes could therefore influence the natural history of the disease, the response to drug therapy and the clinical outcomes related to STN-DBS intervention (Katz et al., 2015).

Recently, a classification of non-motor phenotypes of PD has been proposed by Sauerbier et al. who identified, among patients with dominant non-motor symptoms, six different non-motor phenotypes (Sauerbier et al., 2016). These phenotypes would be the clinical expression of the variable neuropathological involvement of different specific transmission circuits (cholinergic,

serotonergic, adrenergic) (Sauerbier et al., 2016). According to the authors, the cholinergic phenotype would be associated with a PIGD motor phenotype associated with FOG in the ON medication condition and cognitive impairment (Titova et al., 2017). This hypothesis was also confirmed by Muller et al. which found a correlation between the presence of cortical cholinergic denervation evaluated by PET with tracer for acetylcholinesterase ([(11) C] PMP) and the presence of RBD, falls, walking disorders and cognitive dysfunctions (Müller et al., 2015).

Furthermore, comparing PD-fallers vs PD non-fallers, emerged that the acetylcholinesterase levels (indirect markers of cholinergic denervation) at pedunculopontine nucleus and basal nucleus of Meynert (the two main cerebral cholinergic centers) were significantly lower in the fallers subgroup regardless of the degree of dopaminergic denervation (Perez-Lloret et al., 2016).

Bohnen et al. analyzed the correlation between cortical cholinergic denervation, beta-amyloid deposition, and FOG (Bohnen et al., 2014). The results of the study conducted on 143 patients showed a direct correlation between the presence of FOG, the degree of cholinergic denervation and the deposition of beta-amyloid at cortical level (Bohnen et al., 2014). The frequency of FOG was also higher in subjects who had both cholinopathy and amyloidopathy at neo-cortical level. 90% of patients with FOG also had at least one of the two pathological conditions (Bohnen et al., 2014). Different cross-sectional studies confirmed the correlation between beta-amyloid deposition and the PIGD motor phenotype (Alves et al., 2013; Bohnen et al., 2014; Kang et al., 2014). Alves et al. found significantly lower cerebrospinal fluid (CSF) levels of Aβ42, Aβ38, Aβ42/40 and Aβ38/40 in patients with the PIGD phenotype compared to the tremor dominant phenotype. Multivariate regression analyzes documented a significant association between CSF beta-amyloid levels, severity of the PIGD motor phenotype, and lower limb bradykinesia (Alves et al., 2013). A subsequent prospective study has confirmed that low CSF levels of Aβ42 in the early stages of the disease are predictive of the development of dopa-resistant gait disturbances (variability of gait duration,

variability of gait length) with a three-years follow-up (Rochester et al., 2017). The pathophysiological basis of cognitive alterations in PD are complex and could involve both the dopaminergic and cholinergic circuits through a synergistic effect between alpha-synuclein, beta-amyloid and tau protein (Perez-Lloret & Barrantes, 2016). In addition, the activity of acetylcholinesterase (marker of cholinergic terminals) in the hippocampus is reduced in demented PD patients compared to non-demented PD patients and healthy subjects (Hall et al., 2014). The presence of mild cognitive impairment, older age, male sex, PIGD phenotype, cholinergic non-motor phenotype and the presence of other non-motor symptoms represent the main risk factors for the development of PD-dementia (Titova & Chaudhuri, 2017). The progression of cognitive impairment, however, varies from patient to patient, highlighting the need to find biomarkers predictive of the progression of cognitive alterations. This aspect is particularly relevant in order to allow a better selection of patients for pharmacological trials. Literature data suggest that quantifying the presence of beta-amyloid deposits, using selective tracer PET methods, may represent a predictive biomarker of cognitive decline in PD (Lim et al., 2019). It has been shown that about 10-15% of patients with PD, in the absence of cognitive impairment, have a positive PET for beta-amyloid deposits; this percentage rise to 25-30% in patients with PD dementia (Lim et al., 2019). To summarize, cholinergic involvement in PD can be associated with pathological accumulations of beta-amyloid and plays a key role in the development the cholinergic phenotype, characterized by a greater severity of axial symptoms. New studies are needed to better investigate and define the relationship between the cholinergic phenotype of the disease and the deposition of beta-amyloid. To date, however, there are no studies in the literature that analyze the correlation between axial symptoms, cognitive aspects and beta-amyloid deposition in patients undergoing STN-DBS or that analyze the relationship between beta-amyloid deposits and speech alterations in PD patients.

Treatment of PD

Symptomatic pharmacological treatment in PD aims to supply the dopaminergic deficit due to the neurodegeneration of mesencephalic Substantia Nigra (SN). Hornykiewicz and Birkmayer were the first to demonstrate that levodopa, an intermediate of the biosynthetic pathway responsible for the synthesis of dopamine administered intravenously, could be used as an antiparkinsonian drug (Birkmayer & Hornykiewicz, 1961). But it was Cotzias who demonstrated that even the administration of high doses of levodopa by mouth had an antiparkinsonian effect (Cotzias & Van Woert, 1967). Levodopa was initially administered orally at very high doses since at the peripheral level it underwent metabolism by various enzymes including dopa-decarboxylase, catechol-O-methyltransferase (COMT) and mono-amino oxidase (Khor & Hsu, 2007). However, the newly formed dopamine is not able to cross the blood-brain barrier and is therefore ineffective. Since the first half of the 1970s, two pseudoirreversible peripheral inhibitors of the dopa decarboxylase enzyme, benserazide and carbidopa, have been associated with levodopa. This association allows to reduce the peripheral metabolism of levodopa leading to a better clinical efficacy for the same dose administered with a reduction of side effects (Khor & Hsu, 2007). The administration of levodopa associated with a dopa decarboxylase inhibitor shifts its metabolism towards the COMT pathway, leading to the formation of the compound 3-oxy-methyldopa. To block this metabolic pathway, drugs with inhibitory action on COMT have been developed. By inhibiting the peripheral metabolism of levodopa, these molecules further increase its bioavailability, and therefore its efficacy, centrally. The three compounds currently available are tolcapone, entacapone and opicapone (Rinne et al., 1998; Poewe et al, 2002; Fabbri et al. 2018). The second group of drugs used in the treatment of PD are dopamine receptor agonists. These molecules directly bind dopamine receptors not requiring the presence of dopaminergic neurons to be pharmacodynamically effective. Dopamine agonists are currently used in two different disease

contexts: as monotherapy in the initial stages or as adjuvants of dopaminergic therapy in the control of motor complications. If administered in the early stages of the disease, they allow to postpone the introduction of levodopa and therefore the onset of motor complications related to chronic treatment (Bonuccelli et al., 2009). After several years of use, chronic levodopa therapy can lead to the development of so-called motor complications, which characterize the complicated phase of the disease. Motor complications can be divided in motor and non-motor fluctuations (wearing-off, delayed-on, no-on, sudden off) and dyskinesia, involuntary choreic or dystonic movements that can occur during the peak blood concentration of drugs (peak dyskinesias), or while the concentration of levodopa is increasing or decreasing (biphasic dyskinesias). In the advanced stage of the disease, characterized by a poor control of motor symptoms despite multiple adjustments of oral drugs, the so-called advanced therapies represent a possible therapeutic option in selected patients. They include continuous subcutaneous infusion of apomorphine, Intrajejunal Infusion of Levodopa/Carbidopa (Duodopa) and DBS.

Subthalamic Nucleus Deep Brain Stimulation (STN-DBS)

Since 2003 the Food and Drug Administration has approved the use of STN-DBS for advanced PD patients. STN-DBS is a surgical procedure in which electrodes are implanted in specific brain nuclei thanks to a combination of stereotaxic and neuroimaging techniques. Through a subcutaneous impulse control generator (IPG), continuous electrical impulses are generated and released through the electrodes in the specific brain nucleus targeted by stimulation, modulating his activity (Sironi, 2011). To maximize the benefit and minimize the unfavorable effects, the device can be controlled by an external programmer which allows to adjust the parameters of the stimulation. Indeed, the external programmer allows to modify the configuration of the electrodes, the voltage, the frequency and the duration of the pulse. In cases of need (surgical operations or instrumental

diagnostics) the stimulation can be also switched off. Several open, controlled, and randomized studies have confirmed the clinical efficacy of STN-DBS in PD (Deuschl, et al., 2006; Schüpbach, et al. 2007; Follett, et al., 2010). All data from the studies that investigated the clinical outcomes of STN-DBS were summarized in published meta-analysis (Kleiner-Fisman, et al., 2006) and subsequent reviews (Rodriguez-Oroz, Moro, & Krack, 2012; Deuschl, Paschen, & Witt, 2013). Randomized trials have confirmed the greater efficacy of STN-DBS in improving the motor symptoms of the disease compared to the best pharmacological treatment in a time interval between six months and two years (Deuschl, et al., 2006; Okun, et al., 2012; Schüpbach, et al., 2007; Williams, et al., 2010). The 2006 meta-analysis by Kleiner-Fisman et colleagues, confirmed that STN-DBS led to significant reduction in the severity of motor symptoms after surgery, quantified by the difference of the UPDRS part III score in the postoperative stim-on/med-off condition compared to the pre-operative med-off condition. This comparison was considered in all studies as the yardstick of motor improvement related to the surgery. The reduction of UPDRS part III score after surgery ranged from 28.6% (Weaver, et al., 2009) to 41% in controlled studies (Deuschl, et al., 2006). In the 22 uncontrolled studies, the mean improvement was 52% overall (Kleiner-Fisman, et al., 2006). The reduction of UPDRS part III in stim-on/med-off conditions compared to baseline was also confirmed in long-term studies with a follow-up ≥ 8 years (Fasano et al. 2010; Castrioto et al. 2011). The greatest improvement was found in the first year following the surgery, subsequently decreasing as the duration of the follow-up increases. Regarding the relationship between the stim-on/med-on condition and the pre-operative med-on condition, the available data show an initial non-statistically significant reduction of the score compared to pre-operative values already in the short/medium term follow-up (Gervais-Bernard, et al., 2009; Krack, et al., 2003; Schüpbach, et al. 2005). In the long term (≥ 8 years) a progressive worsening of motor scores (indicative of greater disease severity) has been found with 8-years postoperative UPDRS part III scores higher than the

pre-operative values (Fasano, et al., 2010; Zibetti, et al., 2011; Aviles-Olmos, et al., 2014). Concerning the different motor symptoms of the disease, short-term studies have shown a 50-60% percentage improvement of akinesia after surgery (Hamani et al., 2005). However, long-term data show how this improvement decreases over time particularly with respect to axial akinesia which becomes less and less responsive to stimulation with prolonged follow-up (Krack, et al., 2003). On the contrary, UPDRS III rigidity subscore has shown a constant improvement in both the short- and long-term follow-up (Deuschl, Paschen, & Witt, 2013). Tremor subscores also show significant improvement after surgery in both short- and long-term (Hamani et al., 2005). Indeed, long-term studies confirm the persistent improvement of tremor and rigidity even at follow-up of 8 years or more in the stim-on/med-off condition, while the improvement of the subscore related to akinesia is kept at 8 and 9 years but not at 10 years of follow-up (Rodriguez-Oroz, Moro, & Krack, 2012). Regarding the combined effect of dopamine replacement therapy and stimulation compared to the pre-operative med-on condition, the long-term data show that tremor subscore does not improve already at 5 years of follow-up although two studies at 8 and 10 years show the opposite (Rodriguez-Oroz, Moro, & Krack, 2012; Fasano, et al., 2010; Zibetti, et al., 2011). Overall, there is a worsening of total UPDRS part III score and of subscores relating to bradykinesia, FOG, postural stability and in general axial scores already at 5 years (Rodriguez-Oroz, Moro, & Krack, 2012; Fasano, et al., 2010; Zibetti, et al., 2011). The STN-DBS allows a reduction of between 23 and 50% of the Levodopa Equivalent Daily Dose (LEDD), that is the equivalent dose, expressed in milligrams of levodopa, of the dopaminergic drugs taken by the patient during the day (Weaver, et al., 2009; Deuschl, et al., 2006). The Kleiner-Fisman meta-analysis confirmed that LEDD decreases by 56% one year after surgery (Kleiner-Fisman, et al., 2006). Long-term data (follow-up ≥ 8 years) confirm the persistent reduction in LEDD compared to baseline (Fasano, et al., 2010; Bove et al., 2021). Motor complications are traditionally quantified through the UPDRS part IV total score and subscores

relating to motor fluctuations and dyskinesias. With regard to motor fluctuations, it was shown that stimulation allows a 25 - 60% reduction of both the frequency and intensity of the OFF phases (Deuschl, Paschen, & Witt, 2013). As regards levodopa induced dyskinesia (LID), an improvement of 40-60% was found after surgery (Deuschl, Paschen, & Witt, 2013). This improvement is primarily related to the postoperative reduction in dopaminergic therapy. Indeed, the stimulation itself does not have a direct anti-dyskinetic effect unless the most dorsal contact is activated (Herzog, et al., 2007). In this case the volume of tissue activated may involve the Forel fields interfering with the pallido-fugal tracts (i.e. fasciculus lenticularis) creating a levodopa-blocking effect (Deuschl, Paschen, & Witt, 2013; Herzog, et al., 2007). The reduction of motor complications persists even in the long term, representing one of the major benefits of stimulation even many years after surgery (Zibetti, et al., 2011; Bove et al., 2021).

To concluded, STN-DBS allows a significant improvement of both cardinal symptoms of the disease and motor complications (fluctuations and dyskinesias) (Bove et al., 2021). Furthermore, there are some preoperative clinical factors that can predict the outcome of STN-DBS both in the short and in the long term in particular: the response to levodopa, the motor phenotype of the disease, the degree of frontal lobe dysfunction, the presence of vascular signs on preoperative MRI and disease severity in the off-medication condition (Cavallieri et al., 2021).

Data from randomized controlled clinical trials showed a short-term improvement of quality of life assessed through the Parkinson's Disease Questionnaire (PDQ-39) compared to the group of patients receiving the best medical treatment with an average score between 5 and 10 points and a given percentage between 13 and 24% (Deuschl, Paschen, & Witt, 2013). Regarding the uncontrolled and open studies summarized in the Kleiner-Fisman meta-analysis, an improvement of about 44% was found (Kleiner-Fisman, et al., 2006). In particular activities of daily living (ADL), mobility, stigma, physical discomfort and emotional well-being domains are most sensitive to

improvement after surgery (Deuschl, et al., 2006; Williams, et al., 2010; Weaver, et al., 2009). In the medium term (3-5 years) the initial improvement of the PDQ-39 scale declines with no significant difference at 5 years (Jiang, et al., 2015; Liang, et al., 2006). Further studies have confirmed that 8 years after surgery the improvement of the PDQ-39 scale found at 1 year is lost with no statically significant differences compared to pre-operative values already at 5 years (Aviles-Olmos, et al., 2014; Lezcano, et al., 2016).

Several randomized studies (STN-DBS vs best medical treatment) have not showed a worsening of the overall cognitive performance, assessed with the Mattis dementia scale, in the operated patients with a two-year follow-up (Deuschl, et al., 2006; Weaver, et al., 2009; Williams, et al., 2010). However, STN-DBS has been found to negatively affect some specific cognitive domains. In particular, a postoperative decline in semantic and phonological verbal fluencies was found (Ardouin, et al., 1999) which progressively worsens over time (Contarino, et al., 2007). Furthermore, this finding was also found in patients operated on but not stimulated leading to the hypothesis that the injury due to the passage of the electrodes represents the major cause of postoperative cognitive alterations (Okun, et al., 2012). However, it is believed that the pathogenesis of cognitive changes resulting from stimulation is more complex and is the result of the combination of several factors: stimulation of the cognitive-limbic area of the STN, post-operative pharmacological changes, passage of the electrodes and cognitive preoperative profile of the patient (Thobois, et al., 2010; Deuschl, Paschen, & Witt, 2013). Advanced age, presence of attention deficit, high LEDD, high axial scores and low response to dopaminergic therapy represent pre-operative risk factors correlated to decline in cognitive performance in the post-operative phase (Daniels, et al., 2010; Smeding et al., 2011). A recent study has found that in patients with PD with longstanding STN-DBS, dementia prevalence and incidence are not higher than those reported in the general PD population. Except for few patients with perioperative cerebral hemorrhage, STN-DBS is cognitively

safe, and does not provide dementia risk factors in addition to those reported for PD itself (Bove et al. 2020).

Concerning the neuropsychiatric effects of STN-DBS, it has been found that the reduction of dopaminergic therapy following STN-DBS surgery can reduce hallucinatory and psychotic phenomena present in the pre-operative phase (Umemura et al., 2011). The fine regulation of stimulation parameters and drug therapy is necessary to prevent the development of pathological behaviors (Castrioto et al., 2014). The reduction of dopaminergic therapy following the surgery does not only lead to positive behavioral effects. Indeed, an excessive reduction of the dopaminergic tone can cause the appearance of apathy which can neutralize the positive effects on the quality of life after surgery (Martinez-Fernandez, et al. 2016; Krack et al., 2010). Typically, apathy arises 3-7 months after surgery and can affect about 50% of operated patients (Martinez-Fernandez, et al. 2016; Krack et al., 2010). The increase in dopamine agonist drugs allows in most cases to reduce or resolve the disorder. Patients who suffer from major non-motor fluctuations and show thymic fluctuations during pre-operative L-DOPA testing are those at greatest risk of developing post STN-DBS apathy (Thobois, et al., 2010). On the contrary, hypomanic, or manic phenomena are in most cases temporally correlated to the onset of stimulation in the immediate post-operative period and to the stimulation of the most ventral contacts in contact with the limbic region of the subthalamus (Herzog, et al., 2003; Mallet, et al., 2007). Regarding ICDs, punding phenomena and DDS, the reduction of dopaminergic therapy leads to a decrease in these disorders even if there have been reports of worsening or development of hyperdopaminergic symptoms after surgery (Ardouin, et al., 2006; Lim, et al., 2009).

Effects of STN-DBS on axial symptoms

Literature data about the effect of STN-DBS on axial symptoms are heterogeneous. STN-DBS improves postural instability and gait disturbances, assessed with the relative subscore of UPDRS part III, in the first year after surgery in the same way as preoperative drug therapy (Bakker et al., 2004). However, several studies have shown that FOG can improve after surgery only if present in the med-off condition (Krack et al., 2003). Unfortunately, however, in the long term there is a deterioration in axial symptoms already 5-8 years after the intervention (Deuschl, Paschen, & Witt, 2013). Indeed, data from long-term studies have confirmed that STN-DBS initially improves the UPDRS compound subscore for postural and gait symptoms (PIGD subscore) in the stim-on/med-off condition, even if the score worsens over time until it reaches or exceeds pre-operative values 8 years after surgery (Deuschl, Paschen, & Witt, 2013). Specifically, the improvement in walking and FOG scores remains up to 9 and 10 years while the improvement in the score relating to postural instability is already inconsistent at 5 years (Rodriguez-Oroz, Moro, & Krack, 2012). As regards the stim-on/med-on condition, there is an earlier and more progressive decline in scores with a return to pre-operative values in the med-on condition already at two years after the intervention (St George et al., 2010). In addition, axial symptoms tend to worsen faster and more rapidly than cardinal disease symptoms over the long term (Rodriguez-Oroz, Moro, & Krack, 2012). It is therefore evident that walking and postural disorders respond only initially to stimulation, improving in the short term but worsening in subsequent years, thus configuring itself as a complex management aspect in the advanced stages with an important effect negative on quality of life.

Data from systematic reviews show that STN-DBS led to improvement of neurophysiological parameters relating to walking and postural control in the short term while it did not improve or even worsen the dynamic postural control parameters (Collomb-Clerc & Welter, 2015).

Concerning speech parameters, STN-DBS can improve the volume, intelligibility, and articulation of speech in the very early stages; however, already one year after surgery, intelligibility worsens by 14% when compared with a control group subjected to the best drug treatment (Pinto et al., 2004; Tripoliti et al., 2011). An association was also found between amplitude and frequency of stimulation at the level of the left subthalamic nucleus and a decrease in intelligibility, with the development of heterogeneous profiles of dysarthria related to the possible diffusion of stimulation at the level of the cerebellothalamic bundles, of the cortical bundles. -bulbar and cortico-spinal and pale-fugal pathways (Tommasi et al., 2008; Aldridge et al., 2016; Tripoliti et al., 2011). Indeed, it is known that up to 90% of medically treated PD patients develop speech and language disorders during the course of the disease in the form of hypokinetic dysarthria (Ho et al. 1998; Darley et al. 1969). On the contrary, patients treated with STN-DBS are characterized by the presence of different speech disorders that go beyond the characteristic parkinsonian hypokinetic dysarthria (Tommasi et al. 2008). These initial observations led Tsuboi et al. in a seminal study to differentiate and characterize the different post-DBS speech alterations by means of a cluster analysis method, identifying 5 different post-surgery speech phenotypes and correlating them with the position of the stimulation electrodes (Tsuboi et al., 2015):

• Phenotype 1: “relatively good speech and voice function type” (25%). Similar profile to PD patients not undergoing STN-DBS except for an improvement in vocal tremor

• Phenotype 2: “stuttering type” (24%). The phenomenon of stuttering is related to dysfunction of the cortico-striatum-thalamus-cortical loops and is found in patients in advanced stages of the disease not undergoing DBS. However, in some cases the stimulation can worsen the phenomenon

• Phenotype 3: “breathy voice type” (16%). Profile characterized by increased dysphonia, hypophonia and laryngeal dysfunction. Primarily related to PD, however, stimulation can aggravate the clinical picture.

• Phenotype 4: “strained voice type” (18%). It improves in stim-off condition and is associated with a more lateral position of the stimulation electrodes. Atypical pattern in PD, probably related to the stimulation of the bulbar cortical bundles with excessive contraction of the laryngeal muscles

• Phenotype 5: “spastic dysarthria type” (17%). Phenotype characterized by nasal voice and consonant alteration, improves in stim-off condition. This phenotype is also associated with a more lateral position of the electrodes and is related to the diffusion of stimulation to the bulbar cortical bundles with prevalent involvement of the lingual muscles, the palatine veil and the lips.

Cohort studies have confirmed that speech worsened in 70% of patients three years after surgery (Piboolnurak et al., 2007), in 57% at 5 years (Gervais-Bernard et al., 2009) and in 90% at 8 years (Fasano et al., 2010). Overall, it can be concluded that speech does not improve following surgery and rather deteriorates over time, undergoing a negative influence from the combined effect of stimulation and drug therapy (Rodriguez-Oroz et al., 2012). The intelligibility of speech and the corresponding UPDRS subscore in fact worsen significantly at 5 years and 8 years after the intervention, both in the condition of stimulation in the absence of drug (STIM-ON/MED-OFF), and in the presence of both (STIM-ON/MED-ON) (Aviles-Olmos et al., 2014; Fasano et al., 2010). However, all these studies were based only on clinical or perceptual evaluation and not on acoustic quantitative analysis.

Aims of this Thesis

This thesis work represents a preliminary analysis of the data collected in the broader BASCOSTIM-PD project (Study on the association between axial symptoms, cognitive impairment, clinical-instrumental variables of motor function and brain amyloid beta-peptide deposition in Parkinson's disease patients with bilateral STN-DBS) involving the Neurology Unit of the AUSL-IRCCS of Reggio Emilia, Italy; the Neurology Unit of the OCB Azienda Ospedaliera-Universitaria, Modena, Italy; and the Movement Analysis Laboratory (LAM) of the San Sebastiano Hospital in Correggio, Italy. This multicentre observational retrospective-prospective study includes all patients who underwent bilateral STN-DBS surgery from 2012 to 2018 at the Neurological Unit of the OCB Azienda Ospedaliera-Universitaria of Modena and who meet the inclusion and exclusion criteria reported in the methods section.

The objectives of the BASCOSTIM-PD project are as follows:

- Assessment of the evolution of axial symptoms (posture, gait and speech) through a standardized clinical-instrumental approach in a cohort of patients with advanced PD from 3 to 7 years after bilateral STN-DBS.
- To evaluate the possible correlation between speech and gait parameters in the different medications and stimulation conditions in a cohort of advanced PD patients operated on with bilateral STN-DBS.
- Evaluate the possible correlations of axial symptoms with the cognitive profile, assessed through the administration of neuropsychological tests, and the possible cerebral deposition of beta amyloid, evaluated through a brain Positron Emission Tomography (PET) with specific tracer (Flutemetamol F-18).
- To evaluate the influence of anatomical location and parameters setting of the active STN-DBS

contact on axial symptoms.

- To compare the efficacy of STN-DBS and levodopa on axial symptoms.

As already mentioned, this thesis represents a preliminary analysis of the data collected in the BASCOSTIM-PD project and has the following objectives:

- To evaluate the effects of STN-DBS and dopaminergic treatment on motor, gait and speech variables through a standardized instrumental approach in the long-term after surgery. As highlighted in the introduction, many studies have assessed the effect of STN-DBS or dopaminergic treatment on axial symptoms with an instrumental approach. However, they have focused only on gait alterations or speech disturbances mainly in the short term, showing heterogeneous results particularly concerning speech (Tripoliti et al., 2011). Based on literature data, we could suppose that both stimulation and medication could have a positive effect on neurophysiological parameters relating to walking with mixed effects on speech (Tripoliti et al., 2011; Collomb-Clerc & Welter, 2015; Cavallieri et al., 2021).
- To evaluate the possible correlation between speech and gait parameters in the different medications and stimulation conditions. The very few studies that have instrumentally assessed the whole spectrum of axial symptoms in PD have showed the presence of similarities between spatial-temporal gait and speech parameters (Cantiniaux et al., 2010; Ricciardi et al., 2016). We could suppose that gait velocity and speech rate may be related with a different response to both stimulation and medication as previously reported by Cantiniaux et al. (Cantiniaux et al. 2010). Furthermore, we may also assume that patients with higher gait impairment may also present a worse speech quality as previously reported (Flood et al., 2020).
- To evaluate the possible correlation between speech and gait parameters and clinical scales.

While the correlation between gait parameters, particularly iTUG duration, and UPDRS scores have been already well reported (Mollinedo et al., 2020), few studies have confirmed the possible relationship between speech variables and clinical scales. In this setting we hypothesize that the main characteristics of hypokinetic dysarthria (i.e., reduced MPT, reduced loudness and lower F0 standard deviation), mainly due to bradykinesia and rigidity of vocal muscles, may correlate with clinical motor scores and subscores.

METHODS

Study design and setting

Multicenter retrospective-prospective observational study approved by the Ethics Committee of the Area Vasta Emilia Nord N° 2019/0056629, 14/05/2019.

Population

All consecutive patients who underwent bilateral STN-DBS from 2012 to 2018 at the Neurological Unit of the OCB University Hospital were recruited. The patients who underwent STN-DBS did not complain significant cognitive or axial alterations before surgery. Indeed, the presence of these features represents a contraindication to surgery (Defer et al., 1999). This has allowed to analyse an homogeneous cohort of parkinsonian patients. All subjects included in the study met the following inclusion and exclusion criteria:

Inclusion criteria:

- Diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria for Parkinson's Disease (Gibb & Lees, 1988).
- Treatment with bilateral STN-DBS performed from 1st January 2012 to December 31st 2018 at the Neurological Unit of the OCB University Hospital.

Exclusion criteria:

• History of surgical complications related to STN-DBS surgery which resulted in neurological deficits.

• History of ischemic or haemorrhagic stroke, head trauma or other focused brain injuries appeared during the postoperative follow-up after surgery.

• History of laryngeal or pharyngeal diseases appeared during the postoperative follow-up after surgery.

• Inability to perform the study protocol.

• Withdrawal of consent.

Written informed consent was obtained from all patients participating in the study in accordance with the Declaration of Helsinki (World Medical Association, 2013).

Preoperative screening

Preoperative data were collected retrospectively from pre-operative assessments, carried out from January 2012 to December 2018 at the Neurological Unit of the OCB, including the following variables and evaluations:

- Demographic characteristics: sex, age at surgery.
- Disease characteristics: age of PD onset, PD duration at surgery.
- Results of genetic analysis: all patients were included in the ROPAD study "The Rostock International Parkinson's Disease Study" which allows to test for the presence of mutations in the 68 genes involved in monogenic forms of PD (Skrahina et al., 2021).
- 3 Tesla Brain MRI which allowed to evaluate the presence/absence of white matter hyperintensities of vascular origin.
- Complete Neuropsychological assessment.
- Neurological evaluation performed both under the effects of dopaminergic treatment and in its absence. The acute pharmacological response to levodopa was systematically assessed in the morning after approximately 12 hours of washout from antiparkinsonian medications (MED-OFF condition) and one hour after the administration of a suprathreshold dose of levodopa (MED-ON condition). The suprathreshold dose of levodopa was calculated by adding 30% of the LEDD calculated on all dopaminergic drugs taken upon awakening. The assessment protocol included

the following scales: UPDRS part III total score and subscores and H&Y staging scale.

- Speech evaluation: performed in both MED-ON and MED-OFF conditions by two speech therapists with a certified experience in movement disorders related speech alterations. Speech assessment in MED-ON condition was performed 1 hour after taking Levodopa, at the end of the neurological examination, thus allowing patients to be tested in their best pharmacological ON condition. Each evaluation lasted about 15 minutes, was performed with a conversation voice intensity in a silent environment (<50 dB of background noise) and was registered through a digital voice recorder (model SONY ICDPX240) maintained 20 cm from the patient's lips. The perceptual and acoustic analysis were performed blinded to the pharmacological condition using the Praat software (Boersma et al., 2013).
- Definition of motor Phenotype: based on the study by Stebbins et al. patients were divided into three motor phenotypes by calculating the ratio between tremor related subscores compared to postural instability/gait disorders subscore. Based on the ratio the patients were classified in tremor dominant phenotype (ratio> 1.5), PIGD phenotype (ratio <1) and indeterminate phenotype (ratio between 1.0 and 1.5) (Stebbins et al., 2013).
- LEDD: the equivalent expressed in milligrams of Levodopa of dopaminergic drugs taken by the patient during the day. The LEDD was calculated using the Tomlinson and Thobois conversion coefficients (Thobois, 2007; Tomlinson et al., 2010).

Surgery procedures

All patients underwent bilateral STN-DBS surgery. Surgical trajectories were calculated using preoperative brain MRI and brain CT after placement of a stereotactic frame. The placement of intracranial electrodes was preceded by intraoperative micro-recording and micro-stimulation

through recording microelectrodes (from 3 to 5 per side). The final quadripolar electrodes and the pulse generator were then placed (pectoral or abdominal region) under general anesthesia.

At the end of surgery, all patients underwent a brain CT scan to rule out the presence of complications related to the surgical procedure.

Postoperative clinical-instrumental evaluation

All subjects were re-evaluated 3 to 7 years after surgery. Neurological evaluation, speech assessment and the instrumental evaluation of movement, were carried out in the same day in the following pharmacological and stimulation conditions:

- Active stimulation without dopaminergic medications: STIM-ON/MED-OFF (this condition allowed to evaluate the effects of stimulation alone)
- Stimulation off without dopaminergic medications: STIM-OFF/MED-OFF (this condition allowed to evaluate the severity of the disease in the absence of any treatment)
- Active stimulation with dopaminergic medications: STIM-ON/MED-ON (this condition allowed to evaluate the effects of both stimulation and medications). Only in this condition the instrumental evaluation of movement was performed also while performing a cognitive task (STIM-ON/MED-ON DUAL TASK) allowing to evaluate gait in a dual task condition. The cognitive task was to pronounce the greatest number of words that began with a specific letter.

Each patient came to the Motion Analysis Laboratory (LAM) of San Sebastiano Hospital in the early morning in the STIM-ON/MED-OFF condition, obtained through a washout of at least 12 hours of dopaminergic medications following the CAPSIT-PD (Defer et al., 1999). In this first condition (STIM-ON/MED-OFF), all patients underwent neurological evaluation with the administration of the UPDRS part III scale, H&Y, speech assessment and instrumental evaluation of movement. At the end of the

above-mentioned evaluations, the stimulation was temporarily turned off for one hour to obtain the STIM-OFF/MED-OFF condition.

In this condition, neurological examination, speech assessment and instrumental evaluation of movement, were carried out again allowing to quantify the real severity of the disease. The results obtained in the STIM-ON/MED-OFF were compared with the STIM-OFF/MED-OFF condition to verify the effect of STN-DBS therapy. After these evaluations, stimulation was turned on and dopaminergic therapy was administered (early morning LEDD plus 30%). After one-hour patients were reevaluated in the "STIM-ON/MED-ON" condition with the same protocol. The results obtained in the STIM-ON/MED-ON were compared with the post-operative STIM-ON/MED-OFF condition to verify the effects of oral pharmacological therapy.

Neurological evaluation and clinical scales

Neurological assessment was performed by a neurologist with a longer experience in Movement Disorders and certified to apply the rating scales used in the study. Motor impairment was quantified applying the Unified Parkinson's Disease Rating Scale (UPDRS); in particular, the motor part of the scale and some specific subscores related to akinesia, tremor and axial symptoms (PIGD). Higher scores are indicative of a higher severity of the disease. Neurological assessment consisted of the following clinical scales with both scores and subscores and the following variables:

- UPDRS part I: evaluation of mentation, behavior, and mood.
- UPDRS part II: self-evaluation of the ADL including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food.
- UPDRS part III total score: motor severity of the disease, calculated in STIM-ON/MED-OFF, STIM-OFF/MED-OFF and STIM-ON/MED-ON conditions. The following subscores related to different motor domains of the disease were calculated from the UPDRS scale:

- Akinesia subscore: UPDRS-III items 23-26 and 31 (score 0 -36)
- Tremor subscore: UPDRS-II items 16 and UPDRS-III items 20 and 21 (score 0-32)
- PIGD subscore: UPDRS-II items 13-15, UPDRS-III items 29 and 30 (score 0-20)
- Speech subscore: UPDRS-III item 18 (score 0-4)

- UPDRS part IV (motor and non-motor complications).
- Stimulation parameters: type of stimulation (single or double monopolar, bipolar), active contact(s), intensity, duration, frequency, and impedance of stimulation. Calculation of the stimulation power using the formula proposed by Koss (Koss et al., 2005).
- Calculation of the daily LEDD.
- Hendrich Fall Risk Model II (HIIFRM): evaluates the risk of falling based on intrinsic risk factors that are added together to obtain an overall score that can range from a minimum of 0 to a maximum of 16. An overall score equal to or greater than 5 indicates a high risk of falling. This scale was administered in the three conditions tested.

Speech evaluation

Speech evaluation was performed in STIM-ON/MED-OFF, STIM-OFF/MED-OFF and STIM-ON/MED-ON conditions by two speech therapists with a long experience in movement Disorders-related speech disturbances. Each evaluation lasted about 15 minutes, were carried out with conversation voice intensity in a silent environment (<50 dB of background noise) and was obtained through a digital voice recorder (model SONY ICDPX240), kept 20 cm from the patient's lips (Rusz et al., 2021). The perceptual-acoustic analysis was performed blinded to the patient's condition using Praat software (Boersma et al., 2013). Speech assessment was composed by the following tasks and corresponding variables:

- Spontaneous speech (30 seconds): mean intensity expressed in decibels (dB)
- Prolonged phonation: sustained production of the phoneme /a/ for as long as possible, performed three times. The average of the following acoustic parameters was obtained:
    - Duration (sec)
    - Intensity (dB)
    - Frequency perturbations (Jitter Local)
    - Amplitude perturbations (Shimmer Local dB)
    - Spectral energy balance (mean noise to harmonic ratio [NHR])
    - Fraction of locally unvoiced frames
- Word intelligibility: reading of a list of randomized 25 words. Word intelligibility was calculated on the percentage of recorded words correctly transcribed by the examiner.
- Speech rate: assessed by asking the patient to count from 1 to 20: syllables/second
- PATAKA: Each participant produced the /pa/, /ta/, /ka/ syllables and the /pataka/ sequence, as fast and as long as they could with habitual pitch and loudness to evaluate oral diadochokinesis:
    - Irregular rhythm (presence of absence)
    - Uncontrolled acceleration (presence of absence)

The parameters included in the analysis were selected because they represent the acoustical characteristics previously reported as altered in hypokinetic dysarthria. In particular, it is expected that the alterations of these acoustic characteristics are correlated to various dysfunctions of the voice: a reduced average intensity of both spontaneous speech and sustained speech would be correlated to a reduced volume; shorter maximum speech time with insufficient air flow (Skodda et

al., 2010). Jitter Local represents the perturbation of the frequency, the extent of the variation of the vocal range, and is defined as the variability of the fundamental frequency from one cycle to another. Shimmer Local Db describes amplitude perturbation, defined as the sequence of maximum extension of signal amplitude within each vocal cycle. NHR is defined as the amount of noise in the speech signal (Rusz et al., 2011). High values of these variables are indicative of poorer voice quality. (Martin et al., 1995; Rusz et al., 2021). Furthermore, all the acoustic characteristics examined in the present study were chosen to allow for an objective and gender-independent evaluation (Rusz et al., 2011). The Fraction of locally unvoiced frames parameter reflects voice breaks indicating the fraction of pitch frames which are analyzed as unvoiced (Boersma et al., 2013).

Instrumental evaluation of movement

The instrumental evaluation of movement was carried out using a wearable inertial sensor, which was placed on the belt at sacrum level (S1). The commercial device G-WALK (BTS Bioenegeering) shown in figure 2 was used. The instrumented TUG test will be indicated below with the initials iTUG.

Fig. 2 G-Walk inertial device used in this thesis and its positioning

The following figure (Fig. 3) shows an example of the traces (accelerations and rotations) obtained by the device during the iTUG.

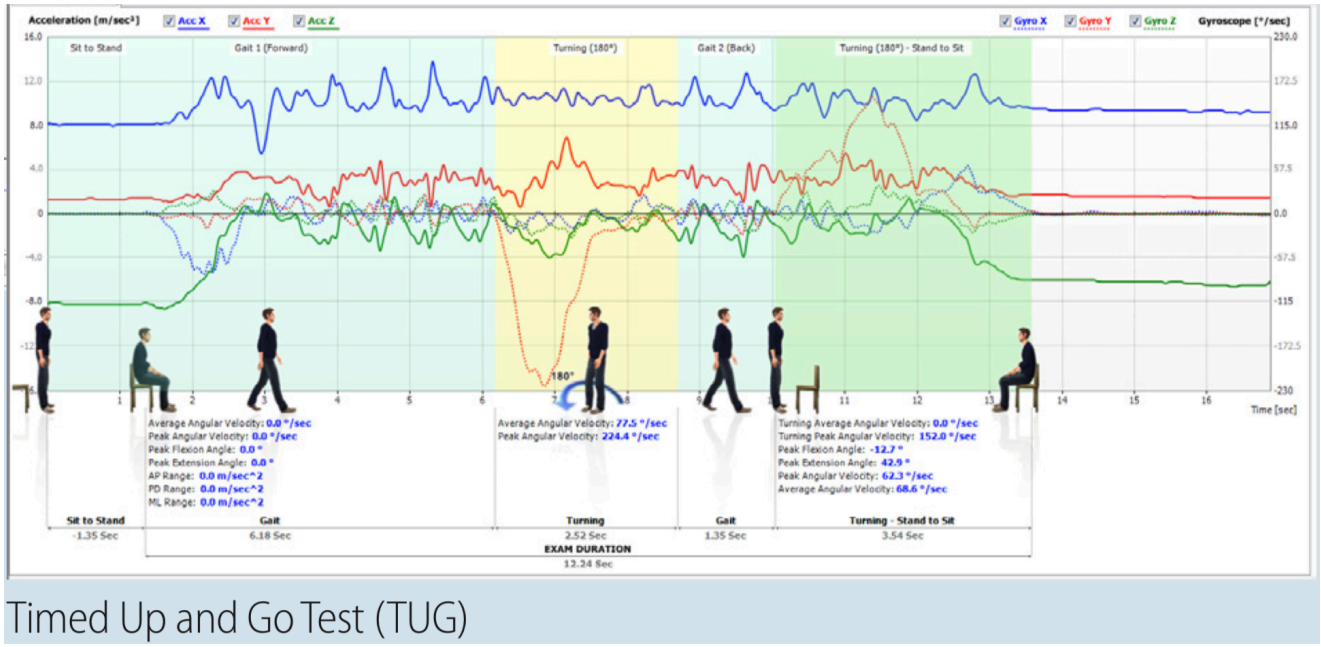


Fig. 3: example of the traces (plot of accelerations and rotations) obtained by the device during the iTUG

A literature search was carried out to analyze the current state of the art about the instrumental evaluation of movement in PD. Articles were collected through a search on Medline and Embase. To obtain reference values with respect to the TUG and clinical scales, the website rehabmeasures.org (S2) was consulted. Table 1 summarized literature values for TUG.

Table 1 Literature values for TUG

Test	Source	Sample, n	Age, mean (SD)	Gender (F, M)	Disease duration, years (DS)	Drug State (ON, OFF)	Mean values, (DS)	MDC	MCID
TUG	(Brusse KJ et al. 2005)	25	76 (7)	17,14	n.a.	ON	14.8 (5.8) s	n.a.	n.a.
	(Dal Bello-Haas et al., 2011)	24	64.9 (8.0)	6, 18	4.5 (4.3)	ON	10.3 (2.5) - 10.6 s (3.7)	4.85s	ns
	(Foreman et al. 2011)	36 (22 f, 14nf)	70.95 (11.41) f, 66.64	12, 24	8.18 (4.58) f, 4.64	ON, OFF	7.94-12.21 (ON); 8.13-	n.a.	n.a.

		(10.05) nf		(3.25) nf		15.5 (OFF)		
(Huang SL et al. 2011)	72	67.5 (11.6)	28,44	2 mesi – 15 anni	ON	11.8 (2.9) s	3.5s	n.a.
(Steffen T et al., 2008)	37	71 (12)	11, 26	14 (6)	31 ON	15 (10) s	11s	n.a.

SD= standard deviation, MCD= minimal detectable change, MCID= minimally clinical important difference, f=fallers, nf=non-fallers, n.a.= not available.

The iTUG test were recorded in the four conditions described above (STIM-ON/MED-OFF, STIM-OFF/MED-OFF, STIM-ON/MED-ON, DUAL TASK). In each condition, the patient was asked to perform the test 3 consecutive times, to obtain a total of 12 acquisitions. All the tests were performed barefoot and required the support (without contact) of an operator to ensure safety. The execution of the entire series of tests and evaluations was documented through video recording. The iTUG test was performed using the standard test procedure, with a chair with armrests positioned 3 meters away from a stool placed as a reference, to turn around. Once the sensor was positioned, the patient was instructed to get up from the chair after the "go", walk along a straight path of 3 meters, turn 180°, return to the chair, rotate again 180° and sit down. The acquisition with the sensor was concluded once the subject had sat down, determining the end of the test. Patients were instructed to walk at spontaneous speed and without keeping their arms behind their back, so as not to interfere with the sensor. During the dual task tests it was required to pronounce a list of common names with the same initial (F, A, S, different for each of the three acquisitions), indicated by the examiner just before the start of the test.

Data processing

Data from the inertial sensor were used to obtain the parameters included in the study, described below. Data were analysed with a dedicated software specifically developed and calibrated for the analysis of the walk of PD patients. The algorithms for data analysis were provided by the Bioengineering of the University of Rome "Foro Italico". The methods implemented are described in the work of Pasciuto and colleagues (Pasciuto et al., 2017; Iosa et al., 2012; Balasubramanian et al., 2015). The algorithms have been adapted to the data format of the sensor used, equipped with a user interface and transformed into executable software, usable only for research purposes (Merlo Bioengineering). The analysis of the traces required the identification by the operator of some specific moments (e.g., beginning of the movement). When the gesture is performed by healthy or slightly compromised subjects, the sub-phases of the gesture can be automatically identified starting from the traces. This however does not apply to very compromised, slow, or abnormal walks and gestures, as in the case of gestures performed by patients with PD. For each recorded test, the operator selected an initial static phase (stationary subject) necessary for sensor calibration and a few specific instants for the gesture. For the iTUG, five events have been included: start of elevation, end of the elevation/start of the walk, end of the walk/start of the turn, end of the turn/start of the walk, end of the turn/end of the session. The events were added based on the trends of the accelerations and angular velocities, according to the indications of the literature (van Lummel et al., 2016), and with the support of the video. After a training phase, we proceeded to define the identification rules of the instants (shown in tables 2 and 3) and to elaborate all the tests. Figure 4 shows an example of paths and their segmentation.

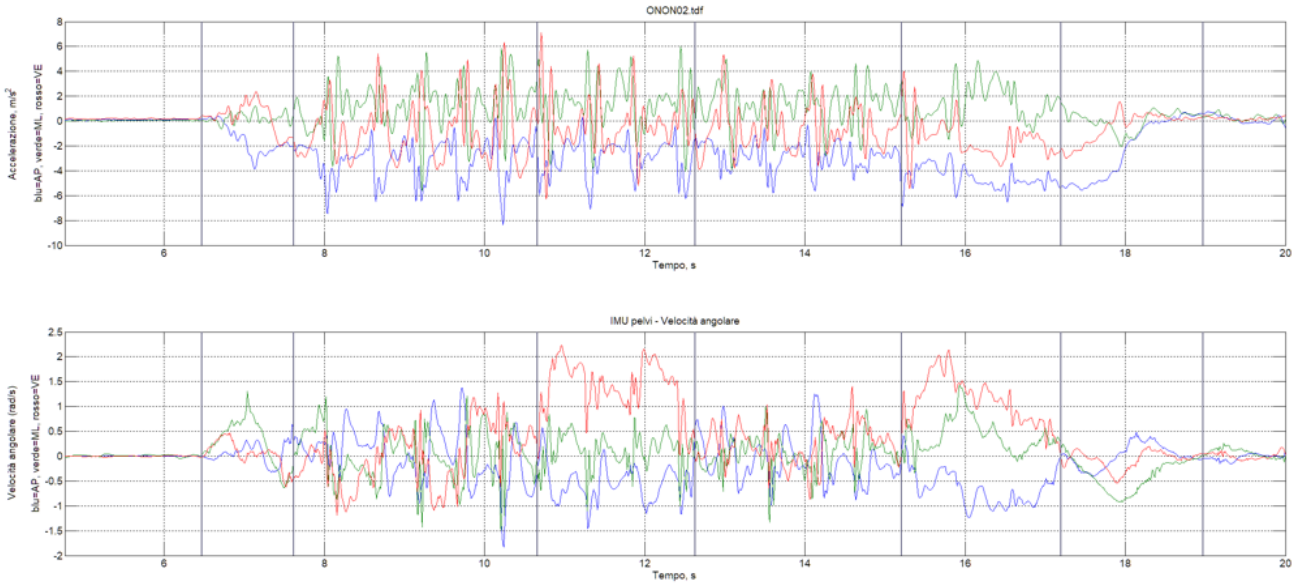


Fig. 4 iTUG plot with phase segmentation: the figure reports the raw signals of accelerometer with the corresponding phase segmentation

Tab. 2 Definition of instants for iTUG

N	Event name	Curve to watch	Event definition detail
1	Beginning of rising from the chair	Plot 2, angular velocity in trunk flexion (with respect to the ML axis)	Passing for 0 uphill
2	End of lift / start of walk	Plot 2, angular velocity in trunk flexion (with respect to the ML axis)	Passing for the 0 uphill or flattening of the M-L curve (just before the peaks of the walk)
3	End of walk / start of turn	Plot 2, angular velocity in trunk rotation (with respect to the VE axis)	Passing for 0 uphill
4	End of turn / start of walk	Plot 2, angular velocity in trunk rotation (with respect to the VE axis)	Pass through the 0 downhill
5	End of walk / start of turn	Plot 2, angular velocity in trunk rotation (with respect to the VE axis)	Pass for the 0 uphill
6	End of turn	Plot 2, angular velocity in trunk flexion (with respect to the ML axis)	- Passing through the 0 downhill (if the end of the turn and the beginning of the session coincide) - Flattening of the turn curve (if the session begins during the turn)
7	End of session	Plot 2, angular velocity in trunk flexion (with respect to the ML axis)	Pass for the 0 uphill

Variables investigated

Based on the sequence of events, the phases of the iTUG test were divided into sit to stand, forward walk, first turn, return walk, second turn, stand to sit. For each of the indicated phases, two variables were selected and investigated.

The variables selected were:

- Overall duration and duration of all the single sub-phases.

- Root Mean Square (RMS) of the acceleration of the trunk, which corresponds to the acceleration of the COM on different axis (vertical, antero-posterior, medio-lateral) and depends on the walking speed of the subject.

- Maximum speed of rotation of the trunk, which corresponds to the subject's ability to rotate quickly as possible.

The following table summarize the variables obtained from the data analysis of inertial sensor in the iTUG, with a brief explanation of their meaning.

Tab. 3 Description of iTUG variables

Phase	**Phase naming**	**Variables**	**Literature values for PD patients***
Overall iTUG	Set of all stages	Duration	11.4 (2.97); 20.2 (12.6) s
Elevation (Sit2St)	Allows the transition from sitting to orthostatic position	Phase duration	1.6 (0.5); 1.8 (0.8) s
		Vertical acceleration of the trunk	2.9 (0.56); 3.5 (1.9) m/s^2
Sitting (St2Sit)	It allows the transition from the orthostatic to the sitting position	Phase duration	2.0 (0.8); 2.4 (0.9) s
		Vertical acceleration of the trunk	5.1 (1.9); 5.2 (1.9) m/s^2

First turn (Turn 1)	Allows 180° rotation to reverse the direction of walking	Phase duration	2.65 (0.57); 4.4 (1.9) s
		Maximum speed of trunk rotation on the vertical axis	123 (40); 146 (42) degrees/s
Second turn (Turn 2)	Allows 180° rotation before sitting	Phase duration	2.33 (0.56); 4.4 (1.9) s
		Maximum speed of rotation of the trunk on the vertical axis	131 (48); 150 (40) degrees/s
Walking forward	Straight walk	Phase duration	2.19 (0.82); 5 (4.5) s
		Vertical acceleration of the trunk	n.d.
Return gait	Straight walk	Phase duration	1.81 (0.66); 3.2 (2.3) s
		Vertical acceleration of the trunk	n.d.

* Values from different studies are reported, for patients with different levels of severity (58.59), where available. n.d. = not available

Cognitive assessment:

Extended neuropsychological assessment including various cognitive functions was performed in each patient. Neuropsychological evaluations have been performed at the Clinical Neuropsychology Service of the OCB Azienda Ospedaliera-Universitaria (Modena). Data obtained from neuropsychological evaluation have been compared with the pre-operative data to evaluate cognitive changes after surgery. The following tests related to the following cognitive functions have been administered:

- *Attention*
    - Trail making test (Giovagnoli et al., 1996)

- Stroop Test (Caffarra et al., 2002)

- *Executive functions*
  - Phonemic and semantic fluencies (Costa et al., 2004)
  - Wisconsin Card Sorting test (Heaton et al. 1993)

- *Logical skills*
  - Raven's Progressive Matrices (Raven. 1969)

- *Memory*
  - Span of cubes (Courses 1972)
  - Direct and inverse digit span (Monaco et al., 2012)
  - Learning associated couples (De Renzi et al., 1977)
  - Free and Cued Selective Reminding Test (FCSRT) (Grober et al., 1987)
  - Benton Visual Retention test (Benton et al., 1992)

- *Visuo-spatial and visual-constructive skills*
  - Immediate and deferred copy of a complex figure of Rey (Caffarra et al., 2002)
  - Visual Object Space Perception (Warrington et al., 1991)

- *Emotions*
  - Battery for the recognition of facial emotions (Dodich et al., 2014)

It should be noted that all the tests and scales used in this extended neuropsychological assessment are calibrated and standardized for the Italian population, therefore reference regulatory data are available. The results (raw score) obtained by each subject in each test have been corrected in relation to the independent variables (gender, education, and age).

[18F] Flutemetamol PET study

Each patient will undergo a [18F] flutemetamol positron emission tomography (PET) with the aim to quantify cerebral Aβ deposition. Unfortunately, due to the COVID-19 outbreak the patients' recruitment for the PET study has been interrupted several times allowing to study only few patients. PET data has been assessed with the CortexID Suite (GE Healthcare^{tm}) a fully automated, post processing software solution capable of quantifying beta amyloid brain scans and allowing the comparison with normal databases of healthy controls. Moreover, it allows to quantify amyloid accumulation in different predefined cortical and subcortical regions obtaining uptake ratio and z-score value.

Statistical analysis

Descriptive statistics of the data were carried out for each variable, with distribution histogram and box plot for the variables in the various conditions. Continuous variables were expressed as mean (±Standard Deviation [SD]) and median (range) while frequencies and percentage were calculated for categorical variables. The variables were tested for normal distribution using the Kolmogorov-Smirnov test of normality. A p-value <0.05 was considered statistically significant. The presence of significant differences in clinical variables and speech parameters in the 3 different conditions tested was calculated using the paired t-test or the Friedman test with subsequent post-hoc Wilcoxon signed rank test depending on the distribution of the continuous and categorical variables. Concerning the variables obtained from the instrumental evaluation of the movement, since the sample size was limited and since the variability within the sample was high compared to the effect due to the change in condition (see the results), the variables have been normalized to the value in the STIM-ON/MED-ON condition. This condition was chosen because it represents the daily condition of the patients. This has allowed to quantify, for each subject, the variations due to the different condition (eg STIM-OFF/MED-OFF) as a percentage of the value that the patient has in

daily life (for example: + 50% compared to the ONON condition). A one-way non-parametric ANOVA was carried out for each normalized variable, with the condition as a factor and significance at 5%. Where appropriate, paired comparisons were made (eg STIM-ON/MED-ON vs. STIM-OFF/MED-OFF) to verify which conditions were different from each other. This analysis was conducted to identify the variables most sensitive to the change in condition, among those available. The possible association between clinical scales, speech parameters and gait variables were assessed through the Spearman correlation coefficient. Statistical analyzes were performed using IBM SPSS Statistics software for Windows version 20.0 (IBM, Armonk, NY, USA) and MatLab.

Results

Description of the cohort

25 PD patients treated with bilateral STN-DBS from January 1st, 2012, to December 31st, 2018, at the Neurology Unit of the OCB were included in the study and recruited from September 2019 to October 2021. All patients underwent post-operative evaluations carried out at the LAM of the San Sebastiano Hospital in the different pharmacological and stimulation conditions previously mentioned in the methods section. Table 4 lists the main preoperative demographic and clinical characteristics of the cohort.

Table 4. Preoperative demographic and clinical characteristics

Variable	No. (%); mean [±SD]; median {range}
Sex	
Male	17 (68.00%)
Female	8 (32.00%)
Brain MRI: presence of WMH	
No	21 (84.00%)
Yes	4 (16.00%)
PD motor subtype	
PIGD	19 (76.00%)
Indeterminate	5 (20.00%)
TD	1 (4.00%)
Genetic analysis	
Negative	22 (88.00%)
Positive	3 (12.00%)
PD duration, yr	10.44 [±4.62]; 8.00 {5.00–25.00}
Age at surgery, yr	58.40 [± 5.73]; 59.00 {46.00–71.00}
Age at PD onset, yr	47.76 [± 5.63]; 47.00 {38.00-57.00}
UPDRS part I	2.04 [± 1.95]; 2.00 {.00-8.00}
UPDRS part II med-off condition	19.92 [± 5.67]; 20.00 {9.00-33.00}
UPDRS part II med-on condition	7.08 [± 4.53]; 7.00 {1.00-17.00}
UPDRS part-III med-off condition	36.64 [± 9.27]; 34.00 {25.00-62.00}
UPDRS part-III med-on condition	14.64 [± 7.38]; 13.00 {3.00-31.00}

UPDRS part IV	7.13 [± 2.40]; 7.00 {4.00-12.00}
L-dopa responsiveness, % of improvement	62.24 [±16.38]; 62.16 {34.00-93.94}
Hoehn & Yahr med-off	2.82 [± .61]; 2.50 {2.00-4.00}
Hoehn & Yahr med-on	1.98 [± .42]; .42 {1.00-2.50}
UPDRS akinesia subscore med-off	12.70 [± 3.18]; 12.00 {7.00-18.00}
UPDRS akinesia subscore med-on	4.48 [± 3.24]; 4.00 {.00-12.00}
UPDRS tremor subscore med-off	4.65 [± 4.11]; 3.00 {.00-14.00}
UPDRS tremor subscore med-on	1.26 [± 2.20]; .00 {.00-9.00}
UPDRS PIGD subscore med-off	8.13[± 3.52]; 8.00 {3.00-16.00}
UPDRS PIGD subscore med-on	2.61[± 1.78]; 2.00 {.00-7.00}
LEDD (mg)	925.10 [± 439.522]; 1045.00 {200.00–1898.00}

Abbreviations: LEDD = L-dopa equivalent daily dose; MRI = magnetic resonance imaging; PD = Parkinson disease; PIGD = dominant postural instability and gait disorder; SD = standard deviation; WMH = white matter hyperintensities of vascular origin; UPDRS = Unified Parkinson's Disease Rating Scale.

The cohort showed a prevalence of male patients (68.0%) compared to female patients (32.0%), with a predominant PIGD phenotype (76.0%) compared to indeterminate phenotypes (20.0%) and tremor phenotype (4.0%). 16.0% of the subjects showed the presence of mild chronic ischemic vascular signs at brain MRI study. Genetic investigations documented the presence of a mutation in the glucocerebrosidase (GBA) gene in 12.0% of patients (n = 3). The mean disease duration at surgery was 10.44 years with a mean age of PD onset of 47.76 years and an age at surgery of 58.40 years. The mean Levodopa responsiveness was 62.24% with a mean LEDD of 925.10 mg (SD: ± 439.522).

Table 5 lists the main demographic and clinical characteristics of the cohort at postoperative assessment.

Table 5. Demographic and clinical characteristics at post-operative evaluation	
Variable	**No. (%); mean [±SD]; median {range}**
Age, yr	63.20 [± 5.35]; 63.00 {52.00–74.00}
Disease duration, yr	15.32 [± 4.42]; 14.00 {8.00–28.00}
Follow-up duration, yr	4.88 [± 1.45]; 5.00 {3.00–7.00}
PD motor subtype PIGD Indeterminate TD	 22 (88.00%) 2 (8.00%) 1 (4.00%)
UPDRS part I	3.00 [± 2.02]; 3.00 {0.00–8.00}
UPDRS part II med-off condition	19.28 [± 5.37]; 21.00 {6.00–29.00}
UPDRS part II med-on condition	13.52 [± 5.73]; 14.00 {4.00-23.00}
UPDRS part-III stim-on/med-off	29.28 [± 12.41]; 26.00 {13.00-58.00}
UPDRS part-III stim-off/med-off	46.20 [± 12.81]; 47.00 {25.00-73.00}
UPDRS part-III stim-on/med-on	15.80 [± 9.07]; 12.00 {5.00-38.00}
UPDRS akinesia subscore stim-on/med-off	11.12 [± 5.45]; 11.00{2.00-23.00}
UPDRS akinesia subscore stim-off/med-off	17.40 [± 5.93]; 18.00 {4.00-28.00}
UPDRS akinesia subscore stim-on/med-on	6.44 [± 4.83]; 5.00 {.00-17.00}
UPDRS PIGD subscore stim-on/med-off	7.92 [± 3.06]; 8.00 {1.00-13.00}
UPDRS PIGD subscore stim-off/med-off	9.40 [± 3.60]; 9.00 {1.00-15.00}
UPDRS PIGD subscore stim-on/med-on	5.04 [± 3.44]; 5.00 {.00-12.00}
UPDRS tremor subscore stim-on/med-off	2.96 [± 2.35]; 3.00 {.00-7.00}
UPDRS tremor subscore stim-off/med-off	4.68 [± 2.86]; 4.00 {.00-10.00}
UPDRS tremor subscore stim-on/med-on	.64 [± .99]; .00 {.00-4.00}

Hoehn & Yahr stim-on/med-off	2.78 [± 0.71]; 2.50 {2.00- 5.00}
Hoehn & Yahr stim-off/med-off	3.64 [± 1.06]; 4.00 {2.00- 5.00}
Hoehn & Yahr stim-on/med-on	2.40 [± 0.50]; 2.50 {2.00- 4.00}
HIIFRM STIM-ON/MED-OFF	4.58 [± 3.02]; 4.00 {1 - 11}
HIIFRM STIM-OFF/MED-OFF	5.08 [± 3.59]; 4.00 {0 - 11}
HIIFRM STIM-ON/MED-ON	3.83 [± 2.60]; 3.50 {0 - 10}
Levodopa dose administered during the acute test, mg	144.00 [±33.29]; {100.00-250.00.}
LEDD, mg	817.36 [± 358.499]; 807.00 {118.00–1500.00}

Abbreviations: HIIFRM: Hendrich Fall Risk Model II; LEDD = L-dopa equivalent daily dose; UPDRS = Unified Parkinson's Disease Rating Scale.

The mean age at postoperative evaluation was 63.20 years, with an average disease duration of 15.32 years and an average duration of follow-up from surgery of about 5 years (4.88 years). The LEDD showed a wide variability in individual patients, with mean values of 817.36 mg (SD: ± 358.49).

Table 6 summarizes stimulation parameters at postoperative evaluation.

Table 6. Stimulation parameters at postoperative evaluation	
Stimulation parameters and settings	**Total *n*= 25** **N. (%), mean, [±SD]; median {range}**
Frequency setting High frequency Low frequency	 18 (72.00%) 7 (28.00%)
Left STN	
Single monopolar stimulation	20 (80.00%)
Bipolar stimulation	1 (4.00%)
Double monopolar stimulation	4 (16.00%)
Contact 0 active as cathode	1 (4.00%)
Contact 1 active as cathode	14 (56.00%)
Contact 2 active as cathode	13 (52.00%)
Contact 3 active as cathode	2 (8.00%)
Voltage (V)	2.704 [± 0.731]; 2.800 {0.652-3.900}
Frequency (Hz)	133.600 [± 31.73]; 130.000 {70.000-180.000}
Pulse width (usec)	64.800 [± 11.225]; 60.000 {60.000 - 90.000}
Power of stimulation	68.230 [± 31.042]; 69.680 {4.240-135.871}
Right STN	
Single monopolar stimulation	23 (92.00%)
Bipolar stimulation	0 (.00%)
Double monopolar stimulation	2 (8.00%)
Contact 0 active as cathode	2 (8.00%)
Contact 1 active as cathode	15 (60.00%)
Contact 2 active as cathode	10 (40.00%)
Contact 3 active as cathode	0 (.00%)
Voltage (V)	2.521 [± 0.775]; 2.700 {0.746-4.100}
Frequency (Hz)	126.320 [± 38.370]; 130.000 {60.000-180.000}
Pulse width (usec)	68.800 [± 17.635]; 60.000 {60.000-130.000}
Power of stimulation	57.289 [± 31.157]; 55.608 {5.281 -121.571}

Abbreviations: STN: Subthalamic Nucleus.

Concerning stimulation parameters, most of the patients were stimulated with a single monopolar setting. Only a minority of patients were programmed with different stimulation programs (i.e. bipolar stimulation or double monopolar stimulation). Contact 1 was the most used on both sides followed by contact 2, while the use of more ventral (contact 0) or dorsal (contact 3) ones was limited.

Motor changes

The Bar graph (figure 5) reports changes of motor scores and subscores in the different postoperative conditions (Friedman Test followed by post-hoc Wilcoxon signed rank test).

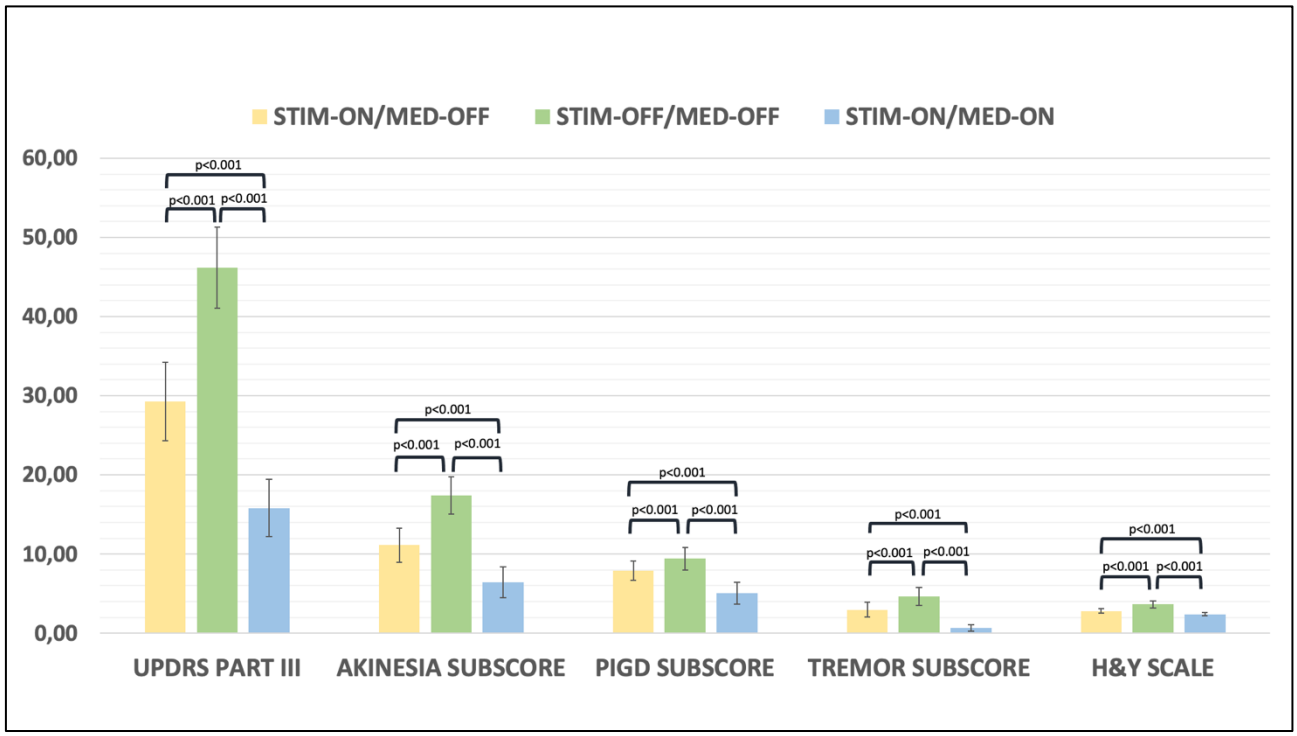


Figure 5: changes in UPDRS part III total score and subscores and Hoehn and Yahr scale in the different conditions tested. Statistical analysis confirmed a significant clinical improvement (score reduction) with both stimulation alone and stimulation plus medication.

We can appreciate that comparing the three postoperative conditions both stimulation alone (STIM-ON/MED-OFF) and the combination of stimulation plus medications (STIM-ON/MED-ON) led to a statistically significant reduction of motor score and subscores (indicative of clinical improvement) if compared with the STIM-OFF/MED-OFF condition. Furthermore, a significant reduction of all scores and subscores was found even if comparing the STIM-ON/MED-OFF and the STIM-ON/MED-ON conditions, meaning that levodopa allowed to improve the main motor features of the disease. Figure 6 shows the evolution of symptoms due to disease progression obtained comparing the preoperative MED-OFF condition with the postoperative STIM-OFF/MED-OFF condition. The different bars in the bar graph represent the percentage increase of each UPDRS score or subscore in the long-term (indicative of worsening of symptoms). At five years after surgery the motor severity of the disease quantified through the UPDRS-III worsens by less than 10 points (2/year) and overall, by 25%. We can observe that the main percentage worsening was found in akinesia (37%) and PIGD (11.56%) subscores.

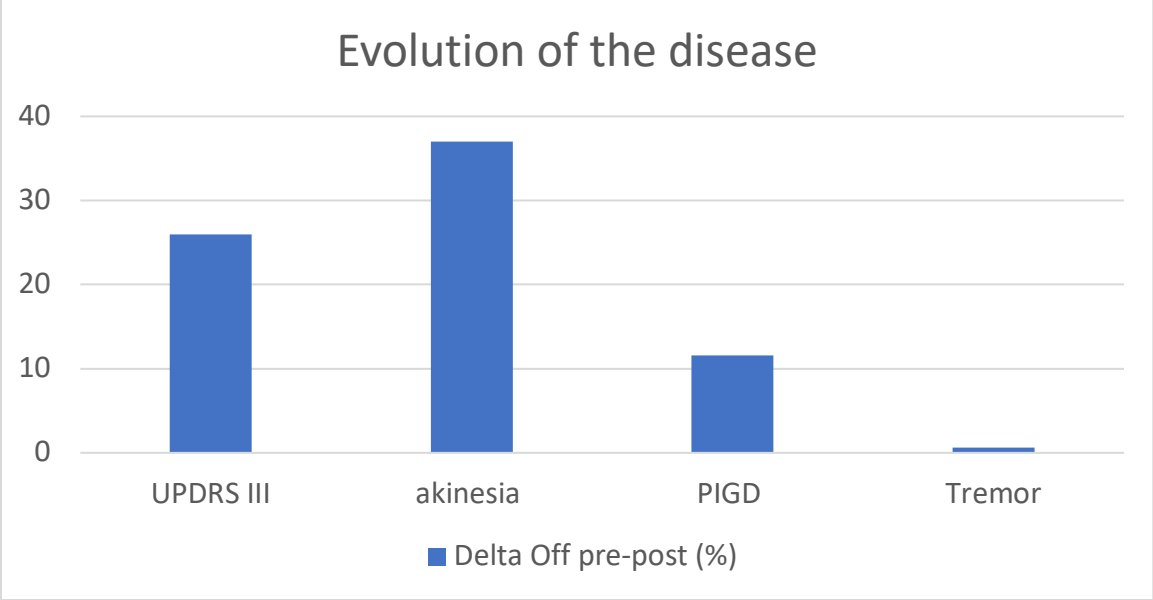


Figure 6: the bar graph shows the percentage worsening of motor symptoms due to the evolution of the disease obtained comparing the preoperative off-medication condition with the post-operative STIM-OFF/MED-OFF condition.

If we consider the acute response to treatment, even facing the evolution of the disease, the combined therapeutic response (stimulation plus medications) remains effective. Furthermore, analyzing the different UPDRS score and subscores, the combined postoperative therapeutic response was superior to preoperative levodopa administration (MED-ON condition) on UPDRS total score and tremor subscore. This response was stable on akinesia subscore and slightly lower on PIGD subscore. These results are summarized in Figure 7.

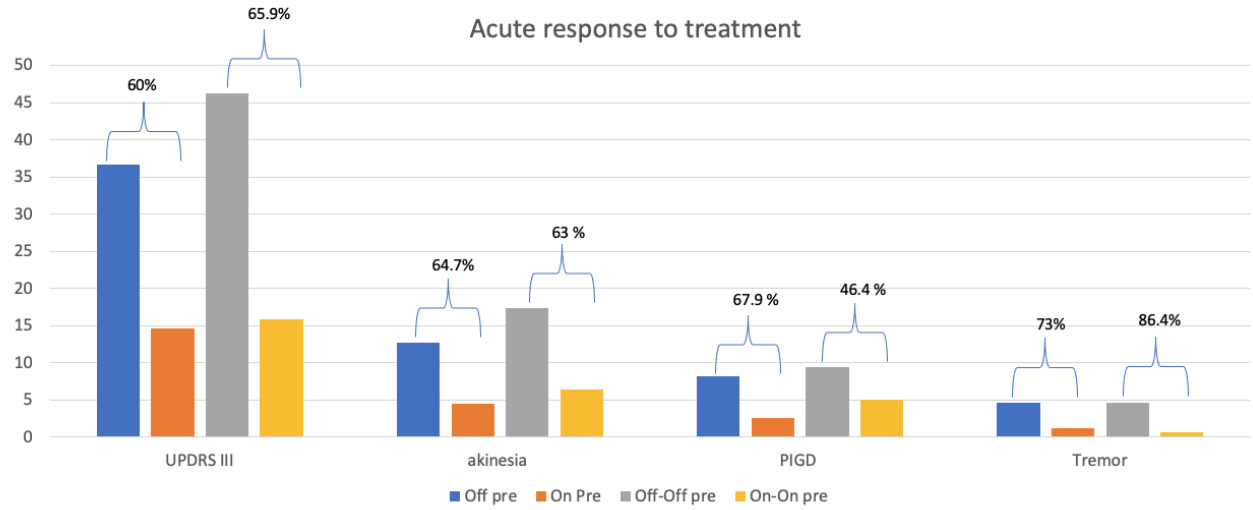


Figure 7: the bar graph shows the preoperative and postoperative acute response to treatment (only medication in the preoperative evaluation; medication plus stimulation in the postoperative assessment)

Overall, the improvement after levodopa intake remains stable and the MED-ON condition remains of good quality except for the PIGD which was significant higher (p=0.005) in the postoperative phase if compared with preoperative values (Figure 8).

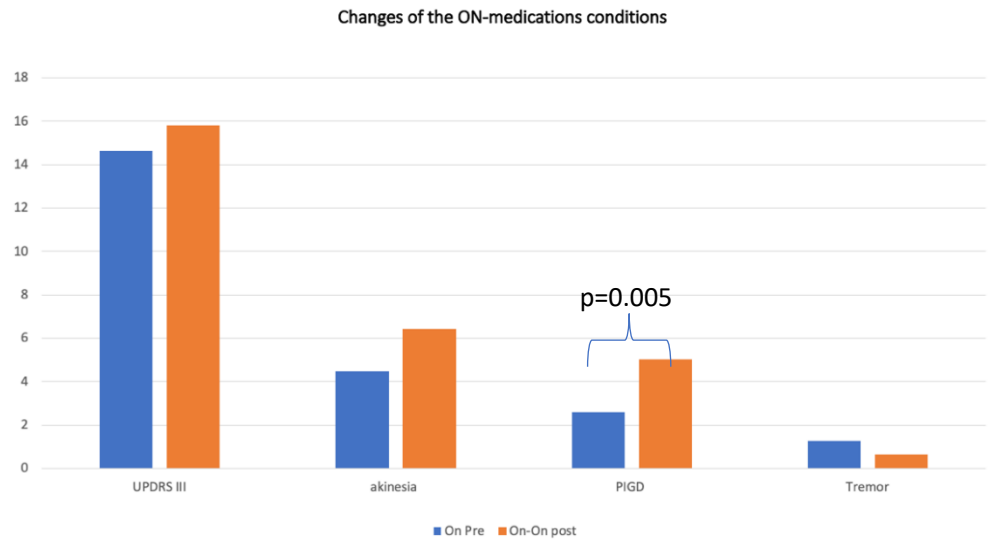


Figure 8: the bar graph shows the changes of the ON-medication conditions obtained comparing the preoperative on-medication condition with the postoperative STIM-ON/MED-ON condition.

Speech changes

Table 7 describes the different speech variables calculated in the 3 postoperative conditions.

Table 7. Post-operative speech changes			
Variable	**No. (%); mean [SD]; median {range}**		
	STIM-ON/MED-OFF	**STIM-OFF/MED-OFF**	**STIM-ON/MED-ON**
Mean intensity of spontaneous speech (dB)	65.32 [± 6.87]; 65.00 **{**52.00–81.00}	63.04 [± 4.76]; 64.00 **{**56.00–70.00}§	65.28 [± 6.02]; 67.00 **{**54.00–74.00}°
F0 SD of spontaneous speech (Hz)	35.13 [± 16.12]; 31.57 {14.98-80.24}	30.03 [± 16.90]; 29.49{7.84-92.56}	32.80 [± 12.74]; 31.42{13.87-63.47}
Maximum phonation time (MPT) (seconds)	15.29 [± 7.00]; 13.00 **{**6.20–32.00}	12.30 [± 5.11]; 12.00 **{**5.00–27.00}*	13.74 [± 5.47]; 13.00 **{**7.00–31.00}
Mean intensity of sustained phonation (dB)	68.80 [± 9.16]; 70.00 **{**52.00–88.00}	67.32 [± 7.20]; 68.00 **{**55.00–85.00}	69.20 [± 8.90]; 71.00 **{**46.00–88.00}
Jitter local of sustained phonation (%)	.80 [± .50]; .59{.25-1.87}	.98 [± .54]; .96 {.28-2.57}§	. 78[± .47]; .68 {.18-2.41}°
Shimmer local of sustained phonation (dB)	0.753 [± .345]; 0.715 **{**0.165–1.448}	0.939 [± .384]; 0.852 **{**0.310–1.603}*	0.831 [± .394]; 0.817 **{**0.168–1.662}
Noise/harmonic ratio of sustained phonation	.12 [± .10]; .08 {.01-.49}	.14 [± .10]; .11 {.01-.41}	.12 [± .123]; .07 {.01-.49}
Count rate (sill/sec)	4.28 [± 1.43]; 4.25 {2.22-7.29}	4.16 [± 1.16]; 4.25 {1.46-6.38}	4.86 [± 1.66]; 4.64 {2.22-9.44}§°
Speech intelligibility (%)	89.52 [± 15.83]; 96.00 {48.00-100.00}	84.34 [± 18.00]; 94.00 {48.00-100.00}*	84.64 [± 18.40]; 92.00 {28.00-100.00}§

Friedman Test followed by Wilcoxon signed rank test post-hoc
* p-value <0.005 with respect to the STIM-ON/MED-OFF condition
§ p-value <0.05 with respect to the STIM-ON/MED-OFF condition
° p-value <0.05 with respect to the STIM-OFF/MED-OFF condition

From the analyses carried out applying the Friedman Test followed by post-hoc Wilcoxon signed rank test, the following significant differences of speech parameters between the different conditions tested were found:

- *Word intelligibility*: the Friedman test revealed a statistically significant difference in the intelligibility of words between the three conditions. Subsequent post-hoc analysis (Wilcoxon Signed Rank Test) showed a significant reduction of intelligibility in the STIM-OFF/MED-OFF condition compared to the STIM-ON/MED-OFF condition, z = –3.500, p =. 000, with a large effect

size (r = .50) and between the STIM-ON/MED-ON and STIM-ON/MED-OFF conditions. These results suggest a significant positive effect of stimulation on intelligibility while on the contrary levodopa led to a worsening on speech intelligibility.

- *Intensity of spontaneous speech*. The results of the Wilcoxon Signed Rank Test showed a statistically significant variation of the intensity of spontaneous speech between both STIM-OFF/MED-OFF - STIM-ON/MED-OFF and STIM-ON/MED-ON - STIM-OFF/MED-OFF conditions. These results suggest a positive influence of both stimulation and levodopa on the intensity of spontaneous speech, showing a greater hypophonia in the absence of stimulation and oral treatment (STIM-OFF/MED-OFF).
- *Maximum phonation time (MPT)*. The Wilcoxon Signed Rank Test showed a statistically significant reduction of MPT in the STIM-OFF/MED-OFF condition if compared with the STIM-ON/MED-OFF condition. These results showed that in the long-term after surgery, stimulation had a positive influence on MPT, which is significantly reduced after the device is turned off.
- *Frequency perturbations during prolonged phonation (Jitter local):* the results of the Wilcoxon Signed Rank Test showed a statistically significant rise of the Jitter in the STIM-OFF/MED-OFF condition compared to the other two conditions studied, suggesting a worse voice quality in the absence of dopaminergic treatment and stimulation.
- *Amplitude perturbations during prolonged phonation (Shimmer local)*: the results of the Wilcoxon Signed Rank Test show significantly higher values in the STIM-OFF/MED-OFF condition compared to the STIM-ON/MED-OFF condition, suggesting a beneficial effects of stimulation on amplitude perturbations during prolonged phonation.
- *Speech rate (sill/sec)*: the Wilcoxon Signed Rank Test showed a statistically significant increase in speech rate in the STIM-ON/MED-ON condition with respect to the STIM-OFF/MED-OFF and

STIM-ON/MED-OFF conditions, highlighting the possible role of dopaminergic therapy in increasing speech rate.

iTUG changes

Figure 9 shows the mean values and SD for the iTUG variables in the different conditions.

Descriptives

	Task	Durata complessiva iTUG	Sit2St_durata	St2Sit_durata	Turn1_durata	Turn2_durata	Andata_durata	Ritorno_durata
Mean	ONON	13.46	1.09	2.28	2.78	2.32	3.18	2.52
	DUALTASK	16.51	1.17	2.38	3.35	2.57	4.07	3.78
	STIMONMEDOFF	17.19	1.15	2.25	3.59	2.55	4.21	3.61
	OFFOFF	18.84	1.52	2.85	4.12	3.02	4.46	3.63
Standard deviation	ONON	3.97	0.48	0.81	0.79	0.76	0.95	0.94
	DUALTASK	4.45	0.66	0.90	0.67	0.84	1.22	1.50
	STIMONMEDOFF	7.48	0.40	1.21	1.61	0.95	2.20	2.23
	OFFOFF	6.11	0.60	0.95	1.89	0.80	1.50	1.47

Fig. 9 iTUG descriptive values in the different conditions tested in the postoperative assessment

Changes of iTUG variables in the different conditions

Table 8 summarizes the results of the non-parametric ANOVA (Kruskal-Wallis test) on the selected iTUG variables, normalized with respect to the value in the STIM-ON/MED-ON condition. The p-value indicates the probability of error in rejecting the null hypothesis of equivalence between the different conditions.

Tab. 8 Kruskal-Wallis analysis of iTUG variables

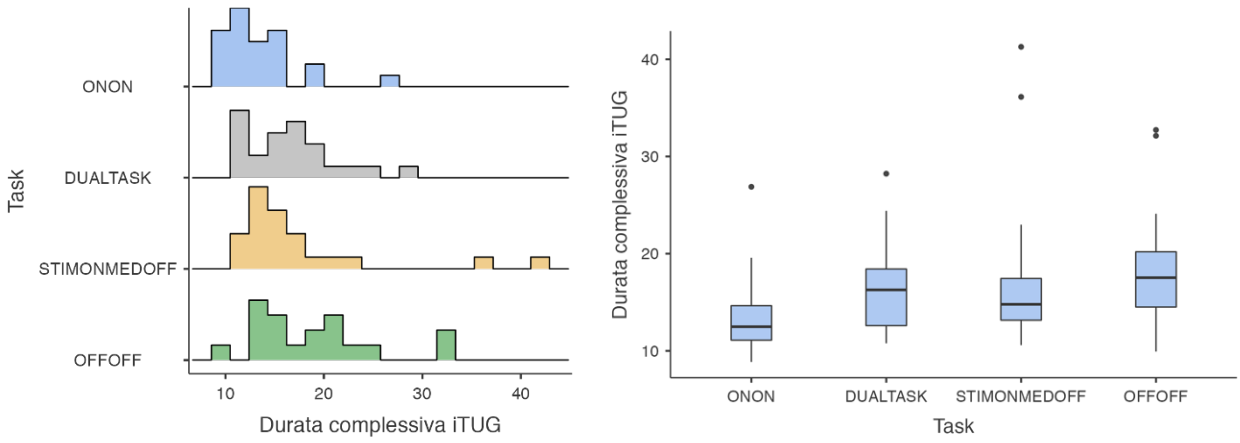
	χ^2	df	p
iTUG duration	52.62	3	< .001
Sit2St duration	27.75	3	< .001
Sit2St vertical acceleration of the trunk	21.93	3	< .001
St2Sit duration	9.55	3	0.023
St2Sit vertical acceleration of the trunk	12.64	3	0.005
Turn1 duration	31.62	3	< .001
Turn1 maximum speed of trunk rotation on the vertical axis	33.05	3	< .001
Turn 2 duration	21.93	3	< .001
Turn2 maximum speed of trunk rotation on the vertical axis	23.57	3	< .001

Tab. 8 Kruskal-Wallis analysis of iTUG variables

	χ^2	df	p
Forward walking phase, duration	38.87	3	< .001
Forward walking phase, vertical acceleration of the trunk	25.62	3	< .001
Walking back phase, duration	34.66	3	< .001
Walking back phase, vertical acceleration of the trunk	16.29	3	< .001

In all cases, the null hypothesis was rejected meaning that the variables assessed were significantly different in at least two conditions. Below the post-hoc analyses of the duration of the different phases obtained comparing the postoperative conditions in pairs (e.g., STIM-ON/MED-ON vs. STIM-OFF/MED-OFF). A <0.05 p value was considered significant. The post-hoc analyses are showed below together with the corresponding bar graphs and box plots relating to the investigated variable. The histogram shows the distribution of the variable within the sample in the different conditions tested. The box plot allows to observe the trend of the variable in the different conditions. Bar graphs and box plots show the raw values of the variables, with the time expressed in seconds, the acceleration expressed in m/s^2 and the angular velocities expressed in degrees/s.

<u>iTug overall duration</u>

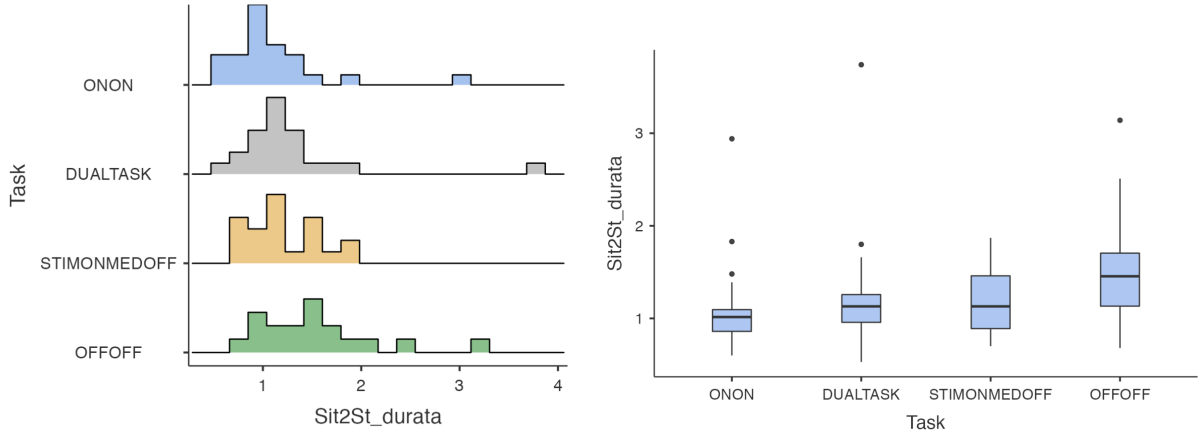


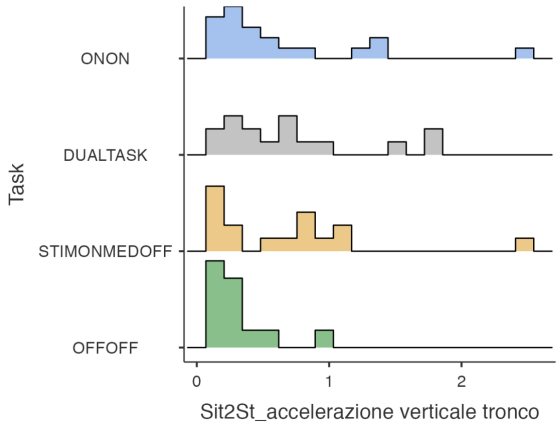
Pairwise comparisons - Durata complessiva iTUG

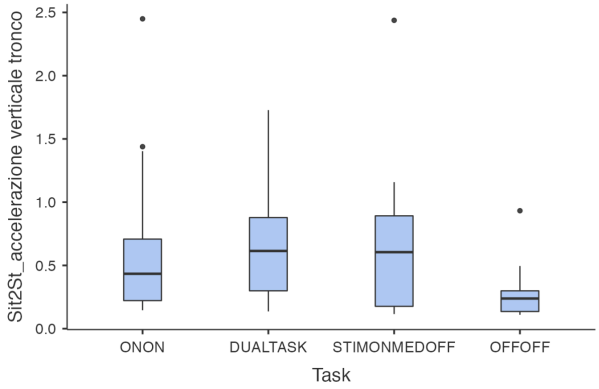
		W	p
ONON	DUALTASK	8.98	<.001
ONON	STIMONMEDOFF	7.37	<.001
ONON	OFFOFF	8.61	<.001
DUALTASK	STIMONMEDOFF	-1.13	0.855
DUALTASK	OFFOFF	3.79	0.037
STIMONMEDOFF	OFFOFF	3.59	0.055

We found a statistically significant reduction in iTUG duration in the STIM-ON/MED-ON condition compared to the STIM-OFF/MED-OFF and STIM-ON/MED-OFF and between the STIM-ON/MED-OFF and STIM-OFF/MED-OFF conditions, meaning that both stimulation and levodopa improved gait. It is interesting to observe that the dual task condition (performed in the STIM-ON/MED-ON condition) significantly increased iTUG duration if compared to the STIM-ON/MED-ON condition, meaning that cognitively complex tasks led to worsening of gait.

Sit to Stand phase (Sit2St)





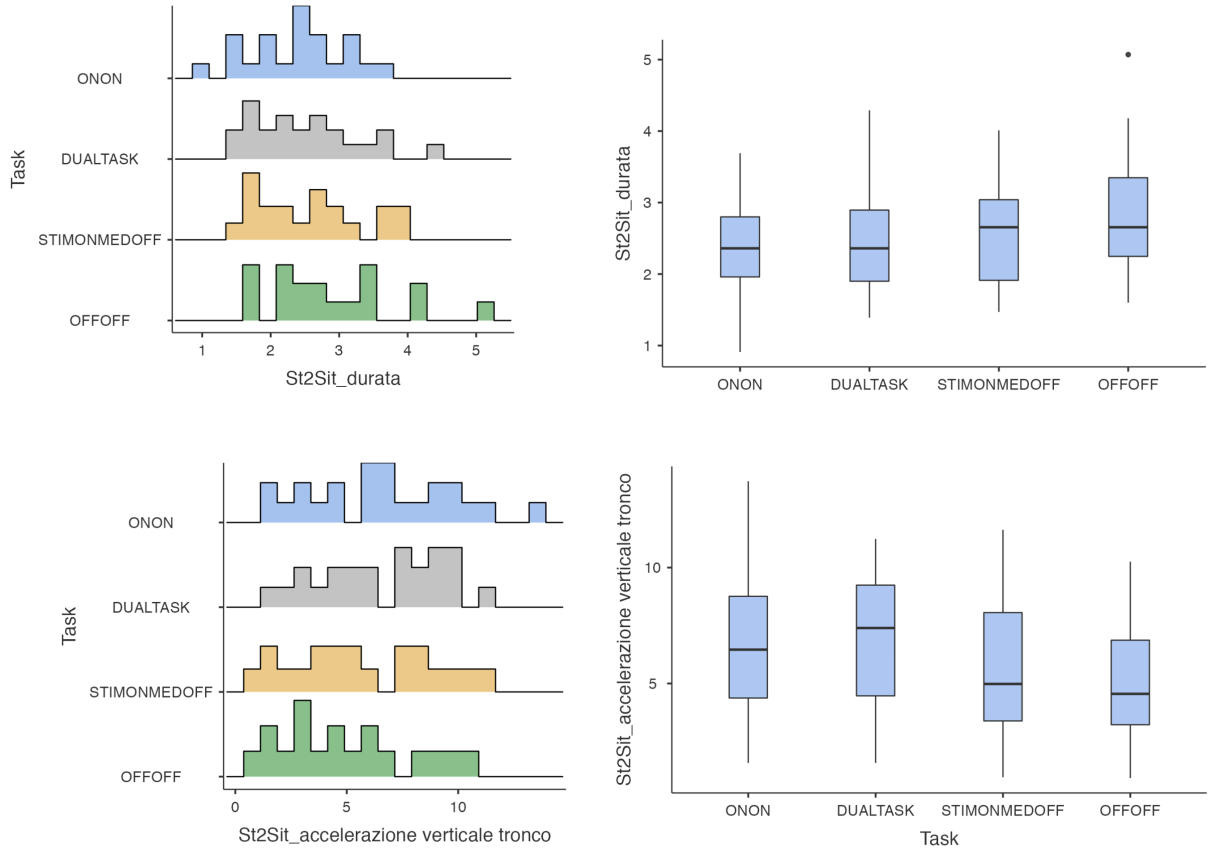


Pairwise comparisons - Sit2St_durata

		W	p
ONON	DUALTASK	0.00	1.000
ONON	STIMONMEDOFF	4.27	0.014
ONON	OFFOFF	6.69	<.001
DUALTASK	STIMONMEDOFF	2.95	0.158
DUALTASK	OFFOFF	5.75	<.001
STIMONMEDOFF	OFFOFF	4.42	0.010

The Sit to stand phase highlighted the importance of stimulation that allowed to reduce the duration of the phase. On the contrary, the cognitive task did not significantly influence the duration of the Sit to stand phase if compared with the STIM-ON/MED-ON condition. This could depend on complexity of the motor task. Indeed, when the motor task becomes very complex the attention is less distracted from the cognitive task, re-establishing a more physiological hierarchy ("posture first") (Bloem et al., 2006).

Stand to Sit phase (St2Sit)

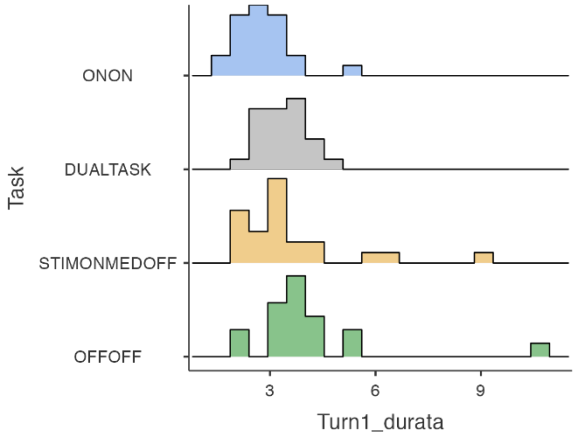


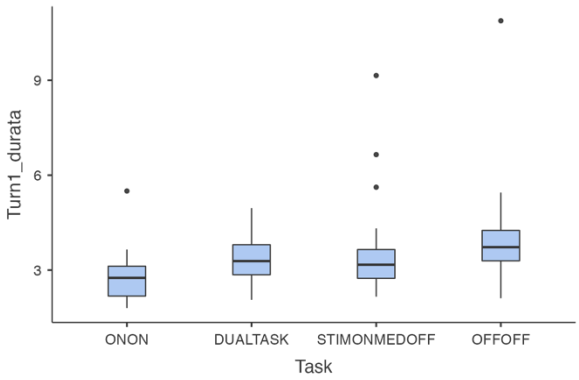
Pairwise comparisons - St2Sit_durata

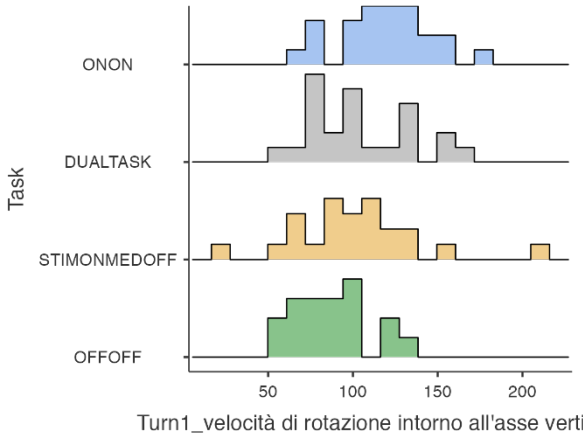
		W	p
ONON	DUALTASK	0.00	1.000
ONON	STIMONMEDOFF	1.57	0.685
ONON	OFFOFF	5.74	<.001
DUALTASK	STIMONMEDOFF	0.02	1.000
DUALTASK	OFFOFF	2.70	0.225
STIMONMEDOFF	OFFOFF	2.38	0.334

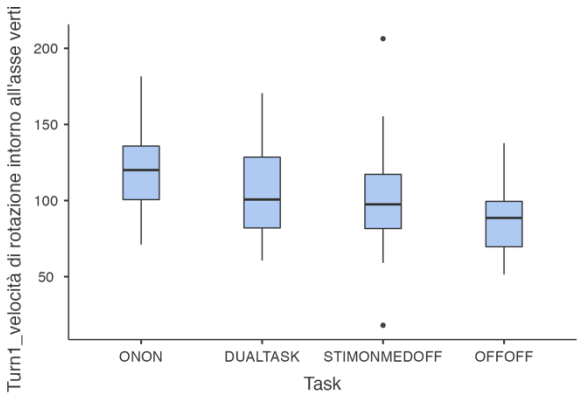
The Stand to Sit phase has a similar trend compared to Sit to Stand phase. However, the effect of stimulation is less evident probably because the sitting phase is less driven by visual cues that are particularly relevant for gait control in PD (Azulay et al., 2006). This could have reduced the differences between the conditions tested in this phase.

First Turn (to go back)







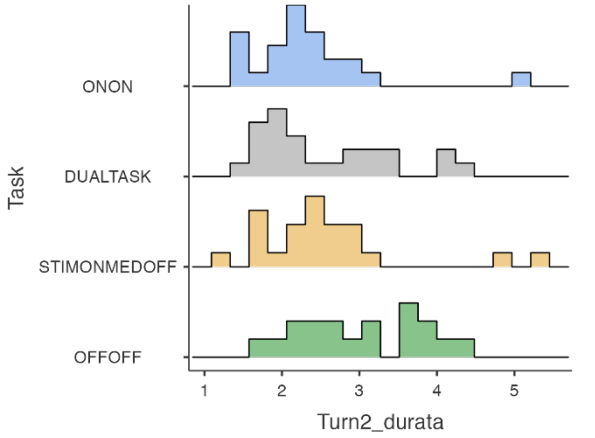


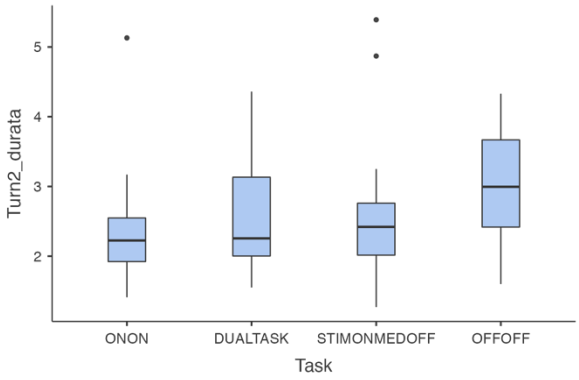
Pairwise comparisons - Turn1_durata

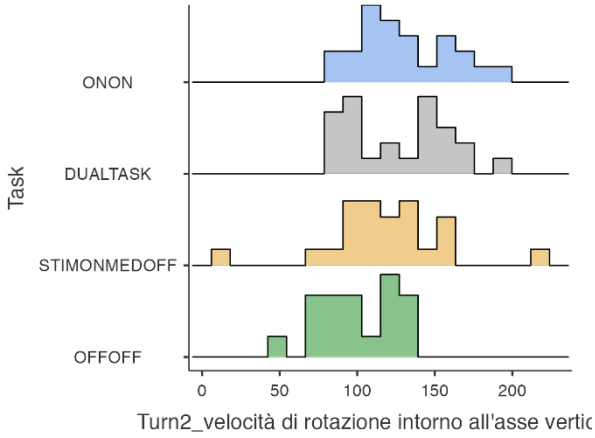
		W	p
ONON	DUALTASK	6.73	<.001
ONON	STIMONMEDOFF	4.70	0.005
ONON	OFFOFF	7.65	<.001
DUALTASK	STIMONMEDOFF	-0.48	0.986
DUALTASK	OFFOFF	3.20	0.107
STIMONMEDOFF	OFFOFF	2.71	0.221

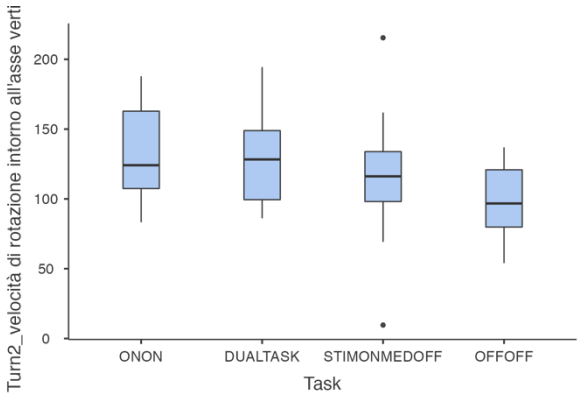
In the first turn phase it appears that the effects of stimulation are less relevant while levodopa significantly reduce the duration of the phase. Moreover, the cognitive task significantly influenced the duration of this phase if compared with the STIM-ON/MED-ON condition.

Second Turn (to sit down)







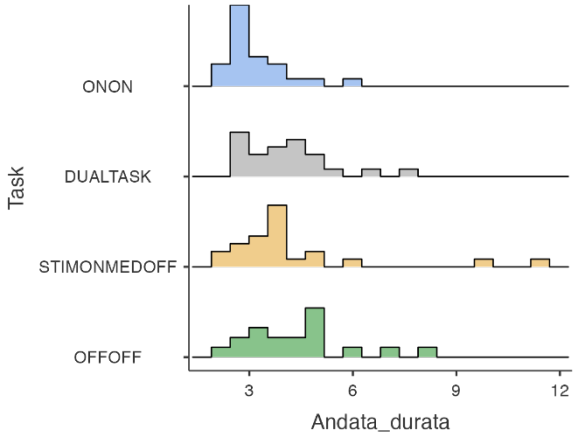


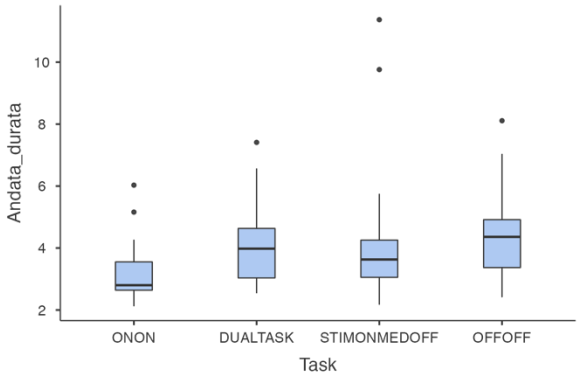
Pairwise comparisons - Turn2_durata

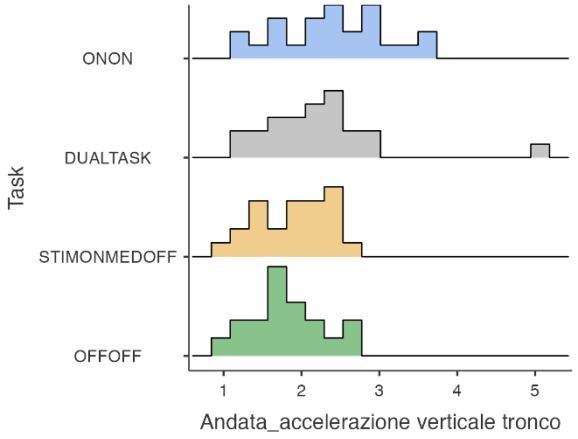
		W	p
ONON	DUALTASK	4.15	0.017
ONON	STIMONMEDOFF	1.94	0.518
ONON	OFFOFF	7.28	<.001
DUALTASK	STIMONMEDOFF	-1.38	0.761
DUALTASK	OFFOFF	3.33	0.087
STIMONMEDOFF	OFFOFF	3.85	0.033

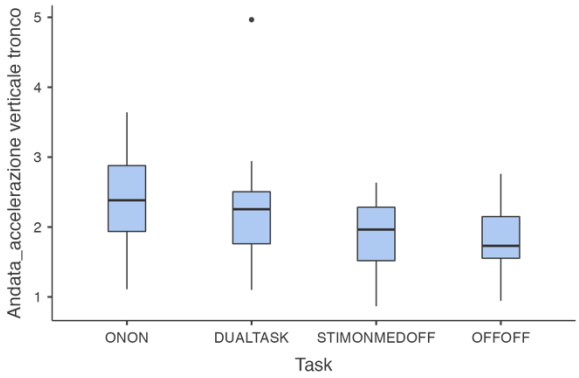
In the second turn phase, the impact of stimulation is relevant while the effects of levodopa are less relevant.

Walking forward phase







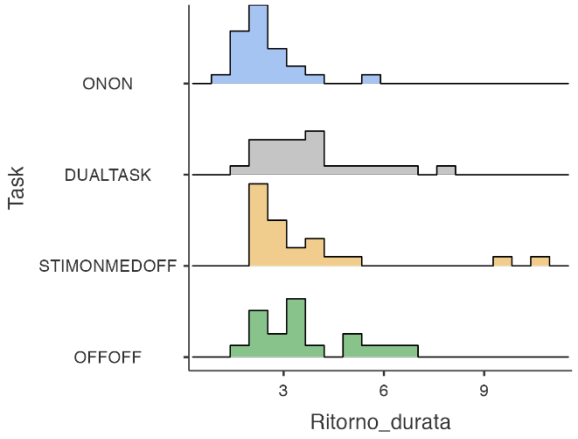


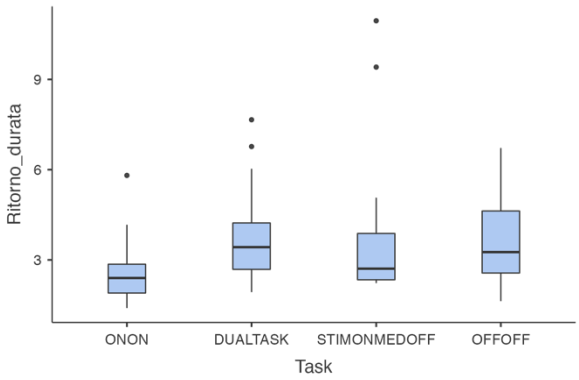
Pairwise comparisons - Andata_durata

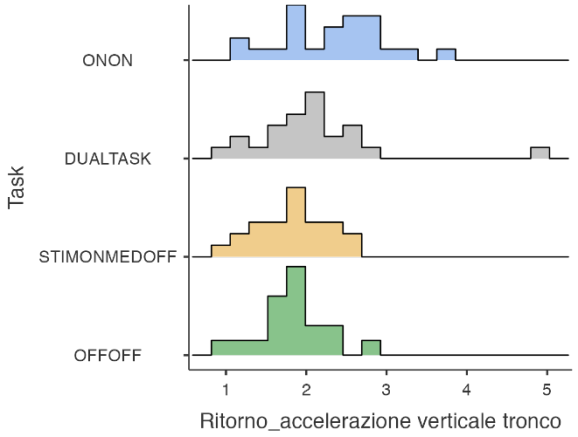
		W	p
ONON	DUALTASK	7.48	<.001
ONON	STIMONMEDOFF	6.59	<.001
ONON	OFFOFF	7.65	<.001
DUALTASK	STIMONMEDOFF	-1.40	0.755
DUALTASK	OFFOFF	2.28	0.371
STIMONMEDOFF	OFFOFF	2.97	0.153

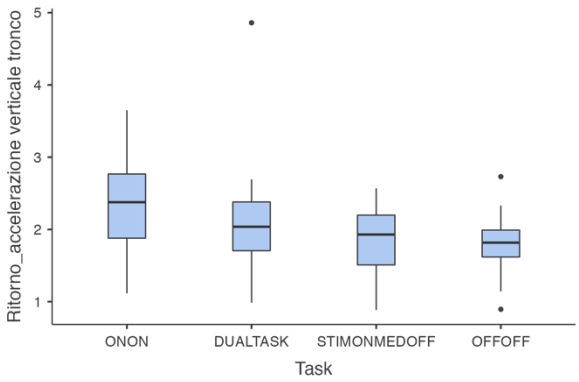
The walking forward phase highlighted the importance of levodopa that allowed to reduce the phase duration. On the contrary, it seems that stimulation has a less relevant effect. Moreover, the cognitive task significantly influenced the duration of the phase.

Walking back phase









Pairwise comparisons - Ritorno_durata

		W	p
ONON	DUALTASK	8.23	<.001
ONON	STIMONMEDOFF	4.27	0.014
ONON	OFFOFF	8.25	<.001
DUALTASK	STIMONMEDOFF	-1.52	0.705
DUALTASK	OFFOFF	0.00	1.000
STIMONMEDOFF	OFFOFF	1.67	0.638

The walking back phase is similar to the forward walking. Indeed, even in this case levodopa significantly reduce the phase duration while it seems that stimulation has a less relevant impact.

Association between iTUG variables and clinical scales

Table 9 shows the non-parametric correlation between the UPDRS-III and HIIFRM clinical scales and the iTUG parameters, measured in the STIM-ON/MED-ON condition. A moderate correlation was observed between the iTUG variables and the UPDRS-III. For the HIIFRM scale, relating to the risk of falling, correlations were found only with the rotation speed during Turn.

Correlation Matrix	UPDRS STIM-ON/MED-ON	Hendrich STIM-ON/MED-ON
UPDRS PART III STIMON/MEDON	—	
Hendrich STIMON/MEDON	0.51 *	—
iTUG duration	0.58 **	0.37
Sit2St duration	0.32	0.31
Sit2St trunk vertical acceleration	-0.53 **	-0.21
St2Sit duration	0.52 **	0.37
Turn1 duration	0.47 *	0.28
Turn1 speed of rotation of the trunk on vertical axis	-0.48 *	-0.46 *
Turn2 duration	0.60 **	0.33
Turn2 speed of rotation of the trunk on vertical axis	-0.54 **	-0.45 *
Gait forward duration	0.47 *	0.29
Gait forward trunk vertical acceleration	-0.57 **	-0.32
Return gait duration	0.47 *	0.25
Return gait trunk vertical acceleration	-0.65 ***	-0.39

Table 9: correlations between iTUG parameters, UPDRS-III and HIIFRM scales in the STIM-ON/MED-ON condition.

Figure 10 shows the scatterplot between UPDRS-III scores in STIM-ON/MED-ON condition and the overall duration of the iTUG.

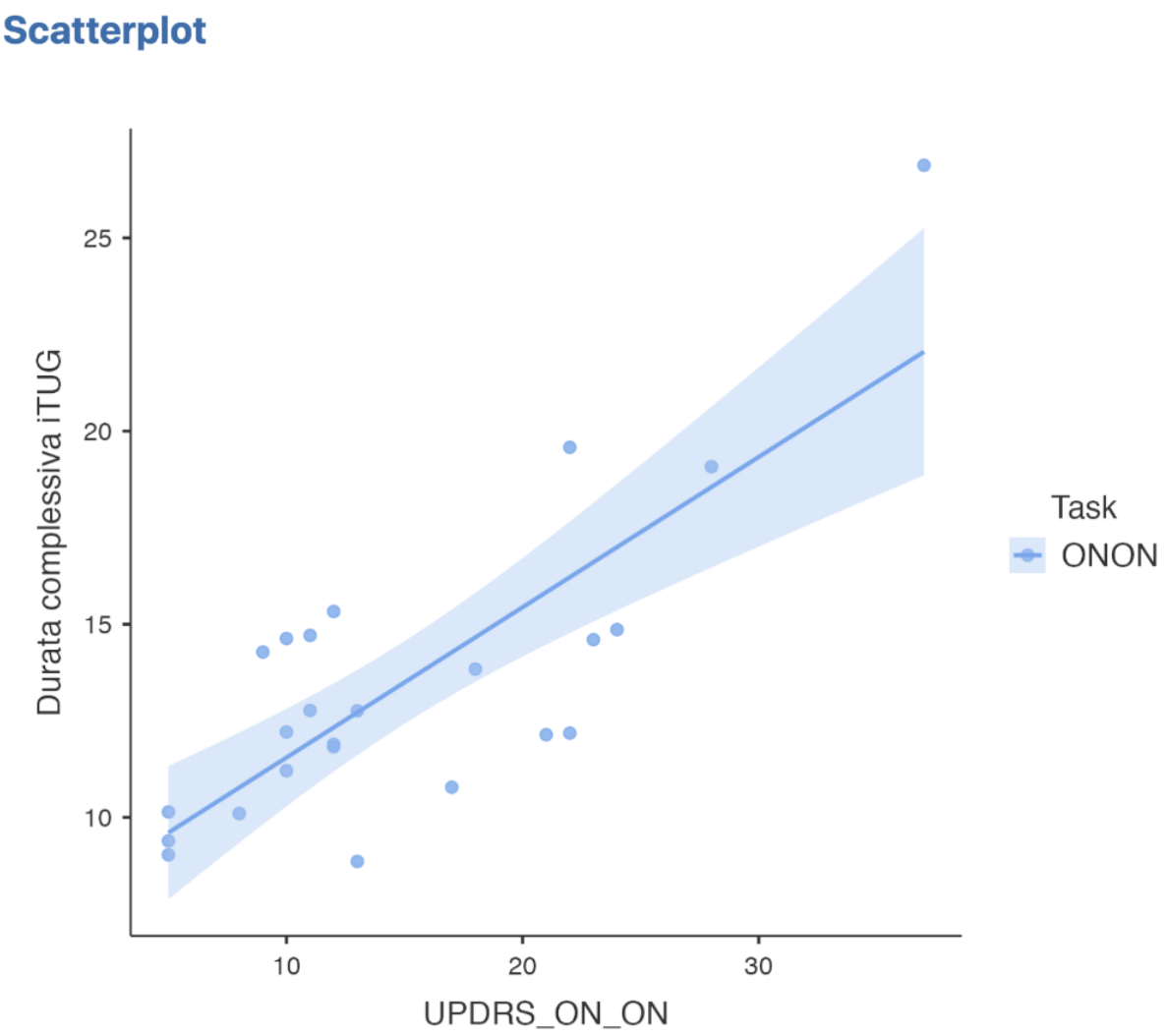


Figure 10: scatterplot between STIM-ON/MED-ON UPDRS-III scores and iTUG duration.

The correlations were even more significant if we consider the variables measured during the dual task condition in which the patient was always under the effects of both stimulation and levodopa (Table 10).

Correlation Matrix	UPDRS STIM-ON/MED-ON	Hendrich STIM-ON/MED-ON
UPDRS PART III STIMON/MEDON	—	
Hendrich STIMON/MEDON	0.51 *	—
iTUG duration	0.64 ***	0.35
Sit2St duration	0.51 *	0.28
Sit2St trunk vertical acceleration	-0.65 ***	-0.41 *
St2Sit duration	0.46 *	0.53 **
Turn1 duration	0.50 *	0.15
Turn1 speed of rotation of the trunk on vertical axis	-0.49 *	-0.43 *
Turn2 duration	0.69 ***	0.43 *
Turn2 speed of rotation of the trunk on vertical axis	-0.48 *	-0.28
Gait forward duration	0.62 **	0.53 **
Gait forward trunk vertical acceleration	-0.63 **	-0.45 *
Return gait duration	0.50 *	0.23
Return gait trunk vertical acceleration	-0.63 **	-0.42 *

Table 10: correlations between iTUG parameters, UPDRS-III and HIIFRM scales in the dual task condition.

Cognitive changes

Table 11 summarizes the changes of cognitive variables between preoperative and long-term evaluation.

Table. 9 Variations of cognitive variables over time			
Variable	**No. (%); mean [SD]; median {range}**		
	Preoperative	**Post-operative**	**P value**
Phonemic fluency	34.47 [± 7.26]; 34.22 {18.29–46.90}	27.66 [± 10.57]; 27.85 {9.75–57.18}	.002
Spatial perception localization of numbers	8.55 [± 1.13]; 9.00 {7.00–10.00}	7.81 [± 8.00]; 8.00 {3.00–10.00}	.131
1947 colored Raven's progressive matrices	28.78 [± 4.34]; 30.24 {21.00–35.61}	24.93 [± 5.79]; 24.59 {16.84–40.52}	.003
Stroop test "time"	20.07 [± 11.45]; 17.70 {8.00–47.00}	27.51 [± 19.60]; 25.12 {6.50–91.50}	.040
Stroop test "errors"	.51 [± .65]; .37 {.00–2.25}	2.70 [± 4.77]; .12 {.00–15.75}	.078
Trail making test part B	101.77 [± 55.76]; 85.50 {33.00–274.00}	168.64 [± 131.24]; 120.00 {27.00–531.00}	.020
BVMT total re-enactment	N/A	10.89 [± 6.24]; 11.00 {1.00–24.00}	N/A

A significant worsening in different cognitive variables was found in particular in phonemic fluency; 1947 colored Raven's progressive matrices; Stroop test "time" and Trail making test part B. We included only these variables because they represent different cognitive domains that are reported to be altered in PD.

[18F] Flutemetamol Pet Study

Due to the COVID-19 outbreak the patients' recruitment for the PET study has been interrupted several times allowing to study only a small subgroup of patients. Indeed, only 10 patients underwent to [18F] FLUTEMETAMOL PET study not allowing to perform statistical analysis in this subgroup of subjects. However, it is interesting to note that four of the ten patients studied had a positive PET study showing cerebral amyloid accumulation in different cortical and subcortical regions. Figure 11 shows one of the positive PET study found in our cohort analyzed with CortexID Suite (GE Healthcare[tm]) software while figure 12 shows a negative PET study.

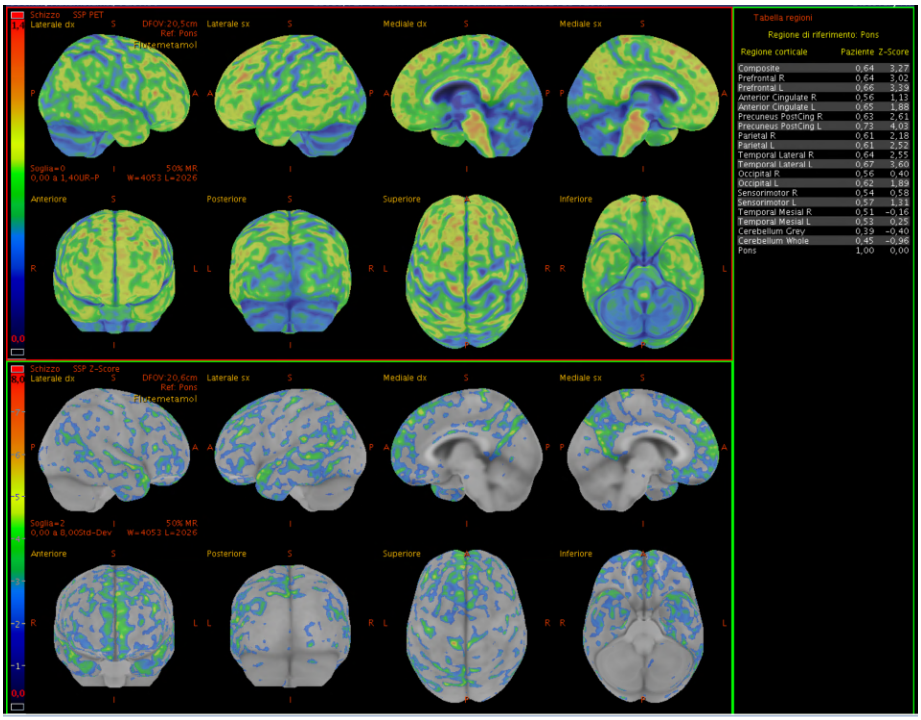


Figure 11: a positive PET study showing cerebral amyloid accumulation assessed with CortexID Suite (GE Healthcare[tm]) software.

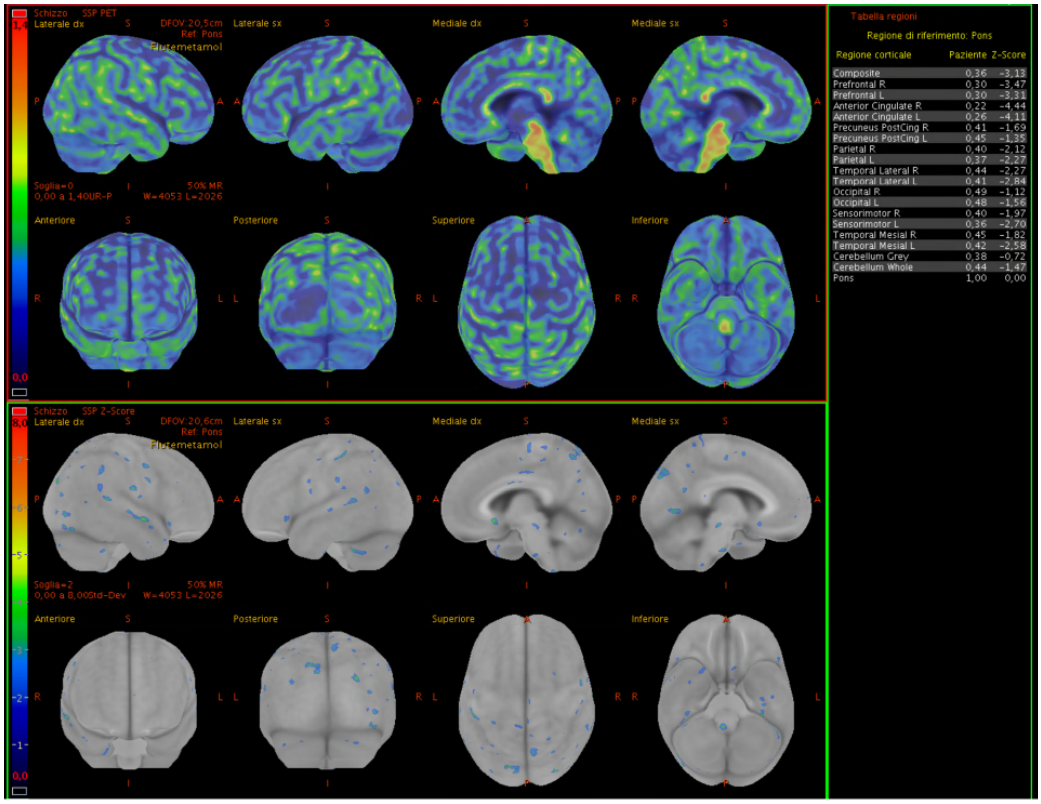


Figure 12: a negative PET study that did not show cerebral amyloid accumulation.

Correlations between speech and gait parameters

One of the main objectives of this project was to find the presence of correlations between speech and gait parameters. Considering that most variables were not normally distributed we used the Spearman's rank correlation coefficient. The correlations analyses were performed including only speech and gait variables for one of the single conditions tested (STIM-ON/MED-OFF; STIM-OFF/MED-OFF; STIM-ON/MED-ON). We found the following correlations in the STIM-OFF/MED-OFF condition:

Condition	Speech variable	iTug variable	Rho	p
STIM-OFF/MED-OFF	Intensity of spontaneous speech (Db)	Walk2_accRMS_x	0,48	0,0456

- Direct correlation between the mean intensity of spontaneous speech and the anterior-posterior acceleration of the trunk during the return gait meaning that patients who spoke loud had a greater acceleration during the return gait of the iTUG.

Concerning the STIM-ON/MED-OFF condition we found the following correlations:

Condition	Speech variable	iTug variable	Rho	p
STIM-ON/MED-OFF	Maximum phonation time (sec)	Walk1_accRMS_mod	0,46	0,0268
STIM-ON/MED-OFF	Speech rate (sill/sec)	Turn2_dur_turn	-0,48	0,0206

- Direct correlation between the MPT and the acceleration of the trunk during the walking forward phase: those who have a better aerodynamic efficiency of the vocal tract indicative of airflow insufficiency had a higher acceleration during the forward walk.
- Inverse correlation between speech rate (sill/sec) and the duration of the second turn meaning that patients with higher speech rate takes less time to turn around before sitting down.

Concerning the STIM-ON/MED-ON condition we found the following correlations:

Condition	Speech variable	iTug variable	Rho	p
STIM-ON/MED-ON	Intensity of spontaneous speech (Db)	Walk1_accRMS_x	0,45	0,0272
STIM-ON/MED-ON	Intensity of spontaneous speech (Db)	Walk2_accRMS_x	0,44	0,031
STIM-ON/MED-ON	Jitter local of sustained phonation (%)	Sit2St_peak_abs_acc_AP	-0,51	0,011
STIM-ON/MED-ON	Jitter local of sustained phonation (%)	Sit2St_peak_abs_acc_V	-0,49	0,0156
STIM-ON/MED-ON	Jitter local of sustained phonation (%)	Walk1_accRMS_mod	-0,54	0,0073
STIM-ON/MED-ON	Jitter local of sustained phonation (%)	Walk2_accRMS_mod	-0,47	0,0223
STIM-ON/MED-ON	Shimmer local of sustained phonation (dB)	Sit2St_peak_abs_acc_AP	-0,62	0,0015
STIM-ON/MED-ON	Shimmer local of sustained phonation (dB)	Sit2St_peak_abs_acc_V	-0,43	0,0353
STIM-ON/MED-ON	Shimmer local of sustained phonation (dB)	Walk1_accRMS_x	-0,43	0,0377
STIM-ON/MED-ON	Shimmer local of sustained phonation (dB)	Walk2_accRMS_x	-0,43	0,0353
STIM-ON/MED-ON	Speech rate (sill/sec)	Turn1_peak_omV	0,43	0,0383
STIM-ON/MED-ON	Speech rate (sill/sec)	Walk2_dur_wal	-0,47	0,0218
STIM-ON/MED-ON	Speech rate (sill/sec)	Turn2_dur_turn	-0,5	0,012

- Direct correlation between the mean intensity of spontaneous speech and acceleration of the trunk during the walking forward and return walking phases meaning that those who have a greater intensity of speech also have a greater acceleration during walk.
- Inverse correlation between the Jitter and Shimmer of sustained phonation and different gait parameters i.e. the anterior-posterior and vertical acceleration of the trunk during the Sit to stand phase and the trunk acceleration during both walking forward and return walking phases meaning that patients with higher Jitter and Shimmer values (indicative of a poorer voice quality) had reduction performances during the sit to stand and gait phases.
- Direct correlation between the count rate (sill/sec) and the angular velocity of the first turn meaning that patients with higher speech rate rotate faster during the turning phase.
- Inverse correlation between the count rate (sill/sec) and the duration of the return walking

and second turn phases meaning that patients with higher speech rate takes less time to go back and to turn around before sitting down.

It is important to underline that in the abovementioned correlations, the rho coefficient was almost always of the order of 0.5, which is considered a large effect size.

Discussion

Motor features

Data from our cohort confirmed that bilateral STN-DBS is effective on PD motor symptoms, quantified with UPDRS part-III total score and subscores, in the long-term after surgery. This finding is not surprising, indeed numerous studies, with longer follow-up, have already been published confirming the long-term efficacy of STN-DBS on motor symptoms (Fasano, et al., 2010; Zibetti, et al., 2011; Aviles-Olmos, et al., 2014; Castrioto et al. 2010; Cavallieri et al. 2021; Bove et al., 2021).

It is interesting to note that the acute motor improvement seen in our cohort also involved the PIGD subscore. However, it is well known that axial symptoms deteriorate in the long-term after surgery if compared with preoperative values (Deuschl, Paschen, & Witt, 2013). Previous studies have found that PIGD subscore in the STIM-ON/MED-OFF condition may worsen over time until reaching or exceeding pre-operative values in the MED-OFF condition eight years after surgery (Deuschl, Paschen, & Witt, 2013). This has been confirmed also in our cohort with a shorter follow-up. In addition, we found a significant worsening of motor symptoms due to disease progression in the long-term (obtained comparing the preoperative MED-OFF with the postoperative STIM-OFF/MED-OFF condition) particularly relevant for akinesia and PIGD subscores. This is in line with the collective body of evidence showing that with disease duration, the prevalence of TD subtype designation decreases and that of PIGD increases, indicating a long-term different worsening of cardinal symptoms more evident for axial symptoms (Eisinger et al., 2017; Josephs et al., 2006; Selikhova et al., 2009). Moreover, the long-term worsening was greater if comparing the preoperative and postoperative ON-medication conditions highlighting that the effect of levodopa on axial symptoms decreased over time.

Cognitive changes

We found a significant long-term postoperative worsening of different cognitive variables in our cohort. This worsening was particularly relevant for phonemic fluency; 1947 colored Raven's progressive matrices; Stroop test “time” and Trail making test part B. Short- and long-term data about cognition after STN-DBS are still controversial (Bove et al., 2020). Some authors have suggested a direct negative impact of STN-DBS in cognition, whereas others have reported positive effects (Bove et al., 2020; Saint-Cyr et al., 2000; Daniele et al., 2003). The incidence of dementia in patients treated with bilateral STN-DBS is largely variable among different centers and there is a lack of long-term studies with large populations and control group. In the short-term three large, randomized, studies have measured general cognitive function (usually the Mattis dementia score) after surgery comparing it with a medically treated control group, showing that cognitive function remained unchanged up to 2-year after surgery (Williams et al., 2010; Deuschl et al., 2013). These results suggest that cognitive alterations after surgery seem to reflect disease progression rather than a side-effect of the intervention (Deuschl et al., 2013). On the contrary, specific, and focal neuropsychological deficits have been described consistently following STN-DBS. Indeed, a postoperative decline of phonological and semantic verbal fluency tasks, detectable few months after surgery has been reported (Ardouin et al., 1999; Daniele et al., 2003) and was found also in our cohort. This decline gradually worsened in the long term, up to 8 years (Contarino et al., 2007; Fasano et al., 2010). However, the available literature data about STN-DBS and dementia in the long-term provides inconclusive and variable results. The few available long-term studies lack of control group and report a dementia prevalence from 5% to 53% (Bove et al., 2020). A recent paper from the Grenoble group found that in patients with PD with longstanding STN-DBS, dementia prevalence and incidence were not higher than those reported in the general PD population (Bove et al., 2020). They claimed that except for few patients with perioperative cerebral hemorrhage, STN-DBS is

cognitively safe, and did not provide dementia risk factors in addition to those reported for PD itself (Bove et al., 2020).

Instrumental evaluation of movement

In this study, through the iTUG test we performed a clinical-instrumental long-term evaluation of gait in advanced PD patients treated with bilateral STN-DBS. Most of the patients were able to perform the test in all the conditions assessed, confirming the feasibility of the protocol applied. The analyses were conducted in different stimulation and medication conditions allowing to obtain relevant information about the effects of stimulation and medication on gait.

The effects of the condition, from STIM-ON/MED-ON to STIM-OFF/MED-OFF, can be clearly appreciated, being characterized by an increase in the duration and reduction in the acceleration and rotation of the trunk. Both stimulation and medication reduced the total duration of the iTUG and most of its different phases meaning that even in the long-term after surgery both stimulation and levodopa can acutely improve gait. However, concerning stimulation, differences in specific phases of the test may be appreciated. Indeed STN-DBS alone reduced total iTUG duration, the Sit to Stand and the second turn phases while it has a less relevant effect on Stand to Sit, first turn, forward walking and walking back phases duration. A previous metanalysis showed that STN-DBS has a beneficial effect on walking speed; however, outcomes varied substantially from large to negligible improvements (Roper et al., 2016). Other studies have reported non-significant or conflicting results (Pötter-Neger and Volkmann, 2013; St George et al., 2014; Collomb-Clerc and Welter, 2015), possibly related to methodological limitations and differences in gait evaluation (i.e., questionnaires, non-instrumented TUG, inertial sensors) (Navratilova et al., 2020). On the contrary, another study reported an improvement in step length with bilateral STN-DBS (Navratilova et al., 2020; Peterson et al., 2020). Anyway, the progressive declines in gait and balance remain one of the major unmet needs in the long-term after surgery (Hurt et al., 2020). In our cohort the Sit to Stand

and the second turn phases were the more sensitive to the beneficial effects of stimulation. Meanwhile, dopaminergic replacement therapy improved almost all gait parameters confirming that levodopa has a strong beneficial effect on walking.

PD patients have difficulties in initiating sit-to-stand tasks, showing slower angular displacements and smaller normalized hip flexion torque than healthy controls (Mak et al., 2003). Moreover, in PD, the anticipatory postural control during the sit-to-stand task may be affected with a reduced preparatory hip flexion and decreased forward displacement of the body center of mass (COM) prior to lift-off of the buttocks from the chair (Inkster et al., 2004). PD in on-medication condition and healthy subjects have the same sit-to-stand duration, while PD patients in the OFF-medication condition have a longer duration of the task (Inkster et al., 2004; Mak et al., 2005). This finding was also confirmed by Weiss et al. who found that the Sit to stand duration was not significantly different between PD patients in the ON medication condition and the control group composed by age matched health subjects (Weiss et al., 2010). However, two different parameters such as the range sit-to-stand (amplitude range during the sit-to-stand time interval) and the jerk sit-to-stand (slope during sit-to-stand time interval) were significantly lower in PD patients (Weiss et al., 2010). This may be related to axial bradykinesia (Weiss et al., 2010; Fatmehsari et al., 2011).

The ability to turn during gait is impaired in PD and has been related to falls and FOG (Weiss et al., 2019). Patients with PD exhibit poorer balance and impaired segmental coordination while turning during walking, compared to healthy older adults. Moreover, they approach turns with a slower step and take slower and wider turns, with narrower and increased number of steps, and significantly decreased rotation of the trunk compared to healthy older adults (Weiss et al., 2019). However, data about the effects of STN-DBS on the turn-to-sit phase are lacking in the literature. In our cohort, stimulation allowed to reduce the duration of this phase leading to a more physiological turn before the sit-to-stand phase probably through its effects on axial bradykinesia and rigidity.

We found a moderate correlation between the first turn phase of the iTUG and the HIIFRM scale. This indicates that patients who perform worse on the turn were at greater risk of falling. For these subjects it could be indicated to set up physiotherapy in order to improve the performance in the circular walk.

We may conclude that the iTUG represents a sensitive test to the patient's condition in particular the overall duration. In addition, the sub-phases of the iTUG are affected in different ways by the different conditions. The presence of the elevation/sitting gestures and the turns give sensitivity to the test. Globally our results underline that in the long-term after surgery STN-DBS may improve gait in the acute setting together with dopamine replacement therapy which has been shown to have a strong effect on walking.

Speech assessment

Literature data show heterogeneous and still debated results about the effects of STN-DBS on different speech parameters (Brabenec et al., 2017). In addition, almost all the published studies were limited to a short-term follow-up (1-year) (Brabenec et al., 2017; Tripoliti et al., 2011). The only currently available data about the long-term effects of STN-DBS on speech came from studies that have only quantify speech with clinical disease rating scales or isolated intelligibility measures (Aviles Olmos et al., 2014; Bove et al., 2021; Fasano et al., 2008). Regarding post-operative speech evaluation, we found a statistically significant improvement of intelligibility in the STIM-ON/MED-OFF condition compared to the STIM-OFF/MED-OFF condition, suggesting a positive effect of stimulation on intelligibility. This result differs from the study by Tripoliti et al. which followed PD patients with and without STN-DBS for 1 year showing a deterioration in the perceptual assessment of intelligibility in the stimulation group (Tripoliti et al., 2011). Similarly, Tsuboi et al. reported that STN-DBS improved some phonatory aspects including voice tremor and speech intensity, while on

the contrary it negatively affects the overall intelligibility in most patients (Tsuboi et al. 2015). Some authors have pointed out that stimulation may positively influence the movement of joint structures, including mouth, jaw and tongue improving intelligibility (Tanaka et al., 2016). In accordance with this view, different studies have reported a positive effect of DBS on intelligibility, which decreased following levodopa administration, in line with what was shown in our cohort (Gentil et al., 1999; Pinto et al., 2004; Pinto et al., 2014).

In addition, we found a statistically significant variation in the intensity of spontaneous speech between the STIM-OFF/MED-OFF condition and the STIM-ON/MED-OFF. This finding has been also reported in previous studies with a short-term follow-up (D'Alatri et al., 2008; Dromey et al., 2000; Tripoliti et al., 2011; Tsuboi et al., al., 2015). The beneficial effects of STN-DBS on speech intensity have been linked to the improvement of hypokinesia and rigidity of language-related organs (Skodda et al., 2014; Tsuboi et al., 2015) which represent the pathophysiological bases of hypokinetic dysarthria. This type of dysarthria is characterized by hypophonia, monotony, hypoarticulation of consonants and inappropriate silences (Rusz et al. 2015). Furthermore, a statistically significant improvement of the MPT in the STIM-ON/MED-OFF condition compared to the STIM-OFF/MED-OFF was found in our cohort. This result confirmed that stimulation, even five years after surgery, can positively influence the MPT. This is in line with previous studies that showed a significant efficacy of stimulation in increasing phonatory duration (Sung Jee Eun et al., 2004). The reduction of the MPT in PD can be due to underlying laryngeal dysfunction and reduced respiratory volume mainly related to rigidity and hypo-bradykinesia of laryngeal and diaphragmatic muscles (Rusz et al. 2015). Stimulation, as well as dopaminergic therapy, acting on the cardinal symptoms of the disease, may favour a longer phonatory duration and a better pneumophonic coordination (Murdoch et al. 2011).

Moreover, stimulation improved jitter and shimmer of sustained phonation, markers of voice quality. On the contrary, the impact of dopaminergic therapy was different on these two parameters. Indeed, the administration of levodopa led to a worsening of shimmer values in the STIM-ON/MED-ON condition compared to the STIM-ON/MED-OFF condition. This data has been correlated in previous studies to the simultaneous presence of axial levodopa-induced dyskinesias (LID), which could negatively affect laryngeal performance during prolonged phonation (Cavallieri et al. 2021). On the contrary, the impact of dopaminergic therapy on the frequency perturbations calculated with Jitter Local was lower, as previously reported (Cavallieri et al. 2021). A recent study that assessed the effects of STN-DBS on voice quality in a cohort of 10 Parkinsonian patients with a 1-year follow-up showed that STN-DBS led to a significant reduction in jitter values (Behroozmand et al., 2019). This confirmed the selective involvement of the subthalamic nucleus in the regulation of speech production and motor control mechanisms and the positive effect of STN-DBS on these functions (Behroozmand et al., 2019). This beneficial effect could be due to better control over the laryngeal muscles involved in voice regulation (Behroozmand et al., 2019).

We also found a statistically significant increase of speech rate in the STIM-ON/MED-ON with respect to STIM-OFF/MED-OFF and STIM-ON/MED-OFF conditions. This finding suggests that levodopa may increase speech rate. Numerous literature data have not found a significant effect of dopaminergic therapy on speech rate (Skodda et al. 2008) but rather on increasing its variability (De Letter et al., 2006). From this perspective, a synergistic effect of the stimulation can be hypothesized which, in addition to dopamine replacement therapy, could have influenced speech rate. It should be kept in mind that a higher speech rate is not always associated with a better intelligibility and quality of speech, as it can lead to the development of oral festination, characterized by an uncontrolled increase in the speed of speech and reduced intelligibility (Moreau et al. 2010).

Correlations between speech and gait parameters

One of the main objectives of this thesis was to find the presence of correlations between speech and gait parameters. Many studies have analyzed axial symptoms in PD patients with an instrumental approach focusing only on gait and postural alterations or speech disturbances. The very few studies that have instrumentally assessed the whole spectrum of axial symptoms in PD have showed the presence of some similarities between spatial-temporal gait and speech parameters (Ricciardi et al., 2016). Only one study has compared the effects of stimulation and dopamine replacement therapy on speech and gait parameters but with a short-term follow-up, confirming that STN-DBS and levodopa increased patients' walking velocity by increasing the step length (Cantiniaux et al. 2010). On the contrary they had no effect on speech velocity (Cantiniaux et al. 2010). As opposed to this study we found that levodopa plus stimulation significantly increase speech rate. Furthermore, we found different correlations between speech and gait parameters. Firstly, the mean intensity of spontaneous speech directly correlates with acceleration of the trunk during gait in both STIM-OFF/MED-OFF and STIM-ON/MED-ON conditions.

In hypokinetic dysarthria speech movements and their timing are generally accurate but individual movements are slowed with a reduced range and force. Furthermore, excessive muscle tone led to resistance to movements in all directions leading to reduction of the movements' range (Duffy., 2013). The reduced range of movement may be the most significant underlying neuromuscular deficit in hypokinetic dysarthria (Duffy., 2013). Reduced loudness can be the presenting and most prominent and debilitating speech feature in dysarthric PD patients (Duffy., 2013). Respiratory and phonatory insufficiency, characterized by reduced vital lung capacity, chest wall rigidity, and glottal incompetence, are the presumed cause of reduced loudness (Lansford et al., 2011). Overall muscle rigidity, abnormal neural drive to speech musculature and abnormal sensorimotor gating has been

hypothesized to cause the respiratory/phonatory insufficiency observed in patients with PD (Lansford et al., 2011). During walking, the gravitational potential energy of the center of body mass is exchanged for forward kinetic energy. Thus, forward motion is mainly caused by AP and V movements in the sagittal plane. ML movement plays only a small role in external work (Sekine et al., 2013). In this setting Root Mean Square (RMS) constitutes a statistical measure of the magnitude of acceleration. Trunk accelerometric gait analysis is a reliable method, which can be used to evaluate acceleration RMS values in three orthogonal directions and calculate average step lengths, stride lengths and cadence. This may be used to detect even minor changes in motor control during walking due to training or other interventions in healthy controls (Henriksen et al., 2004). Indeed, trunk accelerations are considered as measures of balance control during walking and standing (Moe-Nilssen et a., 1998; Moe-Nilssen et al., 2002; Mayagoitia et al., 2002) and can differentiated healthy young subjects from older adults (Vervoort et al., 2016). Interestingly a recent study showed that the Lee Silverman Voice Therapy – BIG (LSVT-BIG®), developed as an exercise for speech improvement in individuals with PD, significantly improved the TUG times also increasing stride length (Flood et al., 2020). In addition, temporal features of the gait cycle were significantly lower following LSVT-BIG® therapy (Flood et al., 2020). Our results move in this direction confirming the possible correlation between speech intensity and gait parameters.

In the STIM-ON/MED-ON condition we found an inverse correlation between the Jitter and Shimmer of sustained phonation and different gait parameters such as the vertical acceleration of the trunk during the Sit to stand phase and the trunk acceleration during both walking forward and return walking phases. This means that patients with higher Jitter and Shimmer values (indicative of a poorer voice quality) had reduction performances during the sit to stand and gait phases. It is well known that the Sit-to-stand phase is abnormal in PD due to disease-related inadequate lower extremity forces, especially at the hip, bradykinesia, and impaired anticipatory postural control,

resulting in a failure to bring the COM adequately forward over the feet prior to the lift-off of the buttocks from the chair (Inkster and Eng 2004; Dibilio et al. 2017).

Moreover, Sit-to-stand acceleration has been identified as a strong indicator of frailty suggesting that this additional kinematic parameter is highly discriminatory for good motor performance (Clement et al., 2008). A reduction in acceleration may represent an impairment of strength, power and motor strategy during the sit to stand phase (De Melo Borges et al., 2015; Williams et al., 2018). Higher levels of jitter (frequency instability of the vocal folds) and shimmer (amplitude instability of the vocal folds), and NHR are associated with harsh voice and poorer voice quality (Rusz et al., 2015). It has been recently reported that in the ON-state the severity and location of LID strongly correlated with Shimmer emphasizing that they negatively influenced speech quality (Cavallieri et al., 2020). In addition, a previous study found a positive correlation between postural instability and phonation instability parameters after levodopa intake meaning that these voice parameters are related to gait and balance symptoms in PD patients (Midi et al., 2008). Our results move in this direction emphasizing the relationship between gait and acoustic parameters related to speech quality. In this setting we may assume that these parameters could be markers of axial impairment less responsive to medication and stimulation. Meanwhile LID could also play a role influencing both gait parameters and voice quality (Bloem et al. 2004; Cavallieri et al., 2020). Finally, we found that patients with a higher speech rate performed well the turning and walking phases in the STIM-ON/MED-OFF and STIM-ON/MED-ON conditions. This is in line with the study of Cantiniaux et al. who reported a correlation between speech and walking velocity (Cantiniaux et al. 2010). Turning velocity has shown to be related with PD progression and to correlate with bradykinesia and gait/posture subscores (Zampieri et al. 2010). Previous studies on severe PD have shown that turning becomes a major problem the advanced phase of the disease (Huxham et al., 2008; Crenna et al., 2007) and is related to falls' frequency (Stack et al., 1999; Zampieri et al., 2010). Literature

data have shown an age-related reduction of articulation rate probably caused by an age-related reduction of elasticity of the respiration system or increased pulmonal comorbidity in the elderly (Weismer et al., 1984; Skodda et al., 2008). In PD rigidity and bradykinesia might affect the movements of the lips and tongue leading to a lower speech rate (Midi et al., 2008). One study did not find correlation between the speech and movement repetitive tasks (finger taps, hand movement, rapid alternating movements and tap heel on ground) which are the measurements of sequential repetition (Midi et al., 2008). Another study found no relationship between speech rate and UPDRS or disease duration in PD patients, group, although one would anticipate a negative influence of rigorous muscle resistance on speech breathing (Skodda et al., 2008). However, in the same study speech rate was influenced by disease duration suggesting other pathophysiological mechanisms than pure motor dysfunction as explanation for impaired articulatory self-timing and control of speech velocity (Skodda et al., 2008). We found an association between speech rate and gait velocity confirming the findings by Cantiniaux et al (Cantiniaux et al. 2010). Considering that this correlation was found in the STIM-ON/MED-OFF and STIM-ON/MED-ON conditions we may assumed that as for Jitter and Shimmer even speech rate and specific gait parameters may be influenced in the same way by levodopa and stimulation. However, it should be kept in mind that a faster speech does not mean a more intelligible and comprehensible speech. Therefore, while the effects on walking parameters correlate from a functional point of view with a better motor performance, the functional results related to speech can be quite heterogeneous.

Study limits

This study has several limitations. Firstly, the sample size (n=25) is limited reducing the statistical power of our results. In addition, the instrumental analysis of movement was not performed in the preoperative phase. Therefore, this did not allow to compare the postoperative data with the preoperative ones. In addition, the follow-up duration after surgery was variable between the patients included so we cannot exclude that it may have influenced our findings. Furthermore, PET study was performed only in a subgroup of patients, limiting its inclusion in statistical analyses. Concerning the iTUG assessment, we evaluated the turn phase without differentiating with respect to the rotation side to perform the change of direction. The patients then took the turn on the side they preferred. In future studies it might be interesting to evaluate the differences in the direction of the turn to understand which phases put the patient most at risk. Furthermore, a univariate analysis of variable correlations was conducted for this study in line with the limited sample size (n=25). However, in order to estimate the extent of these correlations, when the set of variables analyzed is mutually related, a multivariate approach would be more appropriate. Future prospective studies based on larger samples could address this topic.

CONCLUSIONS

This thesis highlighted that bilateral STN-DBS has a positive acute influence on speech, gait, and motor features, including axial ones, in the long-term after surgery. The instrumented gait analysis has allowed to obtain relevant information to support clinical evaluation. The comparison between the different conditions allowed to assess the changes of simple functional activities, such as linear walking, turning, lifting, sitting and speaking. This protocol may represent a valid tool for providing objective data about the effects of stimulation and dopamine replacement therapy on motor, speech and gait parameters after surgery. The use of inertial sensors in a simple administration test such as the iTUG proved to be very useful and feasible in clinical practice allowing to quantify changes in different conditions. Globally our results underline that in the long-term after surgery STN-DBS may improve gait in the acute setting together with the dopamine replacement therapy, that has been shown to have a strong beneficial effect on walking. Moreover, this thesis has allowed to investigate the long-term effects of STN-DBS on speech in patients with advanced PD. To our knowledge this is the first study that assessed the long-term effects of STN-DBS on speech with a standardized acoustic-perceptual approach. The main novelty brought by our study appears to be the possible positive effect of STN-DBS on intelligibility in the long-term after surgery. Moreover, five years after STN-DBS, stimulation can positively influence speech duration, speech intensity and overall voice quality. Different correlations between speech and gait parameters were also found. This may allow to better understand the common pathophysiological basis of these alterations and to develop a more specific and tailored rehabilitation approach after surgery. One of the main objectives for the future will be to increase the sample size adding data relating to the PET in order to test the possible relationship between axial symptoms β-amyloid accumulation and the cholinergic PD phenotype. In conclusion, this study, albeit with all the reported limitations, has

highlighted that the effects of STN-DBS on specific motor, speech and gait parameters may be maintained in the long-term follow-up after surgery.

REFERENCES

Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. 2003 Mar;60(3):387-92.

Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson's disease. Brain Pathol. 2010 May;20(3):633-9.

Aldridge, D., Theodoros, D., Angwin, A., & Vogel, A. Speech outcomes in Parkinson's disease after subthalamic nucleus deep brain stimulation: A systematic review. Parkinsonism Relat Disord. 2016 Dec;33:3-11.

Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. Sleep Med. 2014 Aug;15(8):860-73.

Alves G, Pedersen KF, Bloem BR, Blennow K, Zetterberg H, Borm GF, Dalaker TO, Beyer MK, Aarsland D, Andreasson U, Lange J, Tysnes OB, Zivadinov R, Larsen JP. Cerebrospinal fluid amyloid-β and phenotypic heterogeneity in de novo Parkinson's disease. J Neurol Neurosurg Psychiatry. 2013 May;84(5):537-43.

Ardouin C, Pillon B, Peiffer E, Bejjani P, Limousin P, Damier P, Arnulf I, Benabid AL, Agid Y, Pollak P. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann Neurol. 1999 Aug;46(2):217-23.

Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. JAMA. 2020 Feb

Aviles-Olmos, I., Kefalopoulou, Z., Tripoliti, E., Candelario, J., Akram, H., Martinez-Torres, I., et al. Long-term outcome of subthalamic nucleus deep brain stimulation for Parkinson's disease using an MRI-guided and MRI-verified approach. J Neurol Neurosurg Psychiatry. 2014 Dec;85(12):1419-25.

Azulay JP, Mesure S, Blin O. Influence of visual cues on gait in Parkinson's disease: contribution to attention or sensory dependence? J Neurol Sci. 2006 Oct 25;248(1-2):192-5.

Baker KK, Ramig LO, Johnson AB, Freed CR. Preliminary voice and speech analysis following fetal dopamine transplants in 5 individuals with Parkinson disease. J Speech Lang Hear Res. 1997 Jun;40(3):615-26.

Bakker, M., Esselink, R., Munneke, M., Limousin-Dowsey, P., Speelman, H., & Bloem, B. Effects of stereotactic neurosurgery on postural instability and gait in Parkinson's disease. Mov Disord. 2004 Sep;19(9):1092-9.

Balasubramanian S, Melendez-Calderon A, Roby-Brami A, Burdet E. On the analysis of movement smoothness. J Neuroeng Rehabil. 2015 Dec 9;12:112.

Behroozmand R, Johari K, Kelley RM, Kapnoula EC, Narayanan NS, Greenlee JDW. Effect of deep brain stimulation on vocal motor control mechanisms in Parkinson's disease. Parkinsonism Relat Disord. 2019 Jun;63:46-53.

Benke T, Hohenstein C, Poewe W, Butterworth B. Repetitive speech phenomena in Parkinson’s disease. J Neurol Neurosurg Psychiatry. 2000 Sep;69(3):319–24.

Benton A.L. et al. (1992) “Test di Giudizio di Orientamento di Linee: Manuale” vers. It. Ferracuti S. et al., Giunti O.S. – Firenze

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM, Deuschl G; Tremor Task Force of the International Parkinson and Movement Disorder Society. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018 Jan;33(1):75-87.

BIRKMAYER W, HORNYKIEWICZ O. [The L-3,4-dioxyphenylalanine (DOPA)-effect in Parkinson-akinesia]. Wien Klin Wochenschr. 1961 Nov 10;73:787-8.

Biundo R, Weis L, Antonini A. Cognitive decline in Parkinson's disease: the complex picture. NPJ Parkinsons Dis. 2016 Sep 1;2:16018.

Bloem BR, Grimbergen YA, Cramer M, Willemsen M, Zwinderman AH. Prospective assessment of falls in Parkinson's disease. J Neurol. 2001 Nov;248(11):950-8.

Bloem BR, Grimbergen YA, van Dijk JG, Munneke M. The "posture second" strategy: a review of wrong priorities in Parkinson's disease. J Neurol Sci. 2006 Oct 25;248(1-2):196-204.

Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. Mov Disord. 2004 Aug;19(8):871-84. doi: 10.1002/mds.20115. PMID: 15300651.

Bloem BR, Marinus J, Almeida Q, Dibble L, Nieuwboer A, Post B, Ruzicka E, Goetz C, Stebbins G, Martinez-Martin P, Schrag A; Movement Disorders Society Rating Scales Committee. Measurement instruments to assess posture, gait, and balance in Parkinson's disease: Critique and recommendations. Mov Disord. 2016 Sep;31(9):1342-55.

Bloem BRBK. Gait and balance in basal ganglia disorders. In: Bronstein AMTB, Nutt JG, Woollacott MH, editors. Clinical Disorders of Balance, Posture and Gait. London: Arnold; 2004. pp. 173–206.

Boersma P, Weenink D. Praat: Doing Phonetics by Computer [Computer Program]. Version 5.3.51. (2013)

Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med. 2003 Jul;4(4):281-4.

Bohnen NI, Frey KA, Studenski S, Kotagal V, Koeppe RA, Constantine GM, Scott PJ, Albin RL, Müller ML. Extra-nigral pathological conditions are common in Parkinson's disease with freezing of gait: an in vivo positron emission tomography study. Mov Disord. 2014 Aug;29(9):1118-24.

Bohnen NI, Frey KA, Studenski S, Kotagal V, Koeppe RA, Scott PJ, Albin RL, Müller ML. Gait speed in Parkinson disease correlates with cholinergic degeneration. Neurology. 2013 Oct 29;81(18):1611-6.

Bonuccelli U, Del Dotto P, Rascol O. Role of dopamine receptor agonists in the treatment of early Parkinson's disease. Parkinsonism Relat Disord. 2009 Dec;15 Suppl 4:S44-53.

Boonstra TA, van der Kooij H, Munneke M, Bloem BR. Gait disorders and balance disturbances in Parkinson's disease: clinical update and pathophysiology. Curr Opin Neurol. 2008 Aug;21(4):461-71.

Bouça-Machado R, Jalles C, Guerreiro D, Pona-Ferreira F, Branco D, Guerreiro T, Matias R, Ferreira JJ. Gait Kinematic Parameters in Parkinson's Disease: A Systematic Review. J Parkinsons Dis. 2020;10(3):843-853.

Bove F, Fraix V, Cavallieri F, Schmitt E, Lhommée E, Bichon A, Meoni S, Pélissier P, Kistner A, Chevrier E, Ardouin C, Limousin P, Krack P, Benabid AL, Chabardès S, Seigneuret E, Castrioto A, Moro E. Dementia and subthalamic deep brain stimulation in Parkinson disease: A long-term overview. Neurology. 2020 Jul 28;95(4):e384-e392.

Bove F, Mulas D, Cavallieri F, Castrioto A, Chabardès S, Meoni S, Schmitt E, Bichon A, Di Stasio E, Kistner A, Pélissier P, Chevrier E, Seigneuret E, Krack P, Fraix V, Moro E. Long-term Outcomes (15 Years) After Subthalamic Nucleus Deep Brain Stimulation in Patients With Parkinson Disease. Neurology. 2021 Jun 2:10.1212/WNL.0000000000012246.

Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003 Mar-Apr;24(2):197-211.

Brabenec L, Mekyska J, Galaz Z, Rektorova I. Speech disorders in Parkinson's disease: early diagnostics and effects of medication and brain stimulation. J Neural Transm (Vienna). 2017 Mar;124(3):303-334.

Brognara L, Palumbo P, Grimm B, Palmerini L. Assessing Gait in Parkinson's Disease Using Wearable Motion Sensors: A Systematic Review. Diseases. 2019 Feb 5;7(1):18.

Bronner G, Aharon-Peretz J, Hassin-Baer S. Sexuality in patients with Parkinson's disease, Alzheimer's disease, and other dementias. Handb Clin Neurol. 2015;130:297-323.

Brusse KJ, Zimdars S, Zalewski KR, Steffen TM. Testing functional performance in people with Parkinson disease. Phys Ther. 2005 Feb;85(2):134-41. PMID: 15679464.

Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D. Dementia and survival in Parkinson disease: a 12-year population study. Neurology. 2008 Mar 25;70(13):1017-22.

Caffarra P. et al. (2002) “Una versione abbreviata del test di Stroop: dati normativi nella pop. italiana”, N. R. Neur., 12(4):111-115

Calabrese V, Mancuso C, Calvani M, Rizzarelli E, Butterfield DA, Stella AM. Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity. Nat Rev Neurosci. 2007 Oct;8(10):766-75.

Cambier J, Masson M, Dehen H. Neurologia. 22nd ed. Edra Masson (2013).

Cantiniaux S, Vaugoyeau M, Robert D, Horrelou-Pitek C, Mancini J, Witjas T, Azulay JP. Comparative analysis of gait and speech in Parkinson's disease: hypokinetic or dysrhythmic disorders? J Neurol Neurosurg Psychiatry. 2010 Feb;81(2):177-84.

Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. Arch Neurol. 2011 Dec;68(12):1550-6.

Castrioto, A., Lhommée, E., Moro, E., & Krack, P. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. Lancet Neurol. 2014 Mar;13(3):287-305.

Cavallieri F, Budriesi C, Gessani A, Contardi S, Fioravanti V, Menozzi E, Pinto S, Moro E, Valzania F, Antonelli F. Dopaminergic Treatment Effects on Dysarthric Speech: Acoustic Analysis in a Cohort of Patients With Advanced Parkinson's Disease. Front Neurol. 2021 Feb 5;11:616062.

Cavallieri F, Fraix V, Bove F, Mulas D, Tondelli M, Castrioto A, Krack P, Meoni S, Schmitt E, Lhommée E, Bichon A, Pélissier P, Chevrier E, Kistner A, Seigneuret E, Chabardès S, Moro E. Predictors of Long-Term Outcome of Subthalamic Stimulation in Parkinson Disease. Ann Neurol. 2021 Mar;89(3):587-597.

Chaudhuri KR and AH Schapira. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol, 2009. 8(5): p. 464-74

Chou K, Evatt, M, Hinson V, & Kompoliti, K. Sialorrhea in Parkinson's disease: a review. Mov Disord. 2007 Dec;22(16):2306-13.

Clement F, Belleville S, Gauthier S. Cognitive complaint in mild cognitive impairment and Alzheimer's disease. J Int Neuropsychol Soc 2008; 14(2):222-232.

Collomb-Clerc A, Welter ML. Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: A systematic neurophysiological review. Neurophysiol Clin. 2015 Nov;45(4-5):371-88.

Contarino MF, Daniele A, Sibilia AH, Romito LM, Bentivoglio AR, Gainotti G, Albanese A. Cognitive outcome 5 years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007 Mar;78(3):248-52.

Costa A, Bagoj E, Monaco M, Zabberoni S, De Rosa S, Papantonio AM, Mundi C, Caltagirone C, Carlesimo GA. Standardization and normative data obtained in the Italian population for a new verbal fluency instrument, the phonemic/semantic alternate fluency test. Neurol Sci. 2014 Mar;35(3):365-72.

Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. N Engl J Med. 1967 Feb 16;276(7):374-9.

Crenna P, Carpinella I, Rabuffetti M, Calabrese E, Mazzoleni P, Nemni R, Ferrarin M. The association between impaired turning and normal straight walking in Parkinson's disease. Gait Posture. 2007 Jul;26(2):172-8.

Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Objective Gait and Balance Impairments Relate to Balance Confidence and Perceived Mobility in People With Parkinson Disease. Phys Ther. 2016 Nov;96(11):1734-1743.

D'Alatri L, Paludetti G, Contarino MF, Galla S, Marchese MR, Bentivoglio AR. Effects of bilateral subthalamic nucleus stimulation and medication on parkinsonian speech impairment. J Voice. 2008 May;22(3):365-72.

Dal Bello-Haas V, Klassen L, Sheppard MS, Metcalfe A. Psychometric Properties of Activity, Self-Efficacy, and Quality-of-Life Measures in Individuals with Parkinson Disease. Physiother Can. 2011 Winter;63(1):47-57.

Daniele A, Albanese A, Contarino MF, Zinzi P, Barbier A, Gasparini F, Romito LM, Bentivoglio AR, Scerrati M. Cognitive and behavioural effects of chronic stimulation of the subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2003 Feb;74(2):175-82.

Daniels, C., Krack, P., Volkmann, J., Pinsker, M., Krause, M., Tronnier, V., et al. Risk factors for executive dysfunction after subthalamic nucleus stimulation in Parkinson's disease. Mov Disord. 2010 Aug 15;25(11):1583-9.

Darley L., Aronson A.E., Brown J.R. Differential diagnostic patterns of dysarthria. Journal of speech and hearing research. 1969; 12 (2): 246-69.

De Letter M, Santens P, De Bodt M, Boon P, Van Borsel J. Levodopa-induced alterations in speech rate in advanced Parkinson's disease. Acta Neurol Belg. 2006 Mar;106(1):19-22.

De Letter M, Santens P, De Bodt M, Van Maele G, Van Borsel J, Boon P. The effect of levodopa on respiration and word intelligibility in people with advanced Parkinson's disease. Clin Neurol Neurosurg. 2007 Jul;109(6):495-500.

De Letter M, Santens P, Van Borsel J. The effects of levodopa on tongue strength and endurance in patients with Parkinson's disease. Acta Neurol Belg. 2003 Mar;103(1):35-8. PMID: 12704981.

De Letter M, Santens P, Van Borsel J. The effects of levodopa on word intelligibility in Parkinson's disease. J Commun Disord. 2005 May-Jun;38(3):187-96.

De Melo Borges, S, Radanovic M, Forlenza OV. Fear of falling and falls in older adults with mild cognitive impairment and Alzheimer's disease. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2015; 22(3):312-321.

De Renzi E., Faglioni P., Ruggerini C. (1977) Prove di memoria verbale di impiego clinico per la diagnosi di amnesia. Archivio di Psicologia, Neurologia e Psichiatria, 38:303-318.

Defer G, Widner H, Marié R, Rémy P, & Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov Disord. 1999 Jul;14(4):572-84.

Deuschl G, Paschen S, Witt K. Clinical outcome of deep brain stimulation for Parkinson's disease. Handb Clin Neurol. 2013;116:107-28.

Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, Daniels C, Deutschländer A, Dillmann U, Eisner W, Gruber D, Hamel W, Herzog J, Hilker R, Klebe S, Kloss M, Koy J, Krause M, Kupsch A, Lorenz D, Lorenzl S, Mehdorn HM, Moringlane JR, Oertel W, Pinsker MO, Reichmann H, Reuss A, Schneider GH, Schnitzler A, Steude U, Sturm V, Timmermann L, Tronnier V, Trottenberg T, Wojtecki L, Wolf E, Poewe W, Voges J; German Parkinson Study Group, Neurostimulation Section. A

randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med. 2006 Aug 31;355(9):896-908.

Dibilio V, Nicoletti A, Mostile G, Toscano S, Luca A, Raciti L, Sciacca G, Vasta R, Cicero CE, Contrafatto D, Zappia M. Dopaminergic and non-dopaminergic gait components assessed by instrumented timed up and go test in Parkinson's disease. J Neural Transm (Vienna). 2017 Dec;124(12):1539-1546.

Dodich et al. Emotion recognition from facial expressions: a normative study of the Ekman 60-Faces Test in the Italian population.Neurol Sci. 2014 Jul;35(7):1015-21.

Doherty KM, van de Warrenburg BP, Peralta MC, Silveira-Moriyama L, Azulay JP, Gershanik OS, Bloem BR. Postural deformities in Parkinson's disease. Lancet Neurol. 2011 Jun;10(6):538-49.

Dorsey ER, Sherer T, Okun MS, Bloem BR. The Emerging Evidence of the Parkinson Pandemic. J Parkinsons Dis. 2018;8(s1):S3-S8.

Dromey C, Kumar R, Lang AE, Lozano AM. An investigation of the effects of subthalamic nucleus stimulation on acoustic measures of voice. Mov Disord. 2000 Nov;15(6):1132-8.

Duffy, Joseph R. Motor Speech Disorders : Substrates, Differential Diagnosis, and Management. 3rd ed. St. Louis, Mo.: Elsevier Mosby, 2013.

Earhart GM. Dynamic control of posture across locomotor tasks. Mov Disord. 2013 Sep 15;28(11):1501-8.

Eisinger RS, Hess CW, Martinez-Ramirez D, Almeida L, Foote KD, Okun MS, Gunduz A. Motor subtype changes in early Parkinson's disease. Parkinsonism Relat Disord. 2017 Oct;43:67-72.

Erro R, Vitale C, Amboni M, Picillo M, Moccia M, Longo K, Santangelo G, De Rosa A, Allocca R, Giordano F, Orefice G, De Michele G, Santoro L, Pellecchia MT, Barone P. The heterogeneity of early Parkinson's disease: a cluster analysis on newly diagnosed untreated patients. PLoS One. 2013 Aug 1;8(8):e70244.

Fabbri M, Ferreira JJ, Lees A, Stocchi F, Poewe W, Tolosa E, Rascol O. Opicapone for the treatment of Parkinson's disease: A review of a new licensed medicine. Mov Disord. 2018 Oct;33(10):1528-1539.

Fantini ML, Gagnon JF, Filipini D, Montplaisir J. The effects of pramipexole in REM sleep behavior disorder. Neurology. 2003 Nov 25;61(10):1418-20.

Fasano A, Romito LM, Daniele A, Piano C, Zinno M, Bentivoglio AR, Albanese A. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. Brain. 2010 Sep;133(9):2664-76.

Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol. 2015 Jun;14(6):625-39.

Fatmehsari Y. R., Bahrami F. "Sit-to-stand or stand-to-sit: Which movement can classify better Parkinsonian patients from healthy elderly subjects?," 2011 18th Iranian Conference of Biomedical Engineering (ICBME), 2011, pp. 48-53, doi: 10.1109/ICBME.2011.6168583.

Fereshtehnejad SM, Lökk J. Orthostatic hypotension in patients with Parkinson's disease and atypical parkinsonism. Parkinsons Dis. 2014;2014:475854.

Flood MW, O'Callaghan BPF, Diamond P, Liegey J, Hughes G, Lowery MM. Quantitative clinical assessment of motor function during and following LSVT-BIG® therapy. J Neuroeng Rehabil. 2020 Jul 13;17(1):92.

Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, Marks WJ Jr, Rothlind J, Sagher O, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein JM, Stoner G, Starr PA, Simpson R, Baltuch G, De Salles A, Huang GD, Reda DJ; CSP 468 Study Group. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010 Jun 3;362(22):2077-91.

Foreman KB, Addison O, Kim HS, Dibble LE. Testing balance and fall risk in persons with Parkinson disease, an argument for ecologically valid testing. Parkinsonism Relat Disord. 2011 Mar;17(3):166-71.

Freed D. Le disartrie, diagnosi e trattamento. Edises; 2015.

Gamboa J, Jiménez-Jiménez FJ, Nieto A, Montojo J, Ortí-Pareja M, Molina JA, García-Albea E, Cobeta I. Acoustic voice analysis in patients with Parkinson's disease treated with dopaminergic drugs. J Voice. 1997 Sep;11(3):314-20.

Gentil M, Tournier CL, Pollak P, Benabid AL. Effect of bilateral subthalamic nucleus stimulation and dopatherapy on oral control in Parkinson's disease. Eur Neurol. 1999;42(3):136-40.

Gervais-Bernard H, Xie-Brustolin J, Mertens P, Polo G, Klinger H, Adamec D, Broussolle E, Thobois S. Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: five year follow-up. J Neurol. 2009 Feb;256(2):225-33.

Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry. 1988 Jun;51(6):745-52.

Giladi N, Treves TA, Simon ES, Shabtai H, Orlov Y, Kandinov B, Paleacu D, Korczyn AD. Freezing of gait in patients with advanced Parkinson's disease. J Neural Transm (Vienna). 2001;108(1):53-61.

Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E. Trail making test: normative values from 287 normal adult controls. Ital J Neurol Sci. 1996 Aug;17(4):305-9.

Giovannoni G, O'Sullivan JD, Turner K, Manson AJ, Lees AJ. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol Neurosurg Psychiatry. 2000 Apr;68(4):423-8.

Goberman AM, Blomgren M. Parkinsonian speech disfluencies: effects of L-dopa-related fluctuations. J Fluency Disord. 2003 Spring;28(1):55-70.

Goberman AM, Coelho C. Acoustic analysis of parkinsonian speech I: speech characteristics and L-Dopa therapy. NeuroRehabilitation. 2002;17(3):237-46.

Gratwicke J, Jahanshahi M, Foltynie T. Parkinson's disease dementia: a neural networks perspective. Brain. 2015 Jun;138(Pt 6):1454-76.

Grober, E., Buschke, H. (1987). Genuine memory deficits in dementia. Developmental neuropsychology, 3(1), 13-36.

Hall H, Reyes S, Landeck N, Bye C, Leanza G, Double K, Thompson L, Halliday G, Kirik D. Hippocampal Lewy pathology and cholinergic dysfunction are associated with dementia in Parkinson's disease. Brain. 2014 Sep;137(Pt 9):2493-508.

Hamani C, Richter E, Schwalb JM, Lozano AM. Bilateral subthalamic nucleus stimulation for Parkinson's disease: a systematic review of the clinical literature. Neurosurgery. 2005 Jun;56(6):1313-21; discussion 1321-4.

Harel BT, Cannizzaro MS, Cohen H, Reilly N, Snyder PJ. Acoustic characteristics of Parkinsonian speech: a potential biomarker of early disease progression and treatment. J Neurolinguistics. 2004 Nov 1;17(6):439–53.

Heaton R.K., Chelune G.J., Talley J.L., Kay G.G. e Curtiss G. (1993), Wisconsin Manual Revised and Expanded, PAR Psychological Assesment Resources, Inc., adattamento italiano di Hardoy M.C., Carta M.G., Hardoy M.J. e Cabras P.L. (2000), O.S. Organizzazioni Spaciali, Firenze

Henriksen M, Lund H, Moe-Nilssen R, Bliddal H, Danneskiod-Samsøe B. Test-retest reliability of trunk accelerometric gait analysis. Gait Posture. 2004 Jun;19(3):288-97.

Herzog, J., Pinsker, M., Wasner, M., Steigerwald, F., Wailke, S., Deuschl, G., et al. Stimulation of subthalamic fibre tracts reduces dyskinesias in STN-DBS. Mov Disord. 2007 Apr 15;22(5):679-84.

Ho AK, Iansek R, Marigliani C, Bradshaw JL, Gates S. Speech impairment in a large sample of patients with Parkinson's disease. Behav Neurol. 1998;11(3):131-137.

Huang SL, Hsieh CL, Wu RM, Tai CH, Lin CH, Lu WS. Minimal detectable change of the timed "up & go" test and the dynamic gait index in people with Parkinson disease. Phys Ther. 2011 Jan;91(1):114-21.

Huxham F, Baker R, Morris ME, Iansek R. Head and trunk rotation during walking turns in Parkinson's disease. Mov Disord. 2008 Jul 30;23(10):1391-7.

Inkster LM, Eng JJ. Postural control during a sit-to-stand task in individuals with mild Parkinson's disease. Exp Brain Res. 2004 Jan;154(1):33-8.

Iosa M, Fusco A, Morone G, Pratesi L, Coiro P, Venturiero V, De Angelis D, Bragoni M, Paolucci S. Assessment of upper-body dynamic stability during walking in patients with subacute stroke. J Rehabil Res Dev. 2012;49(3):439-50.

Jacob EL, Gatto NM, Thompson A, Bordelon Y, Ritz B. Occurrence of depression and anxiety prior to Parkinson's disease. Parkinsonism Relat Disord. 2010 Nov;16(9):576-81.

Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008 Apr;79(4):368-76.

Jiang LL, Liu JL, Fu XL, et al. Long-term Efficacy of Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: A 5-year Follow-up Study in China. Chin Med J (Engl). 2015;128(18):2433-2438.

Josephs KA, Matsumoto JY, Ahlskog JE. Benign tremulous parkinsonism. Arch Neurol. 2006 Mar;63(3):354-7.

Jost WH. Gastrointestinal dysfunction in Parkinson's Disease. J Neurol Sci. 2010 Feb 15;289(1-2):69-73.

Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015 Aug 29;386(9996):896-912.

Kamieniarz A, Michalska J, Brachman A, Pawłowski M, Słomka KJ, Juras G. A posturographic procedure assessing balance disorders in Parkinson's disease: a systematic review. Clin Interv Aging. 2018 Nov 12;13:2301-2316.

Kang JH, Irwin DJ, Chen-Plotkin AS, Siderowf A, Caspell C, Coffey CS, Waligórska T, Taylor P, Pan S, Frasier M, Marek K, Kieburtz K, Jennings D, Simuni T, Tanner CM, Singleton A, Toga AW, Chowdhury S, Mollenhauer B, Trojanowski JQ, Shaw LM; Parkinson's Progression Markers Initiative. Association of cerebrospinal fluid β-amyloid 1-42, T-tau, P-tau181, and α-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. JAMA Neurol. 2013 Oct;70(10):1277-87.

Katz M, Luciano MS, Carlson K, Luo P, Marks WJ Jr, Larson PS, Starr PA, Follett KA, Weaver FM, Stern MB, Reda DJ, Ostrem JL; CSP 468 study group. Differential effects of deep brain stimulation target on motor subtypes in Parkinson's disease. Ann Neurol. 2015 Apr;77(4):710-9.

Kemoun G, Defebvre L. Troubles de la marche dans la maladie de Parkinson. Description clinique, analyse de la posture, de l'initiation et de la marche stabilisée. Gait disorders in Parkinson disease. Clinical description, analysis of posture, initiation of stabilized gait. Presse Med. 2001 Mar 10;30(9):452-9. French. PMID: 11285785.

Keus SH, Bloem BR, Hendricks EJ, Bredero-Cohen AB, Munneke M. Evidence-based analysis of physical therapy in Parkinson’s disease with recommendations for practice and research. Mov Disord 2006;4:451-60.

Khor SP, Hsu A. The pharmacokinetics and pharmacodynamics of levodopa in the treatment of Parkinson's disease. Curr Clin Pharmacol. 2007 Sep;2(3):234-43.

Klawans HL. Individual manifestations of Parkinson's disease after ten or more years of levodopa. Mov Disord. 1986;1(3):187-92.

Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, Lang AE, Deuschl G. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Mov Disord. 2006 Jun;21 Suppl 14:S290-304.

Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003 Nov 13;349(20):1925-34.

Krack, P., Hariz, M., Baunez, C., Guridi, J., & Obeso, J. Deep brain stimulation: from neurology to psychiatry? Trends Neurosci. 2010 Oct;33(10):474-84.

Kumar S, Bhatia M, Behari M. Sleep disorders in Parkinson's disease. Mov Disord. 2002 Jul;17(4):775-81.

Kummer A, Cardoso F, Teixeira AL. Loss of libido in Parkinson's disease. J Sex Med. 2009 Apr;6(4):1024-1031.

Lamberti P, Armenise S, Castaldo V, de Mari M, Iliceto G, Tronci P, Serlenga L. Freezing gait in Parkinson's disease. Eur Neurol. 1997;38(4):297-301.

Lansford KL, Liss JM, Caviness JN, Utianski RL. A cognitive-perceptual approach to conceptualizing speech intelligibility deficits and remediation practice in hypokinetic dysarthria. Parkinsons Dis. 2011;2011:150962.

Lechien JR, Blecic S, Huet K, Delvaux V, Piccaluga M, Roland V, et al. Voice quality outcomes of idiopathic Parkinson’s disease medical treatment: a systematic review. Clin Otolaryngol. (2018) 43:882–903.

Lezcano E, Gómez-Esteban JC, Tijero B, Bilbao G, Lambarri I, Rodriguez O, Villoria R, Dolado A, Berganzo K, Molano A, de Gopegui ER, Pomposo I, Gabilondo I, Zarranz JJ. Long-term impact on quality of life of subthalamic nucleus stimulation in Parkinson's disease. J Neurol. 2016 May;263(5):895-905.

Liang GS, Chou KL, Baltuch GH, Jaggi JL, Loveland-Jones C, Leng L, Maccarone H, Hurtig HI, Colcher A, Stern MB, Kleiner-Fisman G, Simuni T, Siderowf AD. Long-term outcomes of bilateral subthalamic nucleus stimulation in patients with advanced Parkinson's disease. Stereotact Funct Neurosurg. 2006;84(5-6):221-7.

Lim EW, Aarsland D, Ffytche D, Taddei RN, van Wamelen DJ, Wan YM, Tan EK, Ray Chaudhuri K; Kings Parcog groupMDS Nonmotor study group. Amyloid-β and Parkinson's disease. J Neurol. 2019 Nov;266(11):2605-2619.

Lim, S., O'Sullivan, S., Kotschet, K., Gallagher, D., Lacey, C., Lawrence, A., et al. Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease. J Clin Neurosci. 2009 Sep;16(9):1148- 52.

Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. Nat Rev Neurol. 2019 Apr;15(4):234-242.

Low, P. Prevalence of orthostatic hypotension. Clin Auton Res. 2008 Mar;18 Suppl 1:8-13.

Mak MK, Hui-Chan CW. The speed of sit-to-stand can be modulated in Parkinson's disease. Clin Neurophysiol. 2005 Apr;116(4):780-9.

Mak MK, Levin O, Mizrahi J, Hui-Chan CW. Joint torques during sit-to-stand in healthy subjects and people with Parkinson's disease. Clin Biomech (Bristol, Avon). 2003 Mar;18(3):197-206.

Mallet, L., Schüpbach, M., N'Diaye, K., Remy, P., Bardinet, E., Czernecki, V., et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. Proc Natl Acad Sci U S A. 2007 Jun 19;104(25):10661-6.

Marras C, Beck JC, Bower JH, Roberts E, Ritz B, Ross GW, Abbott RD, Savica R, Van Den Eeden SK, Willis AW, Tanner CM; Parkinson's Foundation P4 Group. Prevalence of Parkinson's disease across North America. NPJ Parkinsons Dis. 2018 Jul 10;4:21.

Marras C. Subtypes of Parkinson's disease: state of the field and future directions. Curr Opin Neurol. 2015 Aug;28(4):382-6.

Martin D, Fitch J, Wolfe V. Pathologic voice type and the acoustic prediction of severity. J Speech Hear Res. 1995 Aug;38(4):765-71.

Martinez-Fernandez, R., Pelissier, P., Quesada, J., Klinger, H., Lhommée, E., Schmitt, E., et al. Postoperative apathy can neutralise benefits in quality of life after subthalamic stimulation for Parkinson's disease. J Neurol Neurosurg Psychiatry. 2016 Mar;87(3):311-8.

Mayagoitia RE, Lötters JC, Veltink PH, Hermens H. Standing balance evaluation using a triaxial accelerometer. Gait Posture. 2002 Aug;16(1):55-9.

Midi I, Dogan M, Koseoglu M, Can G, Sehitoglu MA, Gunal DI. Voice abnormalities and their relation with motor dysfunction in Parkinson's disease. Acta Neurol Scand. 2008 Jan;117(1):26-34.

Mirelman A, Bonato P, Camicioli R, Ellis TD, Giladi N, Hamilton JL, Hass CJ, Hausdorff JM, Pelosin E, Almeida QJ. Gait impairments in Parkinson's disease. Lancet Neurol. 2019 Jul;18(7):697-708.

Moe-Nilssen R, Helbostad JL. Trunk accelerometry as a measure of balance control during quiet standing. Gait Posture. 2002 Aug;16(1):60-8.

Moe-Nilssen R. A new method for evaluating motor control in gait under real-life environmental conditions. Part 2: Gait analysis. Clin Biomech (Bristol, Avon). 1998 Jun;13(4-5):328-335.

Mollinedo I, Ma Cancela J. Evaluation of the psychometric properties and clinical applications of the Timed Up and Go test in Parkinson disease: a systematic review. J Exerc Rehabil. 2020;16(4):302-312.

Moreau C, Cantiniaux S, Delval A, Defebvre L, Azulay J. Gait disorders in Parkinson's disease: Clinical and pathophysiological approaches. Rev Neurol (Paris). 2010 Feb;166(2):158-67.

Moreau C, Cantiniaux S, Delval A, Defebvre L, Azulay JP. Les troubles de la marche dans la maladie de Parkinson : problématique clinique et physiopathologique. Gait disorders in Parkinson's disease: and pathophysiological approaches. Rev Neurol (Paris). 2010 Feb;166(2):158-67. French.

Moreau C, Ozsancak C, Blatt JL, Derambure P, Destee A, Defebvre L. Oral festination in Parkinson's disease: biomechanical analysis and correlation with festination and freezing of gait. Mov Disord. 2007 Jul 30;22(10):1503-1506.

Moro E, Lozano AM, Pollak P, Agid Y, Rehncrona S, Volkmann J, Kulisevsky J, Obeso JA, Albanese A, Hariz MI, Quinn NP, Speelman JD, Benabid AL, Fraix V, Mendes A, Welter ML, Houeto JL, Cornu P, Dormont D, Tornqvist AL, Ekberg R, Schnitzler A, Timmermann L, Wojtecki L, Gironell A, Rodriguez-Oroz MC, Guridi J, Bentivoglio AR, Contarino MF, Romito L, Scerrati M, Janssens M, Lang AE. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. Mov Disord. 2010 Apr 15;25(5):578-86.

Müller L.T.M., M., Nicolaas, B., Vikas, K., Peter, S., Koeppe, R., Frey, K. A., & Albin, R. L. Clinical Markers for Identifying Cholinergic Deficits in Parkinson's Disease. 2015;30(2), 269–273.

Murdoch B, Whitehill T, de Letter M, Jones H. Communication impairments in Parkinson's disease. Parkinsons Dis. 2011;2011:234657. doi: 10.4061/2011/234657.

Muzerengi S, Lewis H, Edwards M, Kipps E, Bahl A, Martinez-Martin P, et al. Non-motor symptoms in Parkinson's disease: an underdiagnosed problem. Aging Health 2006;2(6):967-82.

Navratilova D, Krobot A, Otruba P, Nevrly M, Krahulik D, Kolar P, Kolarova B, Kaiserova M, Mensikova K, Vastik M, Kurcova S, Kanovsky P. Deep Brain Stimulation Effects on Gait Pattern in Advanced Parkinson's Disease Patients. Front Neurosci. 2020 Aug 14;14:814.

Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol. 2011 Aug;10(8):734-44.

O'Sullivan SB, Schmitz TJ, Fulk GD. Physical Rehabilitation, 6th edition. F.A. Davis Co. (2014).

Oerlemans WG, de Weerd AW. The prevalence of sleep disorders in patients with Parkinson's disease. A self-reported, community-based survey. Sleep Med. 2002 Mar;3(2):147-9.

Okun MS. Deep-brain stimulation for Parkinson's disease. N Engl J Med. 2012 Oct 18;367(16):1529-38.

Palmerini L, Mellone S, Avanzolini G, Valzania F, Chiari L. Quantification of motor impairment in Parkinson's disease using an instrumented timed up and go test. IEEE Trans Neural Syst Rehabil Eng. 2013 Jul;21(4):664-73.

Parkinson, J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci. 2002 Spring;14(2):223-36; discussion 222.

Pasciuto I, Bergamini E, Iosa M, Vannozzi G, Cappozzo A. Overcoming the limitations of the Harmonic Ratio for the reliable assessment of gait symmetry. J Biomech (2017) 53:84–89.

Perez-Lloret S, Barrantes FJ. Deficits in cholinergic neurotransmission and their clinical correlates in Parkinson's disease. NPJ Parkinsons Dis. 2016 Feb 18;2:16001.

Peterson DS, Mancini M, Fino PC, Horak F, Smulders K. Speeding Up Gait in Parkinson's Disease. J Parkinsons Dis. 2020;10(1):245-253.

Piboolnurak P, Lang AE, Lozano AM, Miyasaki JM, Saint-Cyr JA, Poon YY, Hutchison WD, Dostrovsky JO, Moro E. Levodopa response in long-term bilateral subthalamic stimulation for Parkinson's disease. Mov Disord. 2007 May 15;22(7):990-7.

Pickering RM, Grimbergen YA, Rigney U, Ashburn A, Mazibrada G, Wood B, Gray P, Kerr G, Bloem BR. A meta-analysis of six prospective studies of falling in Parkinson's disease. Mov Disord. 2007 Oct 15;22(13):1892-900.

Pinho P, Monteiro L, Soares MFP, Tourinho L, Melo A, Nóbrega AC. Impact of levodopa treatment in the voice pattern of Parkinson's disease patients: a systematic review and meta-analysis. Codas. 2018 Oct 4;30(5):e20170200.

Pinter B, Diem-Zangerl A, Wenning GK, Scherfler C, Oberaigner W, Seppi K, Poewe W. Mortality in Parkinson's disease: a 38-year follow-up study. Mov Disord. 2015 Feb;30(2):266-9.

Pinto S, Ferraye M, Espesser R, Fraix V, Maillet A, Guirchoum J, Layani-Zemour D, Ghio A, Chabardès S, Pollak P, Debû B. Stimulation of the pedunculopontine nucleus area in Parkinson's disease: effects on speech and intelligibility. Brain. 2014 Oct;137(Pt 10):2759-72.

Pinto S, Thobois S, Costes N, Le Bars D, Benabid AL, Broussolle E, Pollak P, Gentil M. Subthalamic nucleus stimulation and dysarthria in Parkinson's disease: a PET study. Brain. 2004 Mar;127(Pt 3):602-15.

Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE. Parkinson disease. Nat Rev Dis Primers. 2017 Mar 23;3:17013.

Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE. Parkinson disease. Nat Rev Dis Primers. 2017 Mar 23;3:17013.

Poewe WH, Deuschl G, Gordin A, Kultalahti ER, Leinonen M; Celomen Study Group. Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). Acta Neurol Scand. 2002 Apr;105(4):245-55.

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015 Oct;30(12):1591-601.

Postuma RB, Bertrand JA, Montplaisir J, Desjardins C, Vendette M, Rios Romenets S, Panisset M, Gagnon JF. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. Mov Disord. 2012 May;27(6):720-6.

Pötter-Nerger M, Volkmann J. Deep brain stimulation for gait and postural symptoms in Parkinson's disease. Mov Disord. 2013 Sep 15;28(11):1609-15.

Powell D, Hanson N, Threlkeld AJ, Fang X, Xia R. Enhancement of parkinsonian rigidity with contralateral hand activation. Clin Neurophysiol. 2011 Aug;122(8):1595-601.

Raven J. C., APM Advanced Progressive Matrices. Curatori edizione italiana: A. Di Fabio e S. Clarotti (1969)

Ricciardi L, Ebreo M, Graziosi A, Barbuto M, Sorbera C, Morgante L, et al. Speech and gait in Parkinson's disease: When rhythm matters. Parkinsonism Relat Disord. 2016 Nov 1;32:42–7.

Rinne UK, Larsen JP, Siden A, Worm-Petersen J. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. Neurology. 1998 Nov;51(5):1309-14.

Rocco A, Gentili S, Capici S, Intiso D, Gigante G. Valutazione fisiatrica e semeiotica strumentale. Fisioter (2011) 3:17–28.

Rochester L, Galna B, Lord S, Yarnall AJ, Morris R, Duncan G, Khoo TK, Mollenhauer B, Burn DJ. Decrease in Aβ42 predicts dopa-resistant gait progression in early Parkinson disease. Neurology. 2017 Apr 18;88(16):1501-1511.

Rodriguez-Oroz MC, Moro E, Krack P. Long-term outcomes of surgical therapies for Parkinson's disease. Mov Disord. 2012 Dec;27(14):1718-28.

Roper JA, Kang N, Ben J, Cauraugh JH, Okun MS, Hass CJ. Deep brain stimulation improves gait velocity in Parkinson's disease: a systematic review and meta-analysis. J Neurol. 2016 Jun;263(6):1195-203.

Rusz J, Bonnet C, Klempíř J, Tykalová T, Baborová E, Novotný M, Rulseh A, Růžička E. Speech disorders reflect differing pathophysiology in Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. J Neurol. 2015;262(4):992-1001.

Rusz J, Cmejla R, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E. Evaluation of speech impairment in early stages of Parkinson's disease: a prospective study with the role of pharmacotherapy. J Neural Transm (Vienna). 2013 Feb;120(2):319-29.

Rusz J, Cmejla R, Ruzickova H, Ruzicka E. Quantitative acoustic measurements for characterization of speech and voice disorders in early untreated Parkinson's disease. J Acoust Soc Am. 2011 Jan;129(1):350-67.

Rusz J, Tykalova T, Ramig LO, Tripoliti E. Guidelines for Speech Recording and Acoustic Analyses in Dysarthrias of Movement Disorders. Mov Disord. 2021 Apr;36(4):803-814

Saint-Cyr JA, Trépanier LL, Kumar R, Lozano AM, Lang AE. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain. 2000 Oct;123 (Pt 10):2091-108.

Salarian A, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Aminian K. iTUG, a sensitive and reliable measure of mobility. IEEE Trans Neural Syst Rehabil Eng. 2010 Jun;18(3):303-10.

Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. Parkinsonism Relat Disord. 2016 Jan;22 Suppl 1:S41-6.

Scaravilli T, Gasparoli E, Rinaldi F, Polesello G, Bracco F. Health-related quality of life and sleep disorders in Parkinson's disease. Neurol Sci. 2003 Oct;24(3):209-10.

Schaeffer E, Berg D. Dopaminergic Therapies for Non-motor Symptoms in Parkinson's Disease. CNS Drugs. 2017 Jul;31(7):551-570.

Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med. 2013 Aug;14(8):744-8.

Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Dopamine agonists for restless legs syndrome. Cochrane Database Syst Rev. 2011 Mar 16;(3):CD006009.

Schoneburg B, Mancini M, Horak F, Nutt JG. Framework for understanding balance dysfunction in Parkinson's disease. Mov Disord. 2013 Sep 15;28(11):1474-82.

Schrempf W, Brandt MD, Storch A, Reichmann H. Sleep disorders in Parkinson's disease. J Parkinsons Dis. 2014;4(2):211-21.

Schüpbach WM, Maltête D, Houeto JL, du Montcel ST, Mallet L, Welter ML, Gargiulo M, Béhar C, Bonnet AM, Czernecki V, Pidoux B, Navarro S, Dormont D, Cornu P, Agid Y. Neurosurgery at an earlier stage of Parkinson disease: a randomized, controlled trial. Neurology. 2007 Jan 23;68(4):267-71.

Sekine M, Tamura T, Yoshida M, Suda Y, Kimura Y, Miyoshi H, Kijima Y, Higashi Y, Fujimoto T. A gait abnormality measure based on root mean square of trunk acceleration. J Neuroeng Rehabil. 2013 Dec 26;10:118.

Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ. A clinico-pathological study of subtypes in Parkinson's disease. Brain. 2009 Nov;132(Pt 11):2947-57.

Simon DK, Tanner CM, Brundin P. Parkinson Disease Epidemiology, Pathology, Genetics, and Pathophysiology. Clin Geriatr Med. 2020 Feb;36(1):1-12.

Sironi VA. Origin and evolution of deep brain stimulation. Front Integr Neurosci. 2011 Aug 18;5:42.

Skodda S, Grönheit W, Schlegel U, Südmeyer M, Schnitzler A, Wojtecki L. Effect of subthalamic stimulation on voice and speech in Parkinson's disease: for the better or worse? Front Neurol. 2014 Jan 13;4:218.

Skodda S, Schlegel U. Speech rate and rhythm in Parkinson's disease. Mov Disord. 2008 May 15;23(7):985-992.

Skodda S, Visser W, Schlegel U. Short- and long-term dopaminergic effects on dysarthria in early Parkinson's disease. J Neural Transm (Vienna). 2010 Feb;117(2):197-205.

Skrahina V, Gaber H, Vollstedt EJ, Förster TM, Usnich T, Curado F, Brüggemann N, Paul J, Bogdanovic X, Zülbahar S, Olmedillas M, Skobalj S, Ameziane N, Bauer P, Csoti I, Koleva-Alazeh N, Grittner U, Westenberger A, Kasten M, Beetz C, Klein C, Rolfs A; ROPAD Study Group. The Rostock International Parkinson's Disease (ROPAD) Study: Protocol and Initial Findings. Mov Disord. 2021 Apr;36(4):1005-1010.

Smania N, Corato E, Tinazzi M, Stanzani C, Fiaschi A, Girardi P, Gandolfi M. Effect of balance training on postural instability in patients with idiopathic Parkinson's disease. Neurorehabil Neural Repair. 2010 Nov-Dec;24(9):826-34.

Smeding, H., Speelman, J., Huizenga, H., Schuurman, P., & Schmand, B. Predictors of cognitive and psychosocial outcome after STN DBS in Parkinson's Disease. J Neurol Neurosurg Psychiatry. 2011 Jul;82(7):754-60.

Snijders AH, van de Warrenburg BP, Giladi N, Bloem BR. Neurological gait disorders in elderly people: clinical approach and classification. Lancet Neurol. 2007 Jan;6(1):63-74.

St George R, Nutt J, Burchiel K, Horak F. A meta-regression of the long-term effects of deep brain stimulation on balance and gait in PD. Neurology. 2010 Oct 5;75(14):1292-9.

St George RJ, Carlson-Kuhta P, Nutt JG, Hogarth P, Burchiel KJ, Horak FB. The effect of deep brain stimulation randomized by site on balance in Parkinson's disease. Mov Disord. 2014 Jun;29(7):949-53.

Stack E, Ashburn A. Fall events described by people with Parkinson's disease: implications for clinical interviewing and the research agenda. Physiother Res Int. 1999;4(3):190-200.

Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. Mov Disord. 2013 May;28(5):668-70.

Steffen T, Seney M. Ambulation Tests, the 36-Item Short- Form Health Survey, and the Unified Parkinson Disease Rating Scale in People With Parkinsonism. Phys Ther (2008) 88:733–746. doi:10.2522/ptj.20070214

Sung JE, Hyanghee K, Hyun SK, Seung-Hun O, Ji-Man H, Myung SL. Effects of Subthalamic Nucleus Deep Brain Stimulation on the Phonation and Articulation of the Patients with Parkinson's Disease. J Korean Neurol Assoc. 2004;22(5): 472-477.

Swinn L, Schrag A, Viswanathan R, Bloem BR, Lees A, Quinn N. Sweating dysfunction in Parkinson's disease. Mov Disord. 2003 Dec;18(12):1459-63.

Thenganatt MA, Jankovic J. Parkinson disease subtypes. JAMA Neurol. 2014 Apr;71(4):499-504.

Thobois S, Broussolle E. Traitement initial de la maladie de Parkinson [Initial management of Parkinson disease]. Presse Med. 2007 Jan;36(1 Pt 2):86-91.

Thobois, S., Ardouin, C., Lhommée, E., Klinger, H., Lagrange, C., Xie, J., et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. Brain. 2010 Apr;133(Pt 4):1111-27.

Titova N, Chaudhuri KR. Personalized Medicine and Nonmotor Symptoms in Parkinson's Disease. Int Rev Neurobiol. 2017;134:1257-1281.

Titova N, Padmakumar C, Lewis SJG, Chaudhuri KR. Parkinson's: a syndrome rather than a disease? J Neural Transm (Vienna). 2017 Aug;124(8):907-914.

Tjaden K. Speech and Swallowing in Parkinson’s Disease. Top Geriatr Rehabil. 2008;24(2):115–26.

Tomlinson C, Stowe R, Patel S, Rick C, Gray R, Clarke C. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010 Nov 15;25(15):2649-53.

Tomlinson CL, Herd CP, Clarke CE, Meek C, Patel S, Stowe R, Deane KH, Shah L, Sackley CM, Wheatley K, Ives N. Physiotherapy for Parkinson's disease: a comparison of techniques. Cochrane Database Syst Rev. 2014 Jun 17;2014(6):CD002815.

Tommasi G, Krack P, Fraix V, Le Bas JF, Chabardes S, Benabid AL, Pollak P. Pyramidal tract side effects induced by deep brain stimulation of the subthalamic nucleus. J Neurol Neurosurg Psychiatry. 2008 Jul;79(7):813-9.

Tripoliti E, Zrinzo L, Martinez-Torres I, Frost E, Pinto S, Foltynie T, Holl E, Petersen E, Roughton M, Hariz MI, Limousin P. Effects of subthalamic stimulation on speech of consecutive patients with Parkinson disease. Neurology. 2011 Jan 4;76(1):80-6.

Tsuboi T, Watanabe H, Tanaka Y, Ohdake R, Yoneyama N, Hara K, Nakamura R, Watanabe H, Senda J, Atsuta N, Ito M, Hirayama M, Yamamoto M, Fujimoto Y, Kajita Y, Wakabayashi T, Sobue G. Distinct phenotypes of speech and voice disorders in Parkinson's disease after subthalamic nucleus deep brain stimulation. J Neurol Neurosurg Psychiatry. 2015 Aug;86(8):856-64.

Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson’s disease. Mov Disord. 2003 1;18(1):19–31

Tykalová T, Rusz J, Čmejla R, Klempíř J, Růžičková H, Roth J, Růžička E. Effect of dopaminergic medication on speech dysfluency in Parkinson's disease: a longitudinal study. J Neural Transm (Vienna). 2015 Aug;122(8):1135-42.

Umemura, A., Oka, Y., Okita, K., Matsukawa, N., & Yamada, K. Subthalamic nucleus stimulation for Parkinson disease with severe medication-induced hallucinations or delusions. J Neurosurg. 2011 Jun;114(6):1701-5.

Van Lummel RC, Walgaard S, Hobert MA, Maetzler W, van Dieën JH, Galindo-Garre F, Terwee CB. Intra-Rater, Inter-Rater and Test-Retest Reliability of an Instrumented Timed Up and Go (iTUG) Test in Patients with Parkinson's Disease. PLoS One. 2016 Mar 21;11(3):e0151881.

Vaugoyeau M, Cignetti F, Eusebio A, Azulay JP. Subthalamic Deep Brain Stimulation Modulates Proprioceptive Integration in Parkinson's Disease During a Postural Task. Neuroscience. 2020 Jun 15;437:207-214.

Vendette M, Gagnon JF, Décary A, Massicotte-Marquez J, Postuma RB, Doyon J, Panisset M, Montplaisir J. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. Neurology. 2007 Nov 6;69(19):1843-9.

Vervoort D, Vuillerme N, Kosse N, Hortobágyi T, Lamoth CJ. Multivariate Analyses and Classification of Inertial Sensor Data to Identify Aging Effects on the Timed-Up-and-Go Test. PLoS One. 2016 Jun 6;11(6):e0155984.

Warrington, E. K., & James, M. (1991). The visual object and space perception battery (Vol. 4). Bury St Edmunds: Thames Valley Test Company.

Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr, Rothlind J, Sagher O, Reda D, Moy CS, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein J, Stoner G, Heemskerk J, Huang GD; CSP 468 Study Group. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009 Jan 7;301(1):63-73.

Weintraub D, David AS, Evans AH, Grant JE, Stacy M. Clinical spectrum of impulse control disorders in Parkinson's disease. Mov Disord. 2015 Feb;30(2):121-7.

Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, Whetteckey J, Wunderlich GR, Lang AE. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010 May;67(5):589-95.

Weismer G. Articulatory characteristics of parkinsonian dysarthria: segmental and phrase-level timing, spirantization, and glottal-supraglottal coordination. In: McNeil MR, Rosenbek AE, editors. The dysarthrias: physiology, acoustics, perception, management. San Diego: College-Hill; 1984. p 101–130.

Weiss A, Herman T, Mirelman A, Shiratzky SS, Giladi N, Barnes LL, Bennett DA, Buchman AS, Hausdorff JM. The transition between turning and sitting in patients with Parkinson's disease: A wearable device detects an unexpected sequence of events. Gait Posture. 2019 Jan;67:224-229.

Weiss A, Herman T, Plotnik M, Brozgol M, Maidan I, Giladi N, Gurevich T, Hausdorff JM. Can an accelerometer enhance the utility of the Timed Up & Go Test when evaluating patients with Parkinson's disease? Med Eng Phys. 2010 Mar;32(2):119-25.

Weiss HD, Marsh L. Impulse control disorders and compulsive behaviors associated with dopaminergic therapies in Parkinson disease. Neurol Clin Pract. 2012 Dec;2(4):267-274.

Wenning GK, Ebersbach G, Verny M, Chaudhuri KR, Jellinger K, McKee A, Poewe W, Litvan I. Progression of falls in postmortem-confirmed parkinsonian disorders. Mov Disord. 1999 Nov;14(6):947-50.

Wijemanne S, Jankovic J. Restless legs syndrome: clinical presentation diagnosis and treatment. Sleep Med. 2015 Jun;16(6):678-90.

Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, Scott R, Ives N, Rick C, Daniels J, Patel S, Wheatley K; PD SURG Collaborative Group. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol. 2010 Jun;9(6):581-91.

Williams JM, Nyman SR. Association between the instrumented timed up and go test and cognitive function, fear of falling and quality of life in community dwelling people with dementia. J Frailty Sarcopenia Falls. 2018;3(4):185-193.

Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol. 2011 Jun;26 Suppl 1:S1-58.

Wood BH, Bilclough JA, Bowron A, Walker RW. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. J Neurol Neurosurg Psychiatry. 2002 Jun;72(6):721-5.

Yamamoto M. Depression in Parkinson's disease: its prevalence, diagnosis, and neurochemical background. J Neurol. 2001 Sep;248 Suppl 3:III5-11.

Yasuyuki O. Practical approach to freezing of gait in Parkinson’s disease. Pract Neurol 2014;14:222–230.

Zampieri C, Salarian A, Carlson-Kuhta P, Aminian K, Nutt JG, Horak FB. The instrumented timed up and go test: potential outcome measure for disease modifying therapies in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2010 Feb;81(2):171-6.

Zibetti M, Merola A, Rizzi L, Ricchi V, Angrisano S, Azzaro C, Artusi CA, Arduino N, Marchisio A, Lanotte M, Rizzone M, Lopiano L. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. Mov Disord. 2011 Nov;26(13):2327-34.