FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

TRABALHO FINAL DO 6º ANO MÉDICO COM VISTA À ATRIBUIÇÃO DO GRAU DE MESTRE NO ÂMBITO DO CICLO DE ESTUDOS DE MESTRADO INTEGRADO EM MEDICINA

[SOFIA ALEXANDRA RODRIGUES DE ALMEIDA]

[GAIT DISORDERS IN PARKINSON'S AND HUNTINGTON'S DISEASES]

[ARTIGO DE REVISÃO]

ÁREA CIENTÍFICA DE NEUROLOGIA

TRABALHO REALIZADO SOB A ORIENTAÇÃO DE:
[CRISTINA JANUÁRIO]

[JANEIRO/2012]

Para ser grande, sê inteiro: nada
Teu exagera ou exclui.
Sê todo em cada coisa. Põe quanto és
No mínimo que fazes.
Assim em cada lago a lua toda
Brilha, porque alta vive.

Ricardo Reis

Gait disorders in Parkinson's and Huntington's diseases

Sofia A. R. Almeida[1]

Under the guidance of Cristina Januário[1,2]

[1] Faculty of Medicine, University of Coimbra, [2] Department of Neurology, Hospital Center of the University of Coimbra, Portugal

Faculdade de Medicina da Universidade de Coimbra
Rua Larga, 3000 Coimbra
Hospitais da Universidade de Coimbra, serviço de Neurologia
Av. Bissaya Barreto - Praceta Prof. Mota Pinto, 1º Andar

Index

Abbreviation List

ABC: Activities-specific Balance Confidence scale

CNS: central nervous system

DBS: deep brain stimulation

DFA: detrended fluctuation analysis

FOG: freezing of gait

FOGQ: Freezing of Gait Questionnaire

FR: Functional Reach scale

GPi: globus pallidus internal

HD: Huntington's disease

MPH: methylphenidate

MRI scans: magnetic resonance imaging scans

PAS: Parkinson-Activity-Scale

PD: Parkinson's disease

PPN: pedunculopontine nucleus

RAS: rhythmic auditory stimulation

SRT: stepping response time

STN: sub-thalamic nucleus

TUG: Timed Up and Go scale

UHDRS: Unified Huntington's Disease Rating Scale

UPDRS: United Parkinson's Disease Rating Scale

VA: ventral anterior nuclei of thalamus

VL: ventral lateral nuclei of thalamus

Abstract

Movement disorders affect gait, which is one of the most disabling manifestations. Analyzing the brain circuits dependent on the basal ganglia (caudate, putamen, globus pallidus, subthalamic nucleus and substantia nigra), also responsible for organizing movement, we were closer to understand the neurophysiological basis of its operation, taking in account, particularly, the pattern of change of neurotransmitters in each pathology.

We considered the Parkinson's and Huntington's diseases as study models, which are characterized by cognitive, behavioral and motor symptoms, as a result of the underlying changes. They were considered in analogy, relating their pathophysiological mechanisms to the circuits of the basal ganglia, which allowed classifying their role in normal gait performance or disease.

The evaluation of these diseases goes through different scales and experimental models, which are also intended to objectify and quantify changes in gait, as festination and freezing. This helps in implementing the pharmacological treatment, which appears still insufficient. In addition, there are techniques of physiotherapy and rehabilitation medicine.

Therefore, making an updated review of the mechanisms underlying changes in gait in movement disorders, clarifying the role of different neurological structures involved in both the disease and in its absence, was the aim of this work.

Keywords

basal ganglia, gait disorders, huntington’s disease, parkinson’s disease, quality of life

Resumo

As doenças do movimento afectam a marcha, sendo uma das manifestações mais incapacitantes. Analisando os circuitos cerebrais dependentes dos gânglios da base (caudado, putamen, globo pálido, substância negra e núcleo subtalâmico), também responsáveis pela organização da locomoção, ficámos mais perto de conhecer as bases neurofisiológicas do seu funcionamento, tendo em conta, nomeadamente, o padrão de alteração de neurotransmissores próprio de cada patologia.

Consideraram-se a Doença de Parkinson e a Doença de Huntington como modelos de estudo, sendo caracterizadas por sintomatologia cognitiva, comportamental e motora, fruto das alterações subjacentes. Foram abordadas numa perspectiva de analogia, relacionando os seus mecanismos fisiopatológicos com os circuitos dos gânglios da base, o que permitiu classificar o seu papel no desempenho da marcha normal ou na doença.

A avaliação destas doenças passa por diferentes escalas e modelos experimentais, que visam também quantificar e objectivar alterações da marcha como a festinação e o freezing. Este facto auxilia na implementação do tratamento farmacológico, o qual se apresenta ainda insuficiente. Como complemento existem técnicas de fisioterapia e medicina de reabilitação.

Foi, por isso, objectivo deste trabalho fazer uma revisão actualizada dos mecanismos subjacentes às alterações da marcha nas doenças do movimento, clarificando o papel das diferentes estruturas neurológicas envolvidas tanto na doença como na ausência dela.

1. Introduction

Gait disorders are very common in patients with Parkinson’s and Huntington’s diseases. This can lead to a huge tendency to fall (because of postural instability), with severe consequences on independence and quality of life, causing an increase in morbidity and mortality among these patients. For that reason, understanding the mechanisms underlying gait disorders is a major public health priority. Recent studies have confirmed the high rate and high risk of falls among these patients, which highlights the importance of a deeply knowledge in this area.

The basal ganglia (BG) have a preponderant role in the initiation and modulation of movements, and constitute many loops that control motor, cognitive and behavioral functions. They integrate sensory and non-sensory, primary and secondary cortical information and give rise to specific directed fascicles that influence the cerebral cortex motor actions.

There are several new approaches that modify this system, such as pharmacological treatment, deep brain stimulation and physical exercises.

The aim of this review is to generalize these possibilities and make patients’ orientation easier.

2. Methods

The basis of this work is an article search and narrative revision, using the most recent published bibliography, and the systematic revisions criteria, explained below.

The main purpose of this review article is to analyze and summarize the existent studies about gait disorders in Parkinson's and Huntington's diseases, in order to help other investigations and offer a more convenient source of desired information.

We did our investigation considering the *5S of Haynes model*, which is a pyramid that includes: Systems, Summaries, Synopses, Syntheses and Studies (from the top to the base).

Beginning with Summaries (because Systems is not used), we searched in DynaMed (www.ebscohost.com/dynamed), where we found one document about Parkinson's disease and another about Huntington's disease, both of them not related with gait. Then, we searched in UpToDate (www.uptodate.com), where we found the following documents: *Clinical manifestations of Parkinson Disease*; *Gait disorders of elderly patients* and *Management of comorbid problems associated with Parkinson Disease*, using the keywords "movement" and "Parkinson". Similarly, with the keywords "gait" and "Parkinson", the results were the same. On the other hand, using the keywords "movement" and "Huntington", we found the document *Huntington Disease: clinical features and diagnosis*. Similarly, with the keywords "gait" and "Huntington", the results were the same.

Secondly, we searched for Synopses in ACP Journal Club (acpjc.acponline.org). We used the keywords "gait" and "Parkinson", and we found 2 documents: *Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial* and *Anticholinergic drugs improve motor function and disability in Parkinson disease*. In the same way, with the keywords "movement" and "Parkinson", we came across the following documents: *Practice Parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American*

Academy of Neurology; *Helicobacter pylori eradication and l-dopa absorption in patients with Parkinson disease and motor fluctuations*; *Practice corner: Sleepless in Sydney-ls valerian an effective alternative to benzodiazepines in the treatment of insomnia?* and *Gabapentin improved sensory and motor symptoms in the restless legs syndrome*. Moreover, using the keywords "gait" and "Huntington", as well as "movement" and "Huntington", no documents were find. Then, we searched in Evidence-Based Medicine (ebm.bmj.com), and: with the keywords "movement" and "Parkinson" we discovered 55 documents; with the keywords "gait" and "Parkinson" we found 30 documents (7 repeated); with the keywords "movement" and "Huntington" we found 41 documents; and finally with the keywords "gait" and "Huntington" we discovered 16 documents (3 repeated).

Thirdly, searching for Syntheses, in Cochrane Library (www.thecochranelibrary.com) we found 24 Cochrane reviews (selecting *Physiotherapy for Parkinson's disease: a comparison of techniques* and *Physiotherapy versus placebo or no intervention in Parkinson's disease*), with the keywords "movement" and "Parkinson". Likewise, using the keywords "gait" and "Parkinson" we came across one document (*Treadmill training for patients with Parkinson's disease*), with "movement" and "Huntington" we found 2 documents (*Therapeutic interventions for symptomatic treatment in Huntington's disease* and *Therapeutic interventions for disease progression in Huntington's disease*), and with "gait" and "Huntington" we discovered also 2 documents (*Treatment of Huntington's disease* and *Treatment of Huntington's chorea with bromocriptine*). In addition, to ameliorate the search, we used PubMed (www.pubmed.gov), with a methodological filter. In PubMed clinical queries, using the systematic reviews' filter, we can find meta-analyses, reviews of clinical trials, evidence-based medicine, consensus and guidelines. To use the filter, we have to assess PubMed tools, clinical queries and then the keywords and the systematic reviews' filter. Using the keywords "(gait disorder OR gait disorders) AND (parkinson OR parkinsons)", we

obtained 30 references; then with the following limits: 2006 till December 2011, English language and only studies in humans, the results diminished to 18 references. Similarly, with the keywords "(movement disorder OR movement disorders) AND (parkinson OR parkinsons)", we obtained 579 references, reducing to 270 with the mentioned limits. Correspondingly, using the keywords "(gait disorder OR gait disorders) AND (huntington OR huntingtons)", we came across 2 references, reducing to 0 with the same limits. At last, using the keywords "(movement disorder OR movement disorders) AND (huntington OR huntingtons)", we found 61 documents, reducing to 28 with the same limits. Then, the document selection was made considering the scientific journal quotation and the number of its references.

Finally, searching for Studies in PubMed (www.pubmed.gov), we used also keywords and MeSH (Medical Subject Headings). With "Gait Disorders, Neurologic" and "Parkinson Disease", we came across 234 references, withdrawing to 170 with the application of the limits mentioned above. With "Movement Disorders" and "Parkinson Disease", we found 8856 references and 1753 review articles, diminishing to 1102 references and 193 review articles with the limits. There are 22 repeated references between these two ways of searching: gait versus movement, only in Parkinson Disease. Then, using the keywords "Gait Disorders, Neurologic" and "Huntington Disease", we discovered 12 references, reducing to 8 with the same limits. At last, using "Movement Disorders" and "Huntington Disease", we found 3536 references, withdrawing to 1281 references and 227 review articles with the limits. There are 8 repeated articles between these two ways of searching: gait versus movement, only in Huntington Disease. Considering both the diseases, there are 3 repeated articles. Afterward, the document selection was made considering the scientific journal quotation and the number of its references.

Besides the articles, we also used 2 chapters of 2 books, mentioned in the References section.

3. Results

3.1. The role of the basal ganglia in movements

Motor regions of the cortex and brainstem contain upper motor neurons that initiate movement by controlling the activity of local circuit and lower motor neurons in the brainstem and spinal cord (pyramidal tract).

Important regions in motor control: the basal ganglia and the cerebellum. They do not project directly to either the local circuit or lower motor neurons, but they influence movement by regulating the activity of upper motor neurons (Ferraye *et al.*, 2010).

The basal ganglia lie deep within the cerebral hemispheres and include: the caudate, putamen, globus pallidus (motor components), substantia nigra and the subthalamic nucleus. They make a subcortical loop and link most areas of the cortex with upper motor neurons in the primary motor and premotor cortex and in the brainstem. Here, the neurons respond in anticipation of and during movements, and their effects are required for the normal course of voluntary movements. When one of these structures is compromised, the patient cannot switch smoothly between initial commands and final commands of a movement. This is due to the absence of the supervisory control normally provided by the basal ganglia (Purves *et al.*, 2001).

3.1.1. The basal ganglia inputs

The corpus striatum includes the caudate and putamen, and comprise the input zone of the basal ganglia. The destinations of the incoming axons from cortical, thalamic, and brainstem structures are the large dendritic trees of the medium spiny neurons. Then, the axons arising from these neurons converge on neurons in the globus pallidus and the substantia nigra pars

reticulata, which are the main sources of output from the basal ganglia complex (Purves *et al.*, 2001).

The cerebral cortex is the source of the largest input to the basal ganglia. The heaviest projections are from association areas in the frontal and parietal lobes, but also from the temporal, insular, and cingulate cortices. They travel through the internal capsule and form the corticostriatal pathway (Crittenden and Graybiel, 2011).

Caudate and putamen have functional differences. The caudate nucleus receives cortical projections from multimodal association cortices, and from motor areas in the frontal lobe that control eye movements. The putamen receives input from the primary and secondary somatic sensory cortices in the parietal lobe, the secondary visual cortices in the occipital and temporal lobes, the premotor and motor cortices in the frontal lobe, and the auditory association areas in the temporal lobe (Purves *et al.*, 2001).

The caudate, putamen, and ventral striatum receive cortical projections primarily from the association areas of the frontal, parietal, and temporal lobes.

The corpus striatum is functionally subdivided according to its inputs. As an example, visual and somatic sensory cortical projections are topographically mapped within different regions of the putamen.

The corticostriatal pathway consists of multiple parallel pathways serving different functions (observed when we analyze either the inputs or the outputs).

Regions of different cortical areas concerned with the hand converge in specific rostrocaudal bands (functional units concerned with the movement of particular body parts) within the striatum; conversely, regions in the same cortical areas concerned with the leg converge in other striatal bands (Crittenden and Graybiel, 2011).

A further indication of functional subdivision within the striatum is the spatial distribution of different types of medium spiny neurons, which occur in clusters of cells called "patches" or

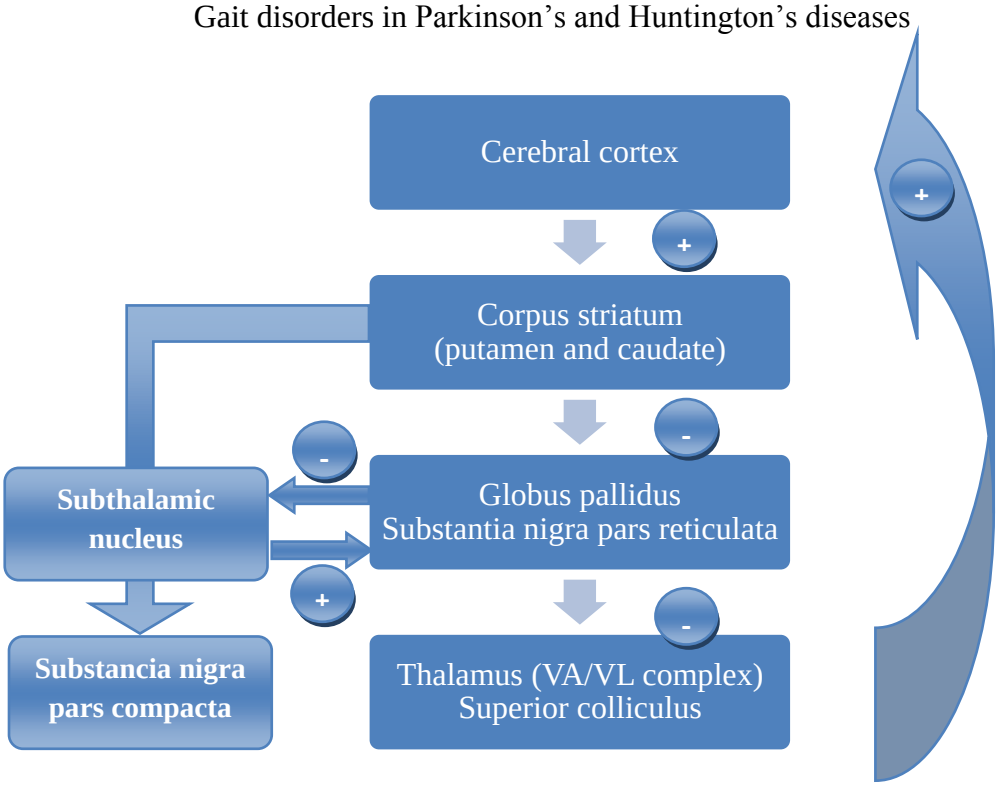
"striosomes", in a surrounding "matrix" of neurochemically distinct cells (limbic areas of the cortex project more heavily to the patches, whereas motor and somatic sensory areas project preferentially to the neurons in the matrix).

Besides the nature of the signals from the cortex to the caudate and putamen are not understood, it is known that collateral axons of corticocortical, corticothalamic and corticospinal pathways originate glutamatergic synapses (excitatory) with medium spiny neurons. Note that the number of contacts established between a cortical axon and a medium spiny cell is very small, but the number of spiny neurons contacted by a single axon is incredibly large, which is named divergence (Purves *et al.*, 2001).

The medium spiny cells also receive noncortical inputs from interneurons, from the midline and intralaminar nuclei of thalamus, and from brainstem aminergic nuclei, which can modulate the effectiveness of cortical synaptic activation (cortical input). The aminergic inputs are dopaminergic and they originate in the substantia nigra pars compacta (Purves *et al.*, 2001).

As a result, the medium spiny neurons must simultaneously receive many excitatory inputs from cortical and nigral neurons to become active. Therefore these cells are usually silent.

The firing of medium spiny neurons is associated with the occurrence of a movement. Neurons in the putamen tend to discharge in anticipation of body movements, whereas caudate neurons fire prior to eye movements. This is part of a movement selection process. It is known that the discharges of some striatal neurons vary according to the location in space of the target of a movement (Fahn and Jankovic, 2007).



Scheme 1: General pathway (adapted from Purves *et al.*, 2001).

3.1.2. The basal ganglia outputs

The medium spiny neurons of the caudate and putamen originate inhibitory GABAergic projections that terminate in the internal division of the globus pallidus and in the substantia nigra pars reticulata. These are the major sources of the output from the basal ganglia. In fact, they have similar output functions, as substantia nigra pars reticulata is part of the globus pallidus, only separate from it by fibers of the internal capsule (Purves *et al.*, 2001).

Note that projections from the medium spiny neurons to the globus pallidus and substantia nigra converge onto pallidal and reticulata cells. On average, more than 100 medium spiny neurons innervate each pallidal cell (Fahn and Jankovic, 2007).

The efferent neurons of the internal globus pallidus and substantia nigra pars reticulate give rise to the major pathways that link the basal ganglia with upper motor neurons in the cortex and in the brainstem. The pathway to the cortex arises in the internal globus pallidus, passes throw the ventral anterior and ventral lateral nuclei of the dorsal thalamus, and reaches the motor cortex. This loop originates in multiple cortical areas and terminates, after relays in the

basal ganglia and thalamus, back in the motor and premotor areas of the frontal lobe. On the other hand, the neurons from substantia nigra pars reticulata synapse in the superior colliculus (monosynaptic projections), commanding eye movements. However, this difference between the globus pallidus and substantia nigra pars reticulata is not absolute.

The main output of the basal ganglia is inhibitory, since the efferent cells are GABAergic (like the projections from the medium spiny neurons). However, in contrast to those quiescent cells, these neurons have high levels of spontaneous activity that tend to prevent unwanted movements by tonically inhibiting cells in the superior colliculus and thalamus (Purves *et al.*, 2001).

The net effect of the excitatory inputs from the cortex to the striatum is to inhibit the tonically active inhibitory cells of the globus pallidus and substantia nigra pars reticulata.

What normally happens in the absence of body movements is that the globus pallidus neurons provide tonic inhibition to the relay cells in the VL and VA nuclei of the thalamus, as the cerebral cortex, the substantia nigra pars compacta and the striatum are silent (Boonstra *et al.*, 2008).

What normally happens in the presence of body movements is that the neurons from cerebral cortex and substantia nigra pars compacta fire, originating the inhibition of the pallidal cells by activity of the medium spiny neurons, and consequently the desinhibition of the thalamic neurons. As a result, they can relay signals from other sources to the upper motor neurons in the cortex, and from there to local circuit and lower motor neurons that initiate movements (Fahn and Jankovic, 2007).

An abnormal increase in the tonic inhibition as a consequence of basal ganglia dysfunction leads to few excitability of the upper motor neurons, and thus to the hypokinetic movement disorders such as Parkinson's disease (PD**)**.

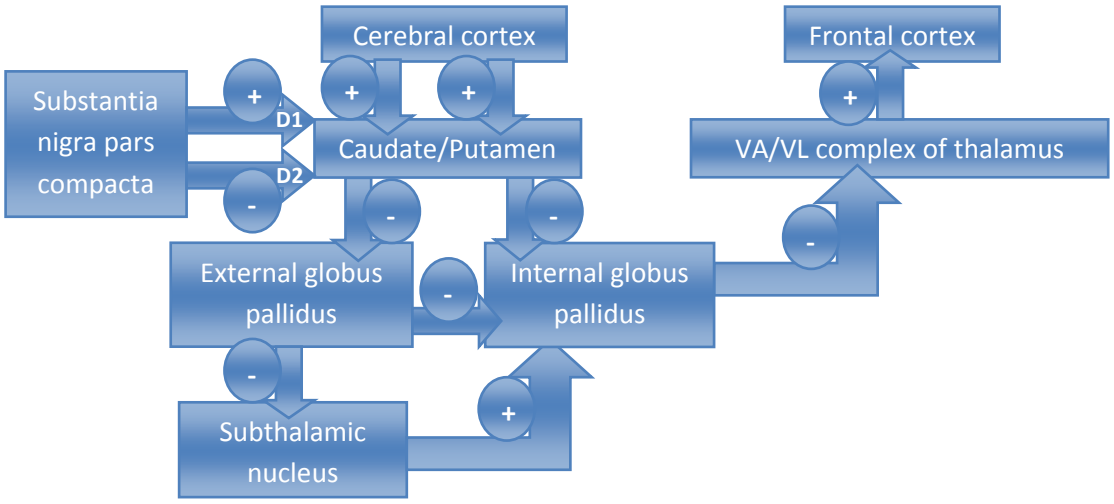
An abnormal reduction in the tonic inhibition as a consequence of basal ganglia dysfunction (because of the indirect pathway, explained later) leads to excessive excitability of the upper motor neurons, and thus to the involuntary movement and hyperkinetic syndromes that are characteristic of basal ganglia disorders such as Huntington's disease (HD) (Fahn and Jankovic, 2007).

3.1.3. The basal ganglia circuits

The projections from the striatum to the globus pallidus internal and substantia nigra pars reticulata form in part a "direct pathway", which serve to release the upper motor neurons from tonic inhibition, and an "indirect pathway", that increases the level of tonic inhibition on the upper motor neurons (Cowie *et al.*, 2010).

In this last pathway, the striatum projects to the external segment of the globus pallidus, which sends projections both to the internal segment of the globus pallidus and to the subthalamic nucleus of the ventral thalamus. This one, with excitatory neurons, projects back to the globus pallidus internal and to the substantia nigra pars reticulata, and then out of the basal ganglia, as described. The indirect pathway serves to modulate the disinhibitory actions of the direct pathway (Fahn and Jankovic, 2007).

What normally happens when the indirect pathway is activated by signals from the cortex is that the striatum inhibits the tonically active GABAergic neurons of the globus pallidus external, making the subthalamic neurons more active and thus increasing the inhibitory outflow of the basal ganglia. The direct and the indirect pathways are an example of interplay between excitation and inhibition, used to achieve control (Purves *et al.*, 2001).



Scheme 2: Indirect and direct basal ganglia pathways (adapted from Purves *et al.*, 2001).

3.2. Verifying disorders in the circuits and pathways

What happens if the fine control of the subthalamic nucleus is destructed is that a source of excitatory input to the globus pallidus internal and reticulata is removed, reducing the inhibitory outflow of the basal ganglia to the upper motor neurons. That result in a syndrome called hemiballismus, characterized by violent and involuntary movements of the limbs (Purves *et al.*, 2001).

The dopaminergic cells in the substantia nigra pars compacta modulate the output of the corpus striatum. This one projects directly to compacta, which sends dopaminergic projections back to the spiny neurons. These influences are complex, because there are: excitatory inputs that project to the internal globus pallidus (D1 type dopaminergic receptors) – direct pathway – and inhibitory inputs that project to the external globus pallidus (D2 type receptors) – indirect pathway. However, these differences between the influences of the nigrostriatal axons produce the same effect: a decrease in the inhibitory outflow of the basal ganglia and thus an increase in the excitability of the upper motor neurons (Cowie *et al.*, 2010).

Disorders in this second internal circuit explain many syndromes. PD, for example, is caused by the loss of nigrostriatal dopaminergic neurons. So, when the compacta cells are destroyed, the inhibitory outflow of the basal ganglia is abnormally high, and activation of upper motor neurons is less likely to occur. Indeed, PD is a hypokinetic movement disorder, where any movement is difficult to initiate and, once initiated, is difficult to terminate. Also, the resulting increase in tonic inhibition in the superior colliculus causes reduction in frequency and amplitude of saccades (Purves *et al.*, 2001).

In the same way, understanding the indirect pathway helps to explain the motor abnormalities seen in HD. In this disease, medium spiny neurons that project to the external globus pallidus degenerate. In the absence of their normal inhibitory input, the external globus pallidus cells become abnormally active, which reduce in turn the excitatory output of the subthalamic nucleus to the internal globus pallidus. The inhibitory outflow of the basal ganglia is, eventually, reduced. Consequently, upper motor neurons can be activated by inappropriate signals, resulting in the ballistic and choreic movements that characterize HD (Fahn and Jankovic, 2007).

Other non-motor systems can be also influenced by the basal ganglia, with similarly important clinical implications (oculomotor loop, prefrontal loop, limbic loop).

The pathological changes in neurological diseases can provide insights about the function of the basal ganglia. For instance, the substantia nigra is largely absent in the region above the cerebral peduncles in patients with PD. Another example is the size of the caudate and putamen (the striatum), which is dramatically reduced in patients with HD (Purves *et al.*, 2001).

3.3. Parkinson's disease

3.3.1. Definition and general features

PD is the second most common degenerative disease of the nervous system (Alzheimer's disease is the leader).

It was described by James Parkinson in 1817 and it is characterized by bradykinesia (slowness of movement) and hypokinesia, resting tremor, altered gait, rigidity of the extremities and neck (muscular rigidity), postural instability, minimal facial expressions, together with autonomic dysfunctions. What's more, gait is characterized by short steps, stooped posture, and a deficit of associated movements like arm swinging. Sometimes this is associated with dementia. Fifteen to twenty years after the onset, the slowly progressive disease can culminate in death (Purves *et al.*, 2001).

The motor defects are the result of the progressive loss of dopaminergic neurons in the substantia nigra pars compacta. The cause (etiology and pathogenesis) of the deterioration of these dopaminergic neurons is largely unknown, but genetic investigations are taking part.

The majority of cases of PD are sporadic; nevertheless there are some susceptibility genes that confer increased risk of acquiring the disease (less than 10 % of all cases) (Purves *et al.*, 2001). Mutations of three distinct genes (*α-synuclein*, *Parkin* and *DJ-1*) have been found in rare forms of PD. Identification of these genes can open more ways of elucidating the pathogenesis and testing therapies (Fahn and Jankovic, 2007).

3.4. Huntington's disease

3.4.1. Definition and general features

HD was described by George Huntington in 1872 and it is characterized by the gradual onset of defects in behavior, cognition and movement, beginning in the fourth and fifth decades of life (occasionally in childhood or adolescence - Juvenile Huntington's disease), lasting ten to twenty years and resulting in death (Roos, 2010).

HD has an autosomal dominant pattern, and usually presents as an alteration in mood (e.g. depression) or a change in personality like increased irritability, suspiciousness and impulsive/eccentric behavior (Purves *et al.*, 2001). Defects of memory and attention can also occur. However, the most remarkable features are: rapid, jerky movements with no clear purpose, which can be confined to a finger or can involve a whole extremity, the facial musculature or even the vocal apparatus, named chorea. They are involuntary, but the patient incorporates them into apparently deliberate actions, in order to hide the problem. There is no weakness, ataxia or sensory deficit. In juveniles, there is rigidity, seizures, augmented dementia and a faster progressive course (Roos, 2010).

A profound but selective atrophy of the striatum, with some associated degeneration of the frontal and temporal cortices are present. These can explain the disorders of movement, cognition and behavior, and the sparing of other neurological functions.

In 1983, the HD mutant gene was mapped to the short arm of chromosome 4 (4p16.3), by DNA polymorphisms. The positional cloning helped to identify the HD gene, HTT gene. Its mutation is an unstable triplet repeat, which passes from 15-34 repeats (in normal individuals) to 36-66+ in HD patients. The repeats consist of a DNA segment (CAG) that codes for the aminoacid glutamine and is present within the coding region of the gene. The longer the CAG

repeats, the earlier the onset of the disease. In cases of Juvenile Huntington's disease the repeat often exceeds 55 (Purves *et al.*, 2001; Roos, 2010).

These increased numbers of glutamines alter protein folding, which somehow triggers a cascade of molecular events culminating in dysfunction and neuronal death.

Unexpectedly, *huntingtin* is also expressed in regions of the brain that are not affected in HD and in many other organs outside the nervous system. Why the mutant *huntingtin* only injures striatal neurons is still unclear (Purves *et al.*, 2001).

3.5. Features of gait disorders in Parkinson's disease

Altered gait (walking pattern) is one of the features of the PD. Stride length, gait variability and fractal-like scaling of gait are all impaired in PD (Hausdorff, 2009).

About 20% of people over the age of 80 have Parkinsonism associated gait disturbances. The major motor disturbances in PD have been yet referred.

3.5.1. Classification

The gait disturbances in PD can be divided into two types: continuous and episodic. The last ones occur occasionally, without an explanation, and include festination, start hesitation, and freezing of gait (FOG) - in patients with advanced PD. On the other hand, the first ones appear to be consistent and persist all the time. They include: shortened stride length, augmented gait variability and diminished fractal scaling. Certain episodic symptoms are associated with other continuous symptoms, for example patients with FOG have increased gait variability. Although both types of gait disturbances are a result of basal ganglia dysfunction, the specific mechanisms responsible for the episodic and continuous gait disturbances are independent. However, both contribute to the risk of falls in PD, which are the most significant consequences of a disturbed gait in PD (Boonstra *et al.*, 2008).

As the disease progresses, gait impairment and falls become one of the principal complaints among PD patients. In a study, 43% of the PD patients reported at least one fall in 12 months (Hausdorff, 2009). Almost a double of what is seen in healthy adults. Fall rates were even higher in studies that also included "near falls" (missteps and loss of balance). And we cannot forget all the negative consequences of falls.

3.5.2. Continuous gait disturbances investigation

Continuous gait disturbances that can be seen using visual observation are: reduced gait speed with decreased arm swing, longer double limb support, and impaired postural control. These may be explained by the reduction and shortening of stride length (Chee *et al.*, 2009).

There is also gait disturbances, like increased gait variability, which only becomes apparent when gait is evaluated quantitatively with gait analysis systems, such as: increased left-right asymmetry, diminished left-right bilateral coordination, and higher stride-to-stride variability. Those characteristics can be seen in all patients with PD.

Gait variability (unsteadiness or inconsistency and arrhythmicity of stepping) is closely associated with risk of falls and postural instability. However it is independent of gait speed. When a long time scale is used, some variability is a sign of health; but in the short time scale, increased variability is a sign of diminished control. The last one can be decreased by therapeutic interventions (levodopa), although it remains always increased in fallers compared to nonfallers. That was confirmed by the findings of Hausdorff (2009) whose results demonstrate that levodopa has a benefic effect on increased gait variability and that dopamine circuits contribute to control gait variability. However, PD patients who fall can regulate this variability better than the others, which probably mean that they have increased impairment in those circuits and respond better to therapy.

Conversely, fall frequency and gait variability are not very related to tremor, rigidity or bradykinesia, in the OFF state (features that arise more than 12h after the last intake of anti-Parkinsonian medication, when the drug effect is minimal) (Moore *et al.*, 2007).

About the pathophysiology of bradykinesia, the dopaminergic projection to the striatum provides a signal for implicit "motor motivation". Patients with PD have a higher probability of moving slowly because of a specific distortion of speed selection mechanisms: movements with lower energy expenditure are favored although a range of normal movements is available. It means that movement speed is determined not only by the speed-accuracy exchange (that can be normal in PD patients) but also by an implicit value assigned to movement energy cost, which is manifested as response intensity: movement vigor (that is altered in PD patients). Thus, dopamine from the substantia nigra to the striatum carries also a signal for "motor motivation" (Mazzoni *et al.*, 2007).

Average stride length, gait variability, and the fractal-like property of gait in PD (continuous gait disturbances) are all related.

3.5.2.1. The fractal-like scaling

How gait changes over time, from one stride to the next within a given walk is explained bellow. In healthy adults, gait is relatively unvarying. Still, closer examination reveals small stride-to-stride changes in the gait pattern. A good example is that the stride time (stride interval: time from initial contact of one foot to subsequent contact of the same foot) varies about its mean (Cowie *et al.*, 2010). For a long time, it was assumed that there is no meaning in these changes, but recently some studies have demonstrated the opposite: each stride time is related to stride times ten and hundreds of strides later. Stride-to-stride fluctuations reflect long-range correlations in the stride time and suggest a wider control (even during slow walking and during running). This is the fractal-like property of gait, which can be quantified

using a modified random walk analysis (detrended fluctuation analysis – DFA) (Moore *et al.*, 2007).

It signifies the presence of long-term memory in the locomotor control system. This scaling reduces the risk of perturbations, because as there is a range of different measures to stride time, it makes more difficult to originate problems in the walking pattern (variety, here, means stability). Thus, a fractal-like gait may be more flexible and adaptable (Hausdorff, 2009).

The fractal dynamics of the stride interval are largely independent of speed and intrinsic to the locomotor system. What is more, different aspects of stride dynamics mature at different ages; the fractal scaling index is lower in the healthy older adults compared to young adults (Hausdorff, 2009) and even lower in PD patients. The fractal-behavior promotes adaptability.

The long-range correlations in gait are related to CNS mechanisms (as it will be described in *Treadmill walking and dual tasking* and *Methylphenidate* sections). The fractal-like scaling has higher-level origins (Cowie *et al.*, 2010).

3.5.3. Gait dynamics

There have been some efforts aimed at measuring the gait rhythm, the timing of the gait cycle (stride time, as described above), the swing time (time when one foot is in the air), and stride length, which seemed to be a much more difficult task (Hausdorff, 2009).

To quantify how the dynamics fluctuate over time during walk, it is usual to apply DFA to each subject's sequence of stride times (Moore *et al.*, 2007).

Many healthy physiologic systems have fractal scaling indices of around 0.8 – 1.0 and values closer to 0.5 reflect a deviation from the healthy state. Previous work has shown that the fractal scaling index provides a measure of subtle changes in gait dynamics, which can separate healthy young from healthy older adults (Hausdorff, 2009).

3.5.4. Changes in the fractal scaling in Parkinson's disease

Among patients with PD, the stride-to-stride fluctuations in gait become more random, and the DFA scaling exponent becomes close to 0.5 (the value for white noise, an absence of long-range correlations) (Moore *et al.*, 2007).

The breakdown of the long-range correlations could be interpreted in different ways; one of them is that among patients with PD, gait loses its automaticity and fluidity. Each stride starts a new process, unrelated to the previous stride, and the memory of the locomotor control system is not long term and fractal-like anymore, but instead it becomes close to zero. Some statistical models have shown that many of the observed changes can be explained by the combination of neighboring neural networks and a loss of neurons (Hausdorff, 2009).

3.5.5. Gait features in mild Parkinson's disease

To better understand the pathophysiological mechanisms that influence gait in PD, it is helpful to identify the early alterations, in patients not yet treated with anti-Parkinsonian medications (*de novo* PD). However, only a few quantitative investigations have already taken part (Chee *et al.*, 2009).

PD alters the generation and regulations of a consistent gait rhythm, even early in the course of the disease, when observed alterations are not the result of any pharmacologic treatment and are largely confined to dopamine depletion in the nigro-striatal pathway.

Patients with early stage PD walk more slowly, with reduced swing times, increased left/right swing asymmetry and marked inconsistencies in the timing of gait (increased variability compared to controls). On the other hand, the fractal scaling exponent is not very different from that seen in healthy people. In *de novo* PD an altered gait pattern is already present, even though without dramatic changes (fairly intact gait speed). They have reduced stride length, increased gait variability and asymmetry in timing (Snijders *et al.*, 2010).

So, in the mild PD the behavior of the stride-to-stride fluctuations (fractal-like scaling) is almost intact, suggesting that this feature only becomes impaired later in the disease process. It is still unknown if there is any compensatory mechanisms or if the basal ganglia are not sufficiently damaged, in this early stage of the disease.

The different gait features are usually associated. Stride length is a fundamental property of gait. Gait speed and stride length are strongly associated. Gait variability is moderately associated with them. Furthermore, the fractal scaling index is not significantly correlated with variability, gait speed, or stride length (Hausdorff, 2009).

3.5.6. Effects of new approaches

3.5.6.1. Rhythmic Auditory Stimulation

Rhythmic auditory stimulation (RAS) can improve many spatiotemporal features of gait in patients with PD by providing an external clock that sets the pace and replaces the impaired internal rhythmicity in PD. It is a kind of physiotherapy (Boonstra *et al.*, 2008).

Using RAS, administered in the form of a metronome, improves: gait speed, stride length, and double support time, both in the ON and OFF states (after taking anti-Parkinsonian medication, when symptoms are minimal, and more than 12h after the last intake of anti-Parkinsonian medication, when the drug effect is minimal, correspondingly). These effects may persist even when walking without stimulation (Moore *et al.*, 2007).

However, when RAS is set to the subject's usual-walking rate, variability doesn't improve significantly. But, when the RAS is set 10% higher than usual-walking pace, variability considerably decreases. Moreover, 15 min after walking with RAS at 10% higher, stride length and variability are still notably better than the baseline values.

Conversely, the fractal scaling index is unresponsive to RAS, and among healthy subjects RAS has no significant effects on stride length, variability or the DFA scaling exponent (Hausdorff, 2009).

Recent preliminary results suggest that auditory stimulation which includes small fluctuations about the mean, and not a simple constant pacing, may have more beneficial effects on the gait of patients with PD, compared to purely RAS (similarly to the constant pacing of a treadmill). However, treatment of movement disorders has not yet adapted this concept (Sollinger *et al.*, 2010).

3.5.6.2. Treadmill walking and dual tasking

Using a treadmill has potential to improve Parkinsonian gait. The treadmill can be used as an external cue to help restore and augment the impaired "pacemaker". It is proved that the treadmill reduces stride time variability and swing time variability, even in PD and healthy subjects, but the fractal scaling index does not change. Nevertheless, walking with a walking aid on level ground improves gait speed, but there is no effect on the fractal scaling or variability (Nilsson and Hagell, 2009).

So, during treadmill walking, PD subjects are able to walk with a less variable and more stable gait. Therefore, treadmill can be used as a pacemaker.

Gait speed and variability have independent natures.

Dual tasking (the performance of another task while walking) can alter the gait pattern. Healthy adults usually reduce the gait speed. Older adults reduce the gait speed and the duration of swing, and increase the support time, while gait variability is not affected. PD patients reduce the gait speed and the swing time, increase gait variability and decrease gait bilateral coordination (Boonstra *et al.*, 2008).

Normally, as the degree of cognitive loading worsens, so do gait variability and the fractal scaling index in PD, compared to usual walking. In contrast, gait speed decreases similarly even in healthy and in PD subjects. The cognitive domain has an extremely important role in the maintenance of a steady gait (Hausdorff, 2009).

3.5.6.3. Methylphenidate

Methylphenidate (MPH) is a central nervous system stimulant derived from amphetamine that works as a potent inhibitor of catecholamine reuptake. It is used to treat attention deficits in children and adults with hyperactivity disorder.

Since dopamine reuptake plays an important role in the regulation of dopamine in the synapse, and the hypodopaminergic state is at the basis of the PD, MPH may improve motor function in PD (Boonstra *et al.*, 2008).

It is known that PD patients have declined attention abilities and the cognitive domain has an extremely important role in the maintenance of a steady gait. That's why MPH can improve gait and reduce fall risk in PD subjects.

In response to MPH, cognitive function (attention and executive function) significantly improves, while memory and visual-spatial performance do not change. Gait speed, stride time variability and the fractal scaling index also notably improve.

Increasing attention can positively impact gait speed, gait variability, and the fractal scaling index in patients with PD, also other mechanisms may intervene here (Hausdorff, 2009).

Therapeutic interventions that improve gait properties have a profound, positive impact on Parkinsonian gait, fall risk, and the health-related quality of life of these patients. It is part of PD pharmacotherapy (Boonstra *et al.*, 2008).

3.5.7. Episodic gait disturbances investigation

Freezing of gait (FOG) has been identified as one of the main contributors to gait disturbances in PD, and it affects more than one-third of the patients mainly in the advanced stage of the disease (Moore *et al.*, 2007). It is known that reduced step length and the step to step reduction in amplitude may lead to the occurrence of FOG. The number of FOG episodes increase in patients with 50% of the normal stride length and further increase in patients with 25% of the normal stride length, compared to other conditions (patients without FOG). When the step length is artificially reduced (increasing step length variability), the same effects are observed as when there is an automatic reduction in step length during normal walking in a variable environment requiring different amounts of conscious attention (Chee *et al.*, 2009).

FOG is a paroxysmal phenomenon commonly seen in advanced PD and can be defined as an unintentional and temporary phenomenon where the feet fail to progress (Cowie *et al.*, 2010). Freezing episodes are transient, generally lasting for a few seconds, and tend to increase in frequency as the disease progresses. An episode of freezing can be considered to have ended when the patient takes at least two steps at or near their normal step length (Boonstra *et al.*, 2008).

FOG that arises after taking anti-Parkinsonian medication, when symptoms are minimal, is named FOG in the ON state. FOG that arises more than 12h after the last intake of anti-Parkinsonian medication, when the drug effect is minimal, is named FOG in the OFF state (Moore *et al.*, 2007).

Environmental constraints requiring a change in the gait speed, pattern or direction, such as an obstacle, turning, walking in confined spaces or on reaching a destination will often trigger a freezing episode (Snijders *et al.*, 2010). They can also occur spontaneously when walking in an open space, in the later stages of PD. FOG is also influenced by cognitive factors, such as

stress, anxiety and attention (dual tasks). The main common cause is the reduction in step length.

FOG is usually evoked in crowded and confined spaces as well as when having limited time, like when crossing a street. It is one of the most distressing symptoms in PD, and it is associated with longer disease duration, more advanced disease stage, falls, dyskinesias, and decreased mobility (Nilsson and Hagell, 2009). Stride-to-stride variability further increases in patients with PD who experience FOG in the OFF state.

Festination is a less severe gait disorder than akinetic FOG, and both forms are less severe compared to a disordered gait with a need for external help to continue walking (Ziegler *et al.*, 2010).

Iansek *et al*. (2006) suggested that FOG during walking was possibly due to the presence of the sequence effect (gradual step to step reduction) in combination with an overall reduced step length which, if small enough, would eventually lead to freezing. However, that hypothesis was based on the duality of basal ganglia function and malfunction in PD in the elaboration of automatic movement in conjunction with the supplementary motor area. The basal ganglia maintains cortically selected motor set in the supplementary motor area and provides internal cues to that motor area in order to enable each sub movement to be correctly linked together. Contrary to hypokinesia, the sequence effect does not respond to medication or attention strategies. It does disappear with the use of external cues: goal directed behavior and gait. It also suggested that the dual causation of hypokinesia and shortening of steps lead to the occurrence of FOG during walking, on the basis that the sequence effect was present before the onset of freezing.

Five subtypes of freezing have been identified: start hesitation at initiation of walking, freezing on turning, freezing in restricted areas, destination freezing, and open space hesitation in the absence of stimuli likely to result in FOG (Chee *et al.*, 2009).

Other possible explanations for FOG include the dysfunctional execution of internally generated motor sequences in gait (asymmetric gait and timing disorder), and spatial vision processing errors (Sollinger *et al.*, 2010). People who experience FOG commonly use "rescue" techniques such as imagery or inverted walking sticks; one theory is that this use of visual information bypasses the basal ganglia and a normal step length is produced. Gait vastly improves when visual cues are set for a normal step length (Chee *et al.*, 2009), exemplifying that there is a perceptual cause for this motor impairment (Almeida and Lebold, 2010). It appears that freezing is related to dopamine deficiency, as levodopa therapy does have some effect on alleviating it, specifically by decreasing the frequency and duration of freezing episodes.

Factors which increase preferred step length may equally eliminate FOG and these include focused attention, attentional strategies, medication and visual cues (goal directed behavior). Only the latter, however, eliminate the sequence effect.

Rehabilitative techniques should focus on assisting PD patients to concentrate on maintaining step length during walking episodes to prevent gait difficulties (Chee *et al.*, 2009).

3.5.8. Axial mobility deficits in Parkinson's disease

Patients with PD often have difficulty turning around, not only while lying in bed, but also while standing upright. Turning problems may result from inability to adequately maintain an interlimb coordination, and also from axial rigidity and loss of intersegmental flexibility (Boonstra *et al.*, 2008).

Another factor that may contribute to postural instability is the osthostatic myoclonus or tremor, which improves on levodopa or clonazepam, correspondingly. In contrast to tremor, axial deficits were related to increases in ventricular volume (seen using MRI). Asymmetries

in gait are also a symptom of early stage PD, present even though stride-to-stride variability is normal, in the early stages.

Walking and standing are not purely automatic tasks, regulated only by subcortical control mechanisms. Gait is a complex "higher-order" form of motor behavior, with varied influences of mental processes, which become evident when PD patients are unable to deal with multiple tasks simultaneously (Iansek *et al*., 2006)

Postural instability is not only a result of disturbed motor programming of postural corrections within the basal ganglia (efferent deficit) but also a result of central proprioceptive disturbances (afferent deficit), seen also in arm movements.

There is some balance correcting strategies to prevent patients from falling, like stretching out the arms and taking compensatory steps. However, PD patients have difficulties initiating a compensatory step, as that failure may be due to impairment of anticipatory postural adjustments. External help or visual inputs (e.g. a visual target) can ameliorate compensatory stepping, but the impossibility to see their own legs deteriorate it (Chee *et al.*, 2009).

3.6. Features of gait disorders in Huntington's disease

HD is a phenotypically heterogeneous disease characterized by chorea, dystonia, bradykinesia, cognitive decline and psychiatric comorbidities. Balance, gait impairments, and falls, are common manifestations of the disease (Goldberg *et al.*, 2010)

The diagnosis of HD is based on the presence of an extrapyramidal movement disorder in the context of a positive family history of HD (Rao *et al.*, 2008). Impairment of voluntary movements and gait are present through the course of the disease and worsen with disease progression, in relation with marked loss of function.

In HD patients, gait is characterized by a timing disorder with marked intraindividual variability in temporal gait parameters (caused by the presence of both hyperkinetic and hypokinetic features) (Delval *et al.*, 2008).

Walking is often described as "drunk" or "cerebellar ataxia"-like. Distinguishing between choreatic and ataxic walking is very difficult. Pyramidal signs (*Babinski* sign) are present incidentally (Roos, 2010).

Gait, bradykinesia and dynamic balance impairments begin in the presymptomatic stage of HD and continue to worsen in the symptomatic stages.

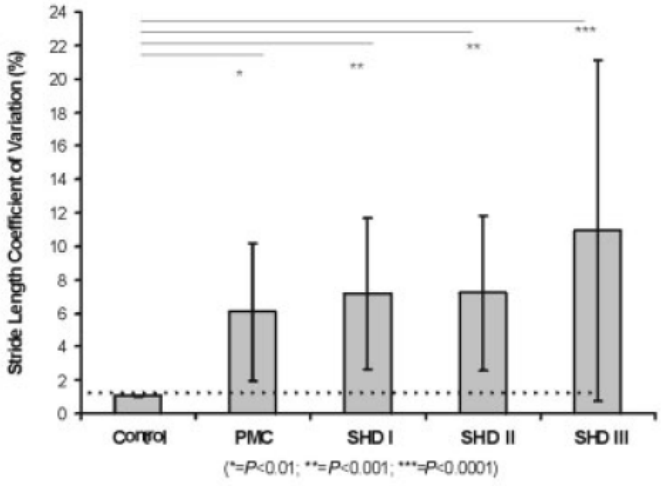
Motor dysfunction including gait and balance disturbances, chorea and dystonia, Parkinsonism, and other signs and symptoms (oculomotor abnormalities, dysarthria, and dysphagia), contribute substantially to the functional burden of the disorder (Feigin, 2011).

3.6.1. Gait impairments in Huntington's disease

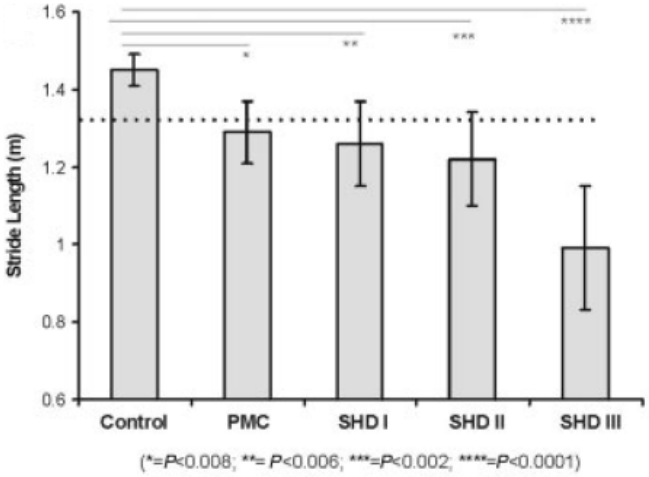
Important gait impairments in symptomatic HD subjects include: decreased gait velocity, decreased stride length, decreased cadence, disordered temporal control of gait, and greater variability in spatial and temporal measures compared with healthy subjects (Delval *et al.*, 2006). Balance impairment has been demonstrated as a compensatory increase in base of support during walking (Paulsen *et al.*, 2006). Gait bradykinesia is a result of decreased stride length and decreased cadence; increased variability in temporal control is caused by inability to modulate internal cues or integrate sensory stimuli for movements (Delval *et al.*, 2006). Increased stride-to-stride variability may reflect defective neural gait machinery, plus a contribution from excessive choreatic movements (Grimbergen *et al.*, 2008).

In Rao *et al.* (2008) study, impairments in stride length (decreased amplitude and increased variability) began in the presymptomatic stage of HD whereas impairments in cadence were only seen in the symptomatic stages of HD. Gait velocity is modulated through control of

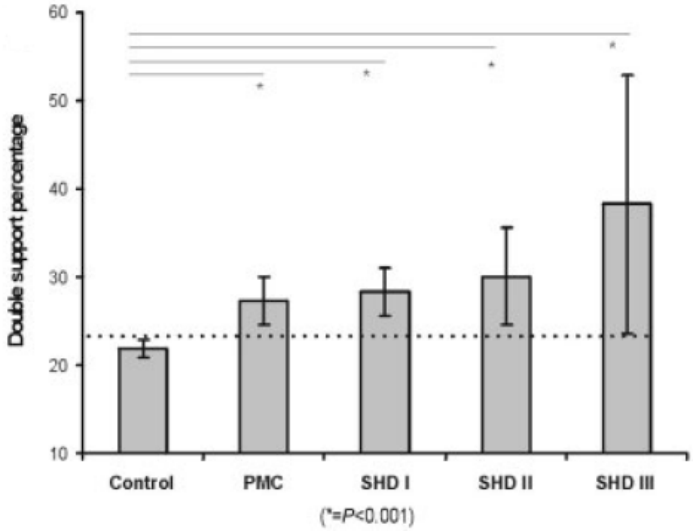
stride length and cadence. Also, impairment in double support time began in the presymptomatic stages of HD, whereas increases in base of support were only seen in symptomatic HD subjects. Gait outcome measures may serve as sensitive behavioral markers, particularly in the early stages of HD, and quantitative gait assessment was very sensitive in differentiating between subjects with and without the HD mutation.



Graphic 1.



Graphic 2.



Graphic 3.

Graphics 1, 2 and 3: Show comparison of stride length, stride length coefficient of variation, and percent time in double support for controls, presymptomatic mutation carriers (PMC), symptomatic HD (SHD) stage I, SHD stage II and SHD stage III subjects. The horizontal lines represent the cutoff value at which sensitivity and specificity were optimal. (Rao *et al.*, 2008)

Also presymptomatic HD subjects have significant gait impairments such as gait bradykinesia and dynamic balance impairment, consistent with reports of bradykinesia in hand and eye movements. In addition, they demonstrate greater variability in gait (compared with non-HD patients), as well as in arm and hand movements. Gait impairments begin very early in HD, before onset of clinically observable symptoms (Paulsen *et al.*, 2006).

The cause of gait bradykinesia in symptomatic HD is unclear: while some studies suggest that bradykinesia may arise due to reduced stride length and cadence (Rao *et al.*, 2008), others indicate that bradykinesia may arise due to a problem with cadence regulation (Delval *et al.*, 2007).

Motor impairments may arise due to pathology in the thalamocortical projections from the basal ganglia, as cellular degeneration in the basal ganglia has been reported well before onset of motor symptoms. Structural MRI scans have shown that basal ganglia volume is decreased

in presymptomatic HD compared with non-HD patients and continues to decrease in the symptomatic stages. Decreased amplitude of somatosensory evoked potencials in the thalamocortical pathway may be related to cellular degeneration, indicating a disorder in the feedback sensory loop between basal ganglia and frontal motor areas (Paulsen *et al.*, 2006).

Gait impairments begin well before clinically observable symptoms, and gait measures may be sensitive markers for detecting subtle changes.

3.6.2. The role of external cueing

A reduction in cadence, walking speed, and stride length, as well as an increase in stride-to-stride variability, are some of the features observed. Executive deficits are also of major importance, as concurrent performance of motor and cognitive tasks can have marked effects on gait in PD patients but also in HD patients. It has been suggested that external auditory and visual cues may be useful for maintaining gait performance by improving attentional resources, directing attention to the task of walking, as rhythmic cues may act by compensating for defective internal cue generation by the basal ganglia in PD, for instance, because they can synchronize their footsteps with a metronome. However, HD patients fail to achieve the cadence set by the metronome, which can be related to the attentional deficits that are present in HD, worse than in PD. Moreover, HD patients present an important inability to suppress interfering information (Delval *et al.*, 2008).

The fact that a metronome (which can replace the internal cueing provided by the basal ganglia and by the internal pallidum) does not improve gait points to the hypothesis that different motor circuits can be altered in HD: the pallidothalamic excitation leading to hyperkinesia can interfere in the early stages of the disease, explaning the gait instability.

Both motor and cognitive circuits are involved in HD patients' failure to synchronize gait with a metronome (Delval *et al.*, 2008).

3.6.3. Risk factors for falls in Huntington's disease

Little is known about the epidemiology, circumstances and consequences of falls, as well as about the pathophysiology underlying falls in HD. Firstly, motor symptoms such as chorea or bradykinesia (leading to inappropriate execution of corrective steps or protective arm movements and reduced step height) may disturb balance and gait, contributing to falls and increasing the risk of tripping. Secondly, balance may be compromised by abnormal postural reflexes, leading to inadequate responses (like balance correcting, in leg muscles) to external perturbations. Thirdly, disturbances in behavior and cognition (like aggression and inattention, respectively) can underlie falls in HD. Factors such as use of sedative medication and alcohol intake can also originate falls (Grimbergen *et al.*, 2008).

In Grimbergen *et al.*, 2008, study quantitative analyses revealed abnormalities of gait and balance that were more pronounced in HD patients with falls compared to patients without falls, and no serious injuries were reported. In addition, only few patients were afraid of falling, which is the opposite of the PD patients. This study also indicate that recklessness do not contribute much to falls and injuries. Balance deficits in HD are not that prominent and may progress slowly, allowing for compensatory strategies to develop.

Factors that may contribute to the pathophysiology underlying falls in HD are: excessive choreatic trunk movements that lead to unstable walking (increased postural sway); bradykinesia (reduced step height and walking speed); balance impairment, but with a minor role; cognitive decline (as observed also in Alzheimer's disease and PD), associated with balance disorder; indeed, the majority of falls in HD occur under so-called "multiple task" circumstances (Camicioli *et al.*, 2006; Pluijm *et al.*, 2006; Pickering *et al.*, 2007; Voermans *et al.*, 2007).

3.6.4. Compensatory techniques

Compensatory rapid stepping to maintain equilibrium in older adults is established, but little is known about the role of stepping response times (SRTs) in balance control in people with HD.

HD patients exhibit slower SRTs, lower balance confidence, and poorer dynamic balance, mobility and motor performance than non-HD patients. SRT appears to be sensitive to detecting real changes in people with HD, and is an objective marker of disease progression (Goldberg *et al.*, 2010).

While walking, humans move the body's center of mass over the base of support to restore equilibrium, and the execution of a compensatory step may be required to rapidly alter the base of support to restore stability during challenges to equilibrium in daily activities (Rao, Louis and Marder, 2009).

HD patients have: slower SRT, slowed gait, prolonged reaction time, slowed movement time of the upper extremity, and longer reaction time and reduction in speed of the first step of ambulation, findings that are consistent with bradykinesia as an integral feature of the disease phenotype (Goldberg *et al.*, 2010).

Deficits in SRT are associated with impairments on clinical measures of balance, mobility, and motor performance. It correlates with gait-related predictors of institutionalization.

SRT may be useful in assessing disease progression, as well as the efficacy of pharmacologic (neuroprotective agents) and rehabilitative interventions. Only SRT changes exceeding 241.8 ms should be considered to reflect real change in people with HD (Goldberg *et al.*, 2010).

3.7. Assessments: scales

The clinical assessment of the symptoms and signs of PD and HD is important for patient, family and care-givers. To follow the patient systematically, mainly for research purposes, several scales have been developed.

Patient-reported assessments (self-evaluation) of FOG in PD, such as FOG Questionnaire (FOGQ), are needed because FOG is difficult to assess objectively. Therefore, Giladi *et al.*, 2000, developed the FOGQ, a clinician administered patient-reported rating scale. FOGQ scores are correlated with PD duration, the Timed Up and Go test (see below), fear of falling, dyskinesia and motor fluctuations, which is not surprising as they are associated with more severe PD and so with FOG. Fallers have higher FOGQ scores than non-fallers (Nilsson and Hagell, 2009).

Among the approaches to achieve a standardized measurement of FOG is the "old" United Parkinson's Disease Rating Scale (UPDRS), which assesses the severity dimension. It does not differentiate the symptom from the cause, and records frequency and consequential falls on one scale. It also does not evaluate FOG in dual-task situations, but only in the context of the Parkinsonian movement disorder (Ziegler *et al.*, 2010). The motor part of the UPDRS emphasizes the classic trias of Parkinsonian symptoms, such as tremor, rigidity, and bradykinesia, and has not been designed to include symptoms of movement initiation, such as freezing (Ziegler *et al.*, 2010).

The 14-item Parkinson-Activity-Scale (PAS) assesses general mobility, and includes six questions that are related to FOG during starts or turns, in the context of the Parkinsonian movement disorder (Ziegler *et al.*, 2010).

To ensure valid and reliable measurement of FOG, a combined methodology with tests of complex gait together with a FOGQ has been recommended, named FOG score (Ziegler *et al.*, 2010).

Fear of falling can be evaluated using the Activities-specific Balance Confidence (ABC) scale, which has been validated for use in PD and HD. It is known that people sense their own instability before doctors can detect that physically. Falls due to syncope are thought to be uncommon in PD (Boonstra *et al.*, 2008). ABC is a measure of balance confidence in which individuals verbally rate their confidence on a scale of 0% (not confident) to 100% (completely confident) in performing a series of 16 balance-challenging tasks of daily living. Balance confidence is low in recurrent fallers with HD (48,9%) (Goldberg *et al.*, 2010) and PD (Boonstra *et al.*, 2008).

The Timed Up and Go (TUG) test is a clinical balance and mobility test, such as the Berg Balance scale. They are a measure of dynamic balance and functional mobility; TUG is the time taken to rise up from the seated position, walk 3 m at "comfortable and safe" walking speed, turn around, and walk 3 m to return to the seated position. TUG scores $\geq$ 14 are associated with an increased risk for recurrent falls in HD patients (Goldberg *et al.*, 2010).

Functional Reach (FR) is a reliable measure of anticipatory balance control and margin of stability. FR is the maximum distance one can reach forward beyond arm's length while maintaining a fixed base of support in standing, and is measured with a yardstick affixed to the wall at the level of the acromion (Rao *et al.*, 2009).

Unified Huntington's Disease Rating Scale (UHDRS) is a standardized clinical rating scale, that measures motor, cognitive, and behavioral function in HD, preceded by a history and medication scheme (Roos, 2010). Example of items: gait, tandem walk, and retropulsion (from 0 – normal, to 4 – maximum disability, each; for a total possible of 12) (Goldberg *et al.*, 2010).

More studies are needed to develop a clinical instrument that is fast, cheap, and allows short-interval assessment.

3.8. Treatment approaches

3.8.1. Parkinson's disease

Gait and balance problems in PD tend to be perceived as being "untreatable", but there are various therapeutic options (Bloem and Geurts, 2008).

The main options are: pharmacotherapy, neurosurgery and physiotherapy, with the last two gaining more and more importance. Various studies highlighted that they may adversely affect balance and gait in PD (Boonstra *et al.*, 2008).

3.8.1.1. Pharmacotherapy

Clissold *et al.* (2006) study showed that, although the proportion of "mid-line" motor disability increases with time, these deficits do not become unresponsive to levodopa. For instance, it can reduce the frequence of FOG episodes (Bloem and Geurts, 2008).

However, levodopa may also adversely affect gait or balance control, leading to an increased risk of fall-related fractures (e.g., hip fractures), because of some adverse effects, such as violent dyskinesias or drug-induced orthostatic hypotension, or simply because patients on levodopa are more mobile and more prone to fall (Almeida *et al.*, 2007). Falls occur despite maximal treatment with levodopa, confirming that axial disability in late stage PD is largely dopa-resistent (likely due to extranigral and nondopaminergic brain lesions – unlike the appendicular movements, which appear to be controlled by separate dopaminergic neural systems) (Boonstra *et al.*, 2008).

A new approach is methylfenidate (as mentioned previously), which can decrease fall risks in community dwelling older adults, by increasing availability of striatal dopamine or by improving attention, and improve gait and FOG in PD (Auriel *et al.*, 2006).

3.8.1.2. Stereotatic neurosurgery: deep brain stimulation

PD symtoms can be improved when electrodes are implanted in deep brain structures and electrical stimulation is delivered chronically at high frequency (**>** 100 Hz). Chronic electrical stimulation of deep neural structures is called deep brain stimulation (DBS). During DBS, these symptoms are improved by different network mechanisms operating at multiple time scales: locomotion takes more hours to improve than rest tremor, as locomotion (an axial symptom) improvement may involve a delayed plastic reorganization and rest tremor (a distal symptom) an instantaneous desynchronization of neural activity in subcortical structures, like subthalamic necleus (STN). Desynchronization and plasticity changes are two mechanisms that are believed to underlie the symptoms (Beuter and Modolo, 2009).

DBS reduces symptoms efficiently in eligible subjects, but its underlying physiological mechanisms are still unclear. Latencies for improvement onset when DBS is turned "on" vary across symptoms (seconds to hours), long-term efficient reduction in symptoms differs across signs (months to years) suggesting strongly that qualitatively different mechanisms are at work (Beuter and Modolo, 2009).

Bilateral STN stimulation is an effective treatment for PD, especially for appendicular symptoms that responded well to levodopa preoperatively. However, the effects of STN stimulation on axial motor signs remain debatable (Boonstra *et al.*, 2008). It has been suggested that medication and deep brain surgery may affect axial mobility deficits by acting on different neural systems; at least some of the effect of STN stimulation may act via "downward" projections onto the PPN (Gan *et al.*, 2007).

Locomotion involves a large network of neuronal structures, requiring more complex modulation. Synaptic reorganization may be due to a gradual modification of synaptic weights in structures down-stream from the STN, in which axonal activation occurs at the same frequency as DBS. As DBS in the STN, pedunculopontine nucleus (PPN), or globus

pallidus internal (GPi) is effective in improving locomotion, DBS of subcortical structures induces a gradual reorganization of synaptic weights in efferent structures, like the cortex. This supports the hypothesis that DBS modulates plasticity. DBS normalizes cortical activity in several areas: supplementary motor area, premotor cortex, and primary motor cortex. It means that electrical stimulation of deep structures (STN or GPi) may have powerful effects on cortical plasticity (Beuter and Modolo, 2009).

Desynchronization is equivalent to increasing cortical inhibition, which is defective in PD patients. To achieve the full potential of brain stimulation in PD, it will be needed to minimize invasiveness, optimize parameter adjustments, and reduce the cost of the procedure (Beuter and Modolo, 2009).

There are increasing concerns that deep brain stimulation may worsen axial mobility, sometimes as an immediate adverse effect of surgery, but also as a longterm complication. This inconsistent response was found in Gan *et al.*, 2007, study. Another particular worry is the development of new gait and balance deficits several years after surgery, even in the face of persistent beneficial effects on appendicular motor control (Boonstra *et al.*, 2008).

It has been speculated that variability in electrode placement can explain the inconsistent effects on axial mobility across patients. It could be that misplaced electrodes project unintentionally to the PPN, which, when stimulated at high frequencies, worsens gait and balance. On the basis of a Moreau *et al.* study, the authors proposed a two-staged STN frequency optimization: 130 Hz during the initial years of STN stimulation; and 60 Hz (at a higher voltage) after gait disorders have become manifest (Boonstra *et al.*, 2008).

Direct PPN stimulation is also possible to treat severe PD. It can improve axial symptoms directly postoperatively, and this persisting for 6 months. However, an extended follow-up is needed to evaluate long-term effects, as well as further research to investigate the effects in more detail and to study the effects of electrode (mis)placements (Ferraye *et al.*, 2010).

There are recent DBS procedures targeting multiple structures, like simultaneous implantation of electrodes in the STN and PPN. PPN stimulation is complementary to STN stimulation, providing greater gait improvement than STN stimulation alone, especially in the advanced stages of the disease. However, implanting double electrodes on each side of the brain appears highly invasive and poses ethical problems (Beuter and Modolo, 2009).

3.8.1.3. Physiotherapy

Visual feedback is really important to compensate for motor disabilities in PD (reminding the perceptual cause for FOG), therefore physiotherapy has a huge potential in the treatment (Boonstra *et al.*, 2008). Many patients with PD receive physiotherapy to alleviate symptoms of the disease, using treatments such as cueing and different forms of exercise.

External cues can raise small but significant improvements in clinical gait and balance scores, FOG severity, gait speed and step length, and timed balance tests. Rhythmic auditory stimulation may improve gait, persisting 2 to 15 min after cueing, suggesting some degree of retention (Boonstra *et al.*, 2008).

However, cueing can also have adverse affects. Arias and Cudeiro (2008) study showed that RAS can differentially affect freezers and nonfreezers, as RAS increased the step length for nonfreezers, but produced the opposite effect for freezers; that study also showed that visual cueing may adversely affect gait, depending on disease severity: falls may paradoxically increase when patients receive cueing treatment, because mobility improves and also because the cueing may distract patients from paying attention to environmental hazards. As a result, cueing should not be prescribed as a universal treatment, but should be carefully tailored to specific factors such as disease severity and individual symptomatology (Boonstra *et al.*, 2008).

Another concern is whether cueing will benefit patients in daily life with its complex situations, as it does in the lab. Some studies showed that auditory cues helped to improve walking speed during a dual task situation, whereas somatosensory cues had no effect, and visual cues had a negative effect (Boonstra *et al.*, 2008).

There is increasing attention for the possible beneficial effects of physical exercise in PD. Physical functioning, balance, gait speed, strength and health-related quality of life improve for people with PD after a physical exercise intervention. Exercise therapy may also lead to a reduction in FOG. However, there is insufficient evidence to support that physical exercise is beneficial for reducing falls or depression (Boonstra *et al.*, 2008).

Muscle rigidity is a predominant feature of PD. Therefore, physiotherapy strategies that are able to reduce muscle stiffeness and increase plantar-flexor power may be of benefit for PD patients and possibly improve their gait (Svehlik *et al.*, 2009).

Treadmill training may be one way to safely exercise patients with PD: because supervision is present and because a safety harness can prevent actual falls. Herman *et al.* (2007) study has shown that treadmill training can improve gait in PD. An alternative and more enjoyable way of exercise training is dancing: Hackney *et al.* (2007) study showed that tango dancing (20 sessions) benefits patients with PD.

The core treatment goals for physiotherapy includes: transfers, posture, reaching and grasping, balance, gait, and physical capacity. Important approaches are: cueing strategies to improve gait, cognitive movement strategies to improve transfers, exercises to improve balance, and training of joint mobility and muscle power to improve physical capacity (Boonstra *et al.*, 2008).

3.8.2. Huntington's disease

There is no cure to HD. Management should be multidisciplinary and is based on treating symptoms with a view to improving quality of life. Chorea is treated with dopamine receptor blocking or depleting agents. Medication and non-medical care for depression and aggressive behavior may be required (Roos, 2010).

Although many signs and symptoms can be treated, it is not always necessary to do so. The patient's limitations in daily life determine whether or not drugs are required. Very little evidence is available about the drug or the dosage to prescribe for any signs and symptoms. Drug treatment is, therefore, individualized and based on expert opinion and daily practice. Treatment consists of drug prescription and non-medication advice. Surgical treatment does not play an important role in HD (Roos, 2010).

3.8.2.1. Motor signs

Hyperkinesia (chorea) is treated with dopamine receptor blocking or depleting agents. Most commonly used drugs (table 1) are typical or atypical neuroleptics (dopamine receptor blocking) and tetrabenazine (dopamine depleting) (Roos, 2010). An extensive review of all medication is given by Bonelli and Wenning (2006) and Bonelli and Hofmann (2007).

Clozapine and olanzapine are atypical neuroleptics. Both have an antichoreatic effect. Clozapine requires white cell control in the blood and is less practical than olanzapine. The most frequently reported side effects are weight increase and anti-depressive effects. Prescribing quetiapine, zotepine, ziprasidone, and risperidone is also accepted (Roos, 2010).

However, only tetrabenazine, a dopamine depleting drug, has been shown in a controlled trial to significantly reduce chorea (Huntington Study Group, 2006; Jankovic and Clarence-Smith, 2011). The most common side effects are depression and sedation.

Tiapride	Max 600 mg
Olanzapine	Max 20 mg
Tetrabenazine	Max 200 mg
Pimozide	Max 6 mg
Risperidone	Max 16 mg
Fluphenazine	Max 10 mg
(drug dosages vary individually; here maximal dosages are given)	

Table 1: Drug treatment for chorea.

Pridopidine is an experimental drug candidate belonging to a class of agents named dopidines. Dopidines are a new class of pharmaceutical compounds that act as dopaminergic stabilizers, enhancing or counteracting dopaminergic effects in the central nervous system, and normalizing dopaminergic neurotransmission. They have a dual mechanism of action, displaying functional antagonism of subcortical dopamine type 2 (D_2) receptors as well as strengthening of cortical glutamate and dopamine transmission. Dopidines are, therefore, able to regulate both hypoactive and hyperactive functioning in areas of the brain that receive dopaminergic input, like cortical and subcortical regions. This potential ability to restore the cortical–subcortical circuitry to normal suggests that dopidines may be able to improve symptoms associated with HD (Feigin, 2011).

In Feigin (2011) studies, pridopidine was safe and well tolerated. They also suggest that pridopidine might benefit features of HD for which there are currently no treatments (eye movements, hand coordination, dystonia, and gait or balance problems). Future trials will be needed to confirm these potential effects, and to investigate whether functional benefits accompany the motor improvements. Moreover, since 90 mg dose was well tolerated, higher doses could be tried in future trials.

Drug treatment for hypokinesia has been tried using antiparkinsonian drugs, but almost always with very disappointing results. Therefore, in practice, they are not prescribed (Roos, 2010).

No drug is available with any neuroprotective or disease-delaying effect. Disease modifying drugs are developed, but not available. Also embryonic cell implants, still under study, are not proven treatment options at the moment (Roos, 2010; Feigin, 2011).

A well tolerated drug that produces even small benefits for patients would be a very welcome addition to the currently available treatments for this debilitating disorder (Feigin, 2011).

Surgical intervention to treat chorea has been described in only a few cases. Deep brain stimulation has a place in other movement disorders like PD, but not in HD.

3.8.2.2. Psychiatric, cognitive and behavioral signs

As depression and aggressive behavior are the most devastating to family life, the majority of drugs are prescribed for these signs (table 2). Non-medical interventions available are: physiotherapy, occupational therapy, speech therapy, dietician, psychologist, social worker, and nurse (Roos, 2010; Jankovic and Clarence-Smith, 2011).

Medical and non-medical treatment must be individually tailored, as the symptoms and signs differ by person and over time. Ideally treatment of patients and their families should be organized by a multidisciplinary team.

Depression		Aggression	
Citalopram	Max 60 mg	Citalopram	Max 60 mg
Fluoxetine	Max 60 mg	Sertraline	Max 200 mg
Mirtazapine	Max 45 mg	Olanzapine	Max 20 mg
Valproinezuur	Max 2000 mg	Dipiperon	Max 360 mg
Carbamazepine	Max 1600 mg	Haloperidol	Max 10 mg
(drug dosages vary individually, here maximal dosages are given)			

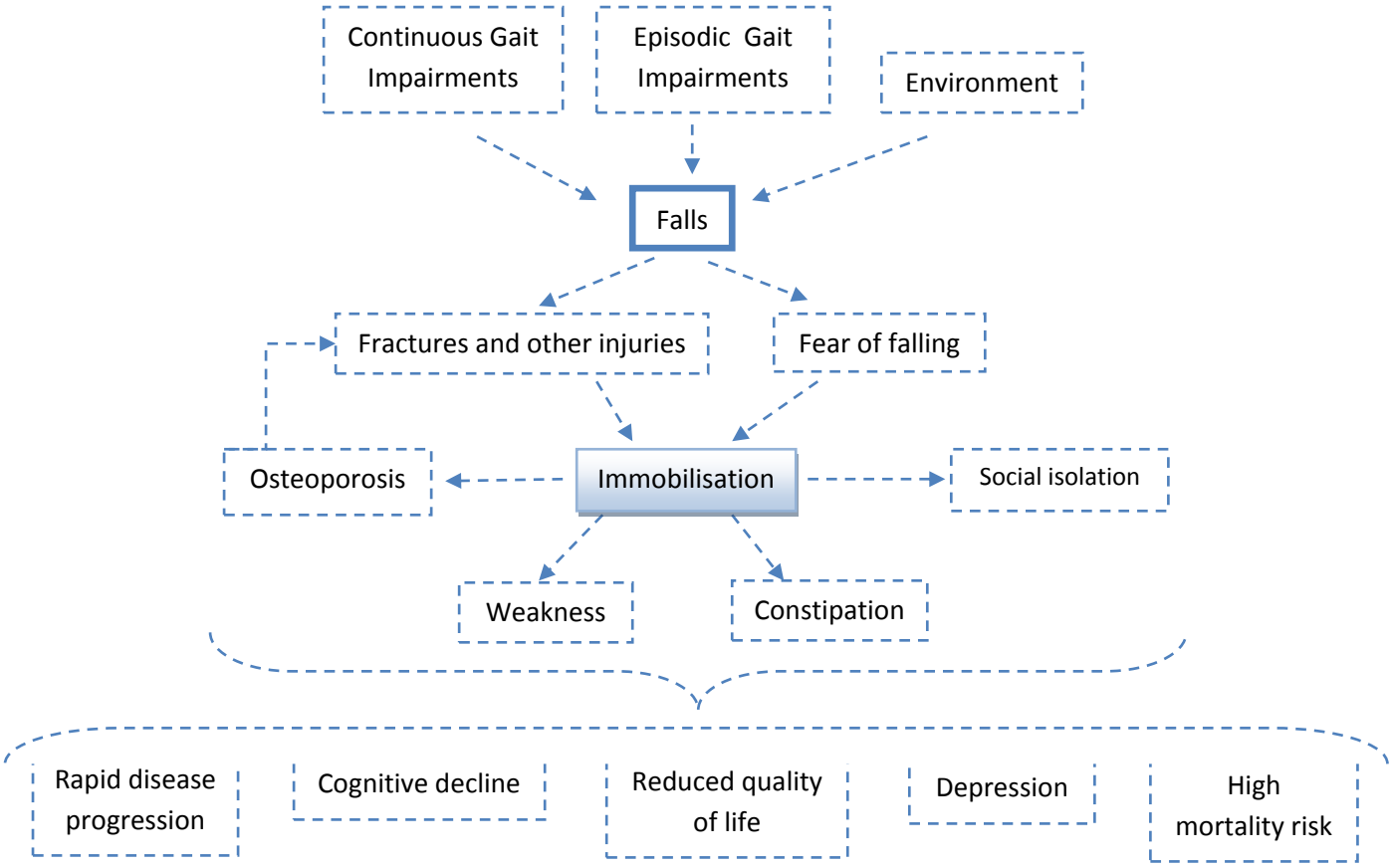
Table 2: Drug treatment for depression and aggression.

A better understanding of the HD pathophysiology will surely lead to drug development to interfere in the pathological process. We consider of major importance the development of effective treatment strategies aimed to reduce falls in HD, therefore more studies are needed.

3.9. Quality of life

PD is an incapacitating disease that negatively affects the quality of life for many reasons, such as: the presence of axial disability, gait disorders (discussed above), balance impairment, falls and fall-related injuries.

The negative impact of gait disorders on quality of life is very important, due to the resultant immobility, loss of independence and the risk of falling. Falls in general and in PD in particular may lead to injuries, hip fractures, fear of falling, and restriction of activities that in turn contribute to institutionalization, loss of independence, and increased mortality (Hausdorff, 2009). However, fall rates tend to decrease with disease progression, because patients become increasingly immobilized.



Scheme 3: Clinical impact of falls in patients with Parkinson's disease (adapted from Hausdorff, 2009).

Episodic gait disorders are particularly incapacitating because patients cannot adjust their behavior to these paroxysmal walking problems. A good example is FOG, which is an important cause of falls and injures, because of its sudden and unpredictable nature. FOG not only hinders efficient locomotion but also affects quality of life beyond gait and mobility (Moore *et al.*, 2007). Therefore, special attention should be given to FOG in the treatment of patients with PD.

Some studies associated FOG with falls, loss of independence and depression in patients with PD (Giladi and Hausdorff, 2006).

The aim of Moore *et al.* (2007) study was to examine the relationships between severity of FOG and quality of life in PD patients, based on the impression that FOG episodes are embarrassing when they occur in public and are a common cause for patients to avoid social interactions. It has not only mobility effects, but also psychological. In that study, FOG was found to have a direct effect on quality of life, beyond its effect on gait and mobility, which means that FOG has an added impact above falls and loss of mobility. Several explanations can be proposed: as an episodic event, FOG frequently catches the patient in the most uncomfortable and unpleasant situation, showing lost of control with regard to their own mobility, which is one of the most important patients' fears; another aspect is its social consequences, as FOG episodes are frequent in crowded situations (like in the theater) and in time restricted situations (like crossing the street), leading to much embarrassment and frustration, with emotional consequences. Those mental aspects of FOG, like emotional, cognition and communication dimensions, have an impact on patients' quality of life above the mobility aspects. Also FOG episodes can have a significant effect on the caregiver's quality of life. Here we can conclude that there is a clear need to assess and treat all those FOG consequences, as an example using behavioral cues (Moore *et al.*, 2007). Men and women are no different (Ho and Hocaoglu, 2011).

The profound impact on HD patients' physical and psychological well-being has been showed through data from generic quality of life questionnaires. On the other hand, interview studies allow patients to freely describe the impact of the disease, and play an important role in providing a meaningful understanding of patients' perspective on their own well-being (Ho and Hocaoglu, 2011).

In HD, a functional consequence of gait and balance impairments is increased risk for falls, as variability in stride length and step time is an established marker of fall risk (Delval *et al.*, 2006). Thus, quantitative examination of gait may be important in the identification of

individuals in the early stages of the disease, which may be at risk for falls later, with devastating consequences. Compared to nonfallers, fallers showed significantly higher scores for chorea, bradykinesia and aggression, as well as lower cognitive scores (Grimbergen *et al.*, 2008).

As a result, contributing factors for falls include a combination of "motor" deficits (mainly gait bradykinesia, stride variability and chorea, leading to excessive trunk sway), as well as cognitive decline and perhaps behavioral changes (Grimbergen *et al.*, 2008).

The influence of motor disturbances on activities of daily life progresses over time. The presence of hyperkinesia and hypokinesia results in difficulties in walking and standing, and frequently leads to an ataxic gait and frequent falls. Furthermore, daily activities such as getting out of bed, taking a shower, dressing, toileting, cleaning the house, cooking and eating become more and more difficult. Depending on the kind of work the patient does, motor signs will sooner or later interfere with performance, even if psychiatric and cognitive changes are still in the background (Roos, 2010).

The Ho and Hocaoglu (2011) study investigated how HD affects the experience of everyday life, in order to understand how the concerns change throughout the trajectory of illness from pre-clinical to end-stage HD. There appeared to be four phases of HD marked by different profiles of HD impact: the pre-HD stage, with emotional, social and self concerns; the stages 1 and 2, with physical/functional and cognitive issues, in recognition and adaptation to the emergence of concrete HD symptoms; the stages 3 and 4, a period of stability in the overall scheme of disease progression; the stage 5, with physical/functional concerns, lack of cognitive concerns due to the cognitive impairment, and persistence of emotional, social and self concerns.

That study also provides an informed basis for the long-term management of health and well-being in HD, and the development of interventions across the spectrum of HD stages (Ho and Hocaoglu, 2011).

The progression of the disease leads to a complete dependency in daily life, which results in patients requiring fulltime care, and finally death. The most common cause of death is pneumonia, followed by suicide (Grimbergen *et al.*, 2008).

Assessing quality of life in movement disorders' patients is very important, because losing control of one of the most fundamental tasks of motor behavior, such as gait and locomotion, is incredibly debilitating.

4. Discussion and Conclusions

This review highlights the questions related to gait disorders in movement disorders to spark an interest and motivate future investigations, like other reports that would describe changes in gait among PD or HD patients and in other populations.

There are many different types of gait disorders in both PD and HD. According to the majority of the authors, FOG is the most disabling gait feature in PD. However, in HD there is not a consensus and opinions diverge: decreased gait velocity, decreased stride length, decreased cadence, disordered temporal control of gait, and greater variability in spatial and temporal measures are the most common gait features.

Considering the pathophysiological mechanisms of PD and HD, related to the circuits of the basal ganglia, they result both from the basal ganglia malfunction. The first one because of sunstantia nigra pars compacta depletion, and the second one being the consequence of the striatum degeneration. Their manifestations are, therefore, opposed: PD is a hypokinetic disease and HD is a hyperkinetic disease. Nevertheless, they have some gait features in common, such as increased gait variability or decreased stride length.

PD is not a simple disease of motor control. It is becoming increasingly apparent that this is a complex neurodegenerative process that affects multiple systems, deteriorating at different rates, and controlled by distinct neural pathways. The neural networks and other pathologic mechanisms responsible for the PD gait alterations overlap, but at the same time, they are also quite distinct. Stride length, gait variability (mild PD), and fractal scaling (advanced PD) are all altered in PD. A therapy that is able to address and restore all these three aspects of gait may prove to be the most optimal. Key targets for new research include development of improved treatment strategies, including both pharmacotherapy (aimed at more than just dopaminergic motor circuitries), stereotactic surgery (optimizing STN stimulation and defining new targets such as the PPN), and physiopherapy.

PD and HD are very different, but at the same time very similar. Both affect gait severely, and this is the most disabling manifestation. However, cognition is differently affected, with HD being the worst. As a result, PD patients have a better capacity to deal with the gait disorders and to solve related problems, whereas HD patients have concentration deficits and cognitive impairments that affect their skills to face the disease. There is also a difference in the therapeutic opportunities between PD and HD, with HD patients having fewer chances to choose their treatment.

Among patients with PD, 53% of fallers expressed a fear of falling, compared to only 15% in the HD group of patients, in the Grimbergen *et al.* (2008) study. Indeed, fallers with HD realized that their balance was disturbed, but as there was a low incidence of severe injuries, and a general indifference to serious consequences, they tended to ignore it more than PD patients.

We leave the challenge of unrevealing the gait and clinical movement analysis research priorities, saying only that gait analysis is an effective tool in the clinical decision making process for improving treatment outcome in individuals, an effective functional outcome measure and an accurate, precise and valid method of quantifying movement.

Indeed, we confirmed that gait disorders are tremendously important features of PD and HD, affecting deeply the patients' life and well-being: somewhere in the course of the disease patients have to stop their normal lives because gait becomes progressively more affected, with increased instability, fear of falling and difficulties in dealing with daily tasks and demands; the social and functional parts of their lives are the most affected, therefore there is still a need to study and to analyze them.

In the last years, many approaches developed, trying to deal with those decisive features, which helped to minimize some of the unwanted consequences of the diseases, like the independence loss. However, this is something that will certainly occur in the normal course

of the disease, even though nowadays we have the possibility to delay it. As a result, there is a need to develop new or even already known approaches that could help improving the impact of those features in daily patients' lives.

In view of the PD treatment, physiotherapy seems to be the most promissory way of management, since pharmacotherapy is very limited and DBS is really expensive. In HD, the most recent drugs do not affect gait in particular, but only the choreatic movements, thus more non-medical approaches are needed with proved efficacy.

We consider that gait is a decisive factor in the management of patients, since when injured it is very disabling and embarrassing, being the most obvious feature of disease allocation. Indeed, patients with gait disorders become more exposed to the environment, more fragile and insecure. Achieving a gait improvement is really important, as it may restore some independence and quality of life. That is also the desire of the patients, helping them to gain the confidence they lost. Contributing to the patients' happiness and well-being is one of our most important goals.

Acknowledgements

I would like to thank Professor Cristina Januário for the support, teaching and invaluable contributions to this work; and to my family and friends for their unconditional support and rationality.

References

Almeida QJ, Frank JS, Roy EA, *et al.* Dopaminergic modulation of timing control and variability in the gait of Parkinson's disease. Movement Disorders 2007; 22:1735-1742.

Almeida QJ, Lebold CA. Freezing of gait in Parkinson's disease: a perceptual cause for a motor empairment? J Neurol Neurosurg Psychiatry 2010; 10:1136-1151.

Arias P, Cudeiro J. Effects of rhythmic sensory stimulation (auditory, visual) on gait in Parkinson's disease patients. Exp Brain Res 2008; 186:589-601.

Auriel E, Hausdorff JM, Herman T, *et al.* Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. Clin Neuropharmacol 2006; 29:15.

Beuter A, Modolo J. Delayed and lasting effects of deep brain stimulation on locomotion in Parkinson's disease. American Institute of Physics CHAOS 2009; 19:026114.1-026114.10.

Bloem BR, Geurts AC. Treatment of gait and balance disorders. In: Hassin-Baer S, Giladi N, Hallett M, Poewe WH, editors. Therapeutics of Parkinson's disease and other movement disorders. New York: John Wiley & Sons, Ltd; 2008 In press.

Bonelli RM, Wenning GK. Pharmacological management of Huntington's disease: an evidence-based review. Curr Pharm Des 2006; 12:2701-2120.

Bonelli RM, Hofmann P. A systematic review of the treatment studies in Huntington's disease since 1990. Expert Opin Pharmacother 2007; 8:141-153.

Boonstra TA, Kooij H, Munneke M, Bloem BR. Gait disorders and balance disturbances in Parkinson's disease: clinical update and pathophysiology. Current Opinion in Neurology 2008; 21:461-471.

Camicioli R, Bouchard T, Licis L. Dual-tasks and walking fast: relationship to extra-piramidal signs in advanced Alzheimer disease. J Neurol Sci 2006; 248:205-209.

Chee R, Murphy A, Danoudis M, Georgiou-Karistianis N, Iansek R. Gait freezing in Parkinson's disease and the stride length sequence effect interaction. Brain 2009; 132:2151-2160.

Clissold BG, McColl CD, Reardon KR, *et al.* Longitudinal study of the mnotor response to levodopa in Parkinson's disease. Movement Disorders 2006; 21:2116-2121.

Cowie D, Limousin P, Peters A, Day BL. Insights into the neural control of locomotion from walking through doorways in Parkinson's disease. Neuropsychologia 2010; 48:2750-2757.

Crittenden JR, Graybiel AM. Basal Ganglia disorders associated with imbalances in the striatal strisome and matrix compartments. Neuroanatomy 2011; 5:59-63.

Delval A, Krystkowiak P, Blatt JL, *et al.* Role of hypokinesia and bradykinesia in gait disturbances in Huntington's disease: A biomechanical study. J Neurology 2006; 253:73-80.

Delval A, Krystkowiak P, Blatt JL, Labyt E, Bourriez JL, Dujardin K, *et al*. A biomechanical study of gait initiation in Huntington's disease. Gait Posture 2007; 25:279-288.

Delval A, Krystkowiak P, Delliaux M, Blatt JL, Derambure P, Destée A, *et al*. Effect of External Cueing on Gait in Huntington's Disease. Movement Disorders 2008; 23:1446-1452.

Engsberg JR, Tucker C, Ounpuu S, Wren TA, Sisto SA, Kaufman KR. Gait and clinical movement analysis research priorities: 2007 Update from the research committee of the gait and clinical movement analysis society. Gait Posture 2009; 29:169-171.

Fahn S, Jankovic J. Functional Neuroanatomy of the Basal Ganglia. In: Joan Ryan, editor. Principles and Practice of Movement Disorders. 2007. p. 66-77.

Feigin A. Pridopidine in treatment of Huntington's disease: beyond chorea? The Lancet 2011; 10:1049.

Ferraye MU, Debû B, Fraix V, Goetz L, Ardouin C, Yelnik J, *et al*. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain 2010; 133:205-214.

Gan J, Xie-Brustolin J, Mertens P, *et al.* Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: three years follow-up. J Neurol 2007; 254:99-106.

Giladi N, Hausdorff JM. The role of mental function in the pathogenesis of freezing of gait in Parkinson's disease. J Neurol Sci 2006; 248:173-176.

Goldberg A, Schepens SL, Feely SME, Garbern JY, Miller LJ, Siskind CE, *et al.* Deficits in stepping response time are associated with impairments in balance and mobility in people with Huntigton disease. J Neurol Sci 2010; 298:91-95.

Grimbergen YAM, Knol MJ, Bloem BR, Kremer BPH, Roos RAC, Munneke M. Falls and Gait Disturbances in Huntington's Disease. Movement Disorders 2008; 23:970-976.

Hackney ME, Kantorovich S, Levin R, *et al.* Effects of tango on functional mobility in Parkinson's disease: a preliminary study. J Neurol Phys Ther 2007; 31:173-179.

Hausdorff JM. Gait dynamics in Parkinson's disease: Common and distinct behavior among stride length, gait variability, and fractal-like scaling. American Institute of Physics CHAOS 2009; 19:026113.1-026113.14.

Herman T, Giladi N, Gruendlinger L, *et al.* Six weeks of intensive treadmill training improves gait and quality of life in patients with Parkinson's disease: a pilot study. Arch Phys Med Rehabil 2007; 88:1154-1158.

Ho AK, Hocaoglu MB. Impact of Huntington's across the entire disease spectrum: the phases and stages of disease from the patient perspective. Clinical Genetics 2011; 80:235-239.

Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology 2006; 66:366-372.

Iansek R, Huxham F, McGinley J. The sequence effect and gait festination in Parkinson's disease: contributors to freezing of gait? Movement Disorders 2006; 21:1419-1424.

Jankovic J, Clarence-Smith K. Tetrabenazine for the treatment of chorea and other hyperkinetic movement disorders. Expert Rev Neurother 2011; 11:1509-1523.

Mazzoni P, Hristova A, Krakauer JW. Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. The Journal of Neuroscience 2007; 27:7105-7116.

Moore O, Peretz C, Giladi N. Freezing of gait affects quality of life of peoples with Parkinson's disease beyond its relationships with mobility and gait. Movement Disorders 2007; 22:2192-2195.

Nilsson MH, Hagell P. Freezing of Gait Questionnaire: validity and reliability of the Swedish version. Acta Neurologica Scandinavica 2009; 120:331-334.

Paulsen JS, Magnotta VA, Mikos AE, *et al.* Brain structure in preclinical Huntington's disease. Biol Psychiatry 2006; 59:57-63.

Pickering R, Grimbergen YA, Rigney U, *et al*. A meta-analysis of six prospective studies of falls in Parkinson's disease. Movement Disorders 2007; 22:1892-1900.

Pluijm SM, Smit JH, Tromp EA, *et al.* A risk profile for identifying community-dwelling elderly with a high risk of recurrent falling: results of a 3-year prospective study. Osteoporosis Int 2006; 17:417-425.

Purves D, Augustine GJ, Fitzpatrick D, *et al*. Modulation of Movement by the Basal Ganglia. In: Neuroscience. 2001. p. 417-434.

Rao AK, Muratori L, Louis ED, Moskowitz CB, Marder KS. Spectrum of Gait Impairments in Presymptomatic and Symptomatic Huntington's Disease. Movement Disorders 2008; 23:1100-1107.

Rao AK, Louis ED, Marder KS. Clinical assessment of mobility and balance impairments in pre-symptomatic Huntington's disease. Gait Posture 2009; 30:391-393.

Rao AK, Muratori L, Louis ED, Moskowitz CB, Marder KS. Clinical measurement of mobility and balance impairments in Huntington's disease: validity and responsiveness. Gait Posture 2009; 29:433-436.

Roos RAC. Huntington's disease: a clinical review. Orphanet Journal of Rare Diseases 2010; 5:40-48.

Snijders AH, Weerdesteyn V, Hagen YJ, Duysens J, Giladi N, Bloem BR. Obstacle avoidance to elicit freezing of gait during treadmill walking. Movement Disorders 2010; 25:57-63.

Sollinger AB, Goldstein FC, Lah JJ, Levey AI, Factor SA. Mild cognitive impairment in Parkinson's disease: Subtypes and motor characteristics. Parkinsonism and Related Disorders 2010; 16:177-180.

Svehlík M, Zwick EB, Steinwender G, Linhart WE, Schwingenschuh P, Katschnig P, *et al.* Gait analysis in patients with Parkinson's disease off dopaminergic therapy. Arch Phys Med Rehabil 2009; 90:1880-1886.

Voermans NC, Snijders AH, Schoon Y, Bloem BR. Why old people fall (and how to stop them). Pract Neurol 2007; 7:158-171.

Ziegler K, Schroeteler F, Baumann AOC, Fietzek UM. A new rating instrument to assess festination and freezing of gait in Parkinsonian patients. Movement Disorders 2010; 25:1012-1018.