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AEROBIC TRAINING: EVIDENCE BASED OPTIONS FOR
COGNITIVE PROTECTION AND ENHANCEMENT IN
PARKINSON'S DISEASE. A LITERATURE REVIEW.

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AEROBIC TRAINING: EVIDENCE BASED OPTIONS FOR COGNITIVE PROTECTION AND ENHANCEMENT IN PARKINSON'S DISEASE

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ABSTRACT

Context: the role of endurance physical activity of moderate and high intensity in Parkinson's disease patients in their mild to moderate phase (Hoehn and Yahr scale: I-III) regarding their cognitive functions.

Objective: determine the typologies of aerobic physical activity that scientific evidence has proved effective in enhancing and/or slowing down the decline of one or more of the cognitive domains as a consequence of the progression of Parkinson's disease. Another objective is to assess whether a specific modality of aerobic exercise could be proved, more effective than the others in terms of cognitive preservation, or even augmentation.

Data sources: this review has been carried out by searching the following databases: PubMed, Cochrane Library and PEDro. Also, additional search has been carried out by screening the references of those articles already selected, in case other relevant articles would have been available from different sources. Search terms included: "Parkinson's disease", "aerobic exercise", "cognition", "cognitive", "endurance", "treadmill", "BDNF" and "hippocampus"; these terms were inserted in the different databases search engines by connecting them with the Boolean term "AND".

Study selection: the studies selected were all those examining any eventual relationship between aerobic physical activity, either alone or having a relevant major role in conjunction with other modalities of exercise, and the cognitive aspects of Parkinson's disease. The search was limited to years 2008 to 2014.

Data extraction: all the data were extracted from the selected material by the author of this thesis. The data that were taken into account were the method of research, the different types of implementations administered to the intervention group and the eventual sample group, the methods of assessment, the results and, when present the reasons of possible bias, including those expressed by the authors of the study themselves.

Results: seven articles were included concerning moderate aerobic physical activity implementation in patients with Parkinson's disease clinical diagnosis.

Limitations: the main limitation were the restricted amount of time, this necessary to present this thesis in the agreed amount of time. A further limitation was the possibil-

ity to access only to those articles which were free or requiring a minimum charge (<10 euros). Search strategy was also limited to only some databases instead of more comprehensive approach.

Conclusions: all the studies shared the conclusion that a regime of aerobic physical activity in a population of patients in their mild stages of Parkinson's disease is significantly beneficial in enhancing and/or slowing down the decline of one or more of the cognitive domains. However, not all of the studies taken into consideration for this review reported the specific type of exercises included or the intensity range within which the activity had been proved to be effective. Future studies should report more accurately these details and include at least one assessment test for each of the subcategories of cognition in order to determine whether one aerobic activity can be objectively considered more efficacious than another in the ambit of cognitive preservation. A more detailed description of the activities implemented (including doses, intensity range and eventual modifications, where these had been applied) would also improve the accessibility of these results also to the public, patients and caregivers included. More thorough systematic review would be beneficial.

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1 INTRODUCTION

Throughout the last decade, physical exercise has come into evidence as a way of treating and even preventing neurodegenerative conditions, Parkinson's disease (PD) being one of those. Its benefits concerning this condition have been proven to span from the syndrome's motor signs to, more recently, the non-motor ones. While it is now relatively easy to design a specific exercise plan addressed to the major motor symptoms a patient is exhibiting, the choice is not as clear cut when addressing the non-motor symptoms. Numerous studies on both animal models (Sung, 2012; Tuon, 2012) and human patients (from the initial to the mild phase of PD) are available nowadays supporting specifically the validity of aerobic exercise, usually in the form of treadmill brisk walking/jogging. What, according to the author of this thesis, still remains unclear, is whether a specific modality has been proved, so far, more effective than another: in particular, when addressing the cognitive deficits of Parkinson's disease, is a (relatively) high intensity aerobic training program more effective than a moderate one of the same type? Having some data concerning this difference may help on one side the patient and his/her caregivers to stay motivated in what should become a life style and not only a cure for a determinate amount of time, and, where possible to upgrade it in intensity (provided that the benefits would largely outweigh the risks). Similarly, further evidence of the neuroprotective role of aerobic activity would be an additional health promoting reminder of the importance of an active lifestyle at any age. Also, a clear display and perhaps a wider diffusion of the studies' results, could positively influence the local competent committees to set funds to promote aerobic activity for this part of population. Finally, the author of this thesis finds of primary importance to make these results available for the population involved, which means the mere publication of results on specialized journals may not be enough: instead, translating them into a more accessible and understandable means of information, such as a leaflet, for example, and giving more than one alternative for the activity to be taken up, may play a key role in involving more the patient himself in his therapy: "why do I have to exercise?" or "it is too late/ I am too old" or "I do not like jogging" , "I cannot jog for –put any reason here–" and "it would not

make any difference now” would receive an answer in a layman language, leaving out technicalisms.

2 OBJECTIVES

With this thesis, the author is aiming to present those exercises that clinical evidence has proved to promote an effective neuroprotective and/or neurotrophic action (expressed as maintained or even improve cognitive functionality) in individuals affected by Parkinson’s disease. The presence of this beneficial effect would have been assessed either by testing different domains of cognition or by laboratory tests measuring the BDNF serum levels. The following review has been organized according to the PICOS principles and the articles had been graded according to the PEDro scale for quality (although one of the articles included, being a single case report, was not particularly suitable for this type of rating).

The PICOS principles regard the population a particular treatment or therapy is directed to, the intervention(s) that have been applied, the control(s), whenever present, the outcome observed from the intervention and the study typology. Pertinently to this review, the PICOS principles have been established as follows.

Population: Idiopathic Parkinson’s disease patients; non-demented; in their mild to moderate stages of the disease (Hoehn & Yahr: from one to three).

Interventions: aerobic/endurance exercise or aerobic/endurance and other training modalities.

Controls: any other treatment or placebo.

Outcome: any cognitive outcome or any significant increase in BDNF serum levels.

Study design: RCTs, CCTs and single cases of study have been included.

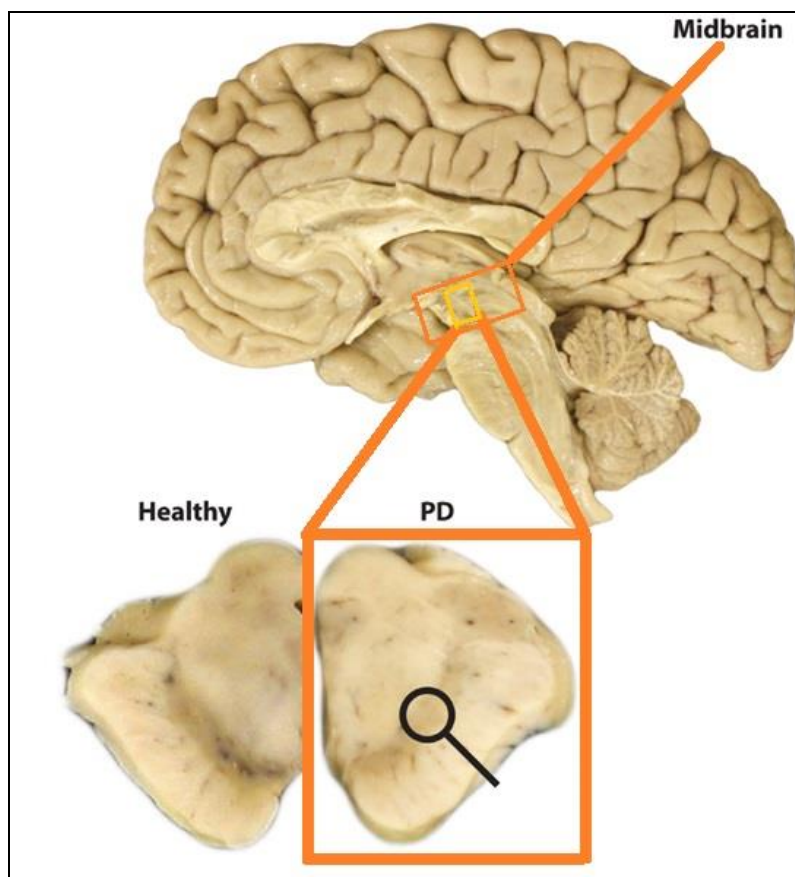
Furthermore the author graded the articles included using the PEDro scaling system.

3 PARKINSON’S DISEASE

Parkinson’s disease was a condition already known for centuries as “Paralysis Agitans”, shaking palsy, when, in 19th century, it got its current name by the French neu-

rologist Jean-Martin Charcot, after Doctor James Parkinson, who first described it in a systematic way in the London of 1817 (Goetz, 2011).

Parkinson's disease (PD) is a chronic neurodegenerative condition affecting, in prevalence, but not exclusively, the dopaminergic neurons of the Substantia Nigra pars compacta (SNpc) (Jankovic, 2002) (see Picture 1).



Picture 1. Sagittal section of a brain, with indication of the Midbrain and the location of the Substantia Nigra. A sample of Substantia Nigra from both a healthy and Parkinsonian brain is shown (reference: Dzamko, 2014).

This degeneration is often accompanied by intracytoplasmatic protein aggregates, the so called Lewy Bodies. Parkinson's disease is considered to be an age-related disease, although genetic autosomal, both dominant and recessive, forms of the syndrome have been observed and studied throughout the years, these affecting a younger minority of patients. Left out this minority, the majority of the patients is affected by the idiopathic form of Parkinson's disease: for this, since no biomarker has yet been found, the diagnosis is based on hallmarks. (Jankovic, 2002)

3.1 Pathophysiology

Despite the progresses in brain imaging and neurology in general, most cases of PD, have no specific causes, therefore the denomination of “Idiopathic PD”; what it is known, however, is the pathophysiology of this condition. Idiopathic Parkinson’s disease is characterized first of all by the depletion of dopaminergic neurons, mainly in the substantia nigra pars compacta (Zigmond, 2002). It has been proven, though, that the very first areas where the condition develops are others, precisely the vagus nerve (dorsal motor nucleus), the olfactory bulbs and nucleus, the locus coeruleus and only then the substantia nigra (Kwan, 2011).

In order the PD hallmark symptoms and signs to develop, a major depletion of dopaminergic neurons has to occur: this because, in the first phases, some compensatory mechanisms (e.g. increase in the amount of dopamine synthesis and release in the remnants neurons) may still permit a normal functioning. With time, catecholaminergic systems other than the dopaminergic can be involved, causing the development of additional symptoms, including cognitive decline and dementia. (Zigmond, 2002)

A second characteristic, pathological sign of this condition is the presence of intracellular aggregates, denominated Lewy Bodies: these are of proteic and lipidic nature and can be observed, particularly, in those areas showing neural loss, although the relationship between these two phenomena is not fully understood (Cookson, 2009). Furthermore, it must be evidenced the presence of α -synuclein as component of the Lewy bodies in those individuals who suffered from idiopathic PD: this protein, which retains the propriety to self-aggregate in a not dissolvable fashion, is involved in the development of the Parkinson’s disease, although to which exact extent is still not known (Zigmond, 2002).

It must be kept in mind, however, the fact that neither the neural loss nor the presence of these aggregates are sufficient determinants of the disease (Cookson, 2009).

3.2 Etiology

Despite the fact PD is diagnosed in the later decades of life, aging has not proved to be an etiologic factor for this condition. This is supported by the fact that striatal and

nigral dopaminergic neurons depletion occurs with different times and modalities in PD patients and healthy subjects. (Zigmond, 2002)

In the etiology of idiopathic Parkinson's disease both environmental and genetic factors have been hypothesized (Keus, 2014).

3.2.1 Environmental factors

Some environmental factors have been related to an increased risk to develop PD, there are most importantly, the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) being the most important. It causes symptoms so similar to those of PD and it has been used to create laboratory models of PD up to now. Also, other environmental factors recognized are exposure to well waters, pesticides (Rotenone), herbicides, industrial chemicals and metals, particularly long term exposure to manganese, copper, alone or in combination with lead and/or iron. (Gorell, 1999)

Viral etiology has been proposed for years, without ever coming to a satisfactory conclusion, not even with the encephalitis lethargica pandemic of the years 1916-1926 which caused in many of the (few) survivors what it is agreed now to be a well distinct condition, currently named "Postencephalic Parkinsonism" (Jankovic, 2002). On the other hand, smoking and any form of caffeine seems to have inverse correlation with the risk of developing PD (Jankovic, 2002), while the results concerning the integration of antioxidants in the diet has given mixed results: for instance, tocopherol (vitamin E) assumption has proven not to be determinant in the prevention of the disorder (Molina, 1997).

3.2.2 Genetic factors

At first, different genetic mutations have been found to cause parkinsonism; however, the same studies helped to better understand the mechanisms behind idiopathic Parkinson's disease as well (Huang, 2003). As the website of Parkinson's disease Foundation (2015) reports, two categories of genes can be individuated concerning idiopathic PD etiology: "causal genes" which are proven to be enough to cause the disease, even without co-factors and "associated genes" which, although not directly causing the condition, predispose an individual to develop it.

Causal gene for PD is the one called SNCA, abbreviation for “synuclein, alpha (non A4 component of amyloid precursor)”, belonging to the PARK family of genes: it carries the instructions for the synthesis of α -synuclein. When SNCA shows some mutations (at least 18 mutations have been reported), this causes the production of misfolded or excessive α -synuclein, which in turn has been shown to be connected to the pathophysiology of PD. (Website of the Genetic Home Reference, 2012) This form of PD, however, remains very rare, involving about one or two percent of the clinical population (Website of Parkinson’s disease Foundation, 2015).

Associated gene for PD is that named LRRK2 (“Leucine-rich repeat kinase 2”) responsible for the synthesis of the protein dardarin; the modifications this gene may exhibit are manifold, as well as the consequences in case of developing PD: age of onset spreading from the 30s to the 80s, disease-specific dementia development, etc (Website of Parkinson’s disease Foundation, 2015)

However, it must also be taken into consideration that individuals belonging to the same familial nucleus and who developed the condition shared not only the genetic pool, but also similar behaviors and environment: therefore familial occurrence of any form of Parkinsonism may be due not only to genetic factors (Jankovic, 2002).

3.3 Epidemiology

According to the European Parkinson’s Disease Association (EPDA), about 6.3 million people are currently diagnosed with Parkinson’s disease worldwide.

In particular, Keus reports in 2014 that 1.2 million people are estimated to be affected with this condition throughout whole Europe. The same guideline predicts that, given the ageing rate of the population, this current number is destined to be doubled by 2030, while, for the incidence, the disease ratio is 1.5 times higher in men than in women. With the exclusion of some genetic forms of this condition, which have been observed to affect individuals even younger than 40 years old, the majority of diagnosis Parkinson’s disease is made in persons over the age of 60 years: this may be due, at least in part, to repetitive, prolonged exposure to predisposing factors (some of them have been listed before in this thesis), together with a decline, partly physiologically age-related, of the neurological repair and of those mechanisms responsible for toxins and oxidation byproducts disposal (Jankovic, 2002).

3.4 Incidence

Only few surveys (Dorsey, 2007) have been carried out about Parkinson's Disease prevalence at worldwide level: the results indicate the prevalence of this condition varies widely from one area of the globe to the other, although this is due to a complex combination of factors, such as age distribution and life expectancy in that specific population, methods of diagnosis, possibility of access to health care facilities and to exposure to either predisposing or protective environmental factors (Muangpaisan, 2011). It has been estimated that PD is 1.5 – 2 times as common in men than women of similar age, independently from geographical location and/or race: this may be caused by multiple factors, such as greater exposure to environmental risk factors, for instance those activity-related, different hormonal influence and ultimately, genetic mutations predisposing to the condition, which mostly occur on the X chromosome (Wooten, 2004). As for age distribution, PD is more common after the fifth decade of age, up to the age of 90, when it is seen to decline again, probably due to the small of this part of the population (de Lau, 2006).

3.5 Diagnosis and classification

Parkinson's disease often presents with one or more typical hallmarks: bradykinesia, tremor at rest, often asymmetrical and starting from a very specific area (a finger, for example, where it can present also in a "pill-rolling"-fashion), muscle stiffness, with consequential difficulties when walking and, more in general, moving; also, impaired posture, mask-like face and micrographia are often present (Sharma, 2013). Diagnosing Parkinson's disease at an early stage is very difficult; on the other hand, with time and the development of the condition, the signs and symptoms become more evident and numerous (Calne, 1992). According to Hughes (1992), the diagnosis of Idiopathic Parkinson's disease is carried out throughout three phases: in the first phase, the patient is referred to a specialist (usually a neurologist), in order to determine whether his/her symptoms and signs do actually fall into the wider group of parkinsonisms (which includes the ones listed just above); secondly, other possible causes for the patient's condition will be ruled out, including head traumas, history of stroke, cerebral tumor, exposure to neurotoxins, the assumption of antipsychotics

and/or drugs affecting the uptake of dopamine, history of encephalitis, or other neurological conditions.

Further evidence for Idiopathic Parkinson's Disease will be sought, instead, in the third phase of the diagnostic process; in particular, three or more of the following signs should be observed:

- unilateral onset, together with perseverant asymmetry of the motor symptoms (or with the side where the onset took place being most affected);
- resting tremor;
- the disorder being degenerating progressively;
- significant excellent response to levodopa, which, on the other hand, can be responsible of peak dose dyskinesia and/or chorea;
- significant responsivity to levodopa for ≥ 5 years.

According to the degree of disability shown by the patient at the moment of the neurological examination, a classification of the stage of the condition can be made; the Hoehn and Yahr classification scale is the most used in clinical settings, mainly because of its easy and almost immediate applicability (see Table 1).

Hoehn and Yahr Scale
1: Only unilateral involvement, usually with minimal or no functional disability
2: Bilateral or midline involvement without impairment of balance
3: Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
4: Severely disabling disease; still able to walk or stand unassisted
5: Confinement to bed or wheelchair unless aided

Table 1: Hoehn and Yahr scale, detail. (Bhidayasiri, 2012)

However, right because of this simplicity and the exclusive focus on motor symptoms and their consequences on the daily life, it must be always kept in mind that this scale is not comprehensive and bears no indication of non-motor symptoms. A modified version of this scale had been designed, including two further stages between grades one-two and two-three. However, despite the availability of this modified ver-

sion, it is recommended to evaluate the context and the purpose of a given research to be carried out before opting for one or the other version. (Goetz, 2004)

3.6 Motor symptoms.

The most recurrent clinical signs of PD are bradykinesia (present in 77-98% of cases), resting tremor (evident already in the beginning phase of the disease about in 70% of cases, increasing then up to 100% of cases in the later stages); rigidity through the whole passive ROM, often accompanied by pain, is also common, recurring in 89-99% of cases: this, in turn, may cause antalgic postural misalignment. (Keus, 2014). Furthermore, other hallmarks of the condition, although occurring usually in the later stages, are the loss of postural reflexes, these causing balance impairments. One exemption, which can be evident even three years after the diagnosis, is the deterioration of the dynamic postural control, evidenced, in clinical assessment, by asking the patient to turning of a 180 degrees angle (Keus, 2014).

In addition, patients suffering either from idiopathic Parkinson's disease or a form of Parkinsonism can exhibit also an irregular posture, in particular in the areas of neck, limbs or trunk; this is true for about a third of the patients, who most often present with a pathological flexion at hip and knee level, accompanied by shoulder protraction; other, postural anomalies can be encountered in this population of patients: camptocormic posture (see Picture 2), pleurothotonus/Pisa's syndrome, antecollis and scoliosis are more serious and more disabling, whose cause, in relation to the Parkinson's pathology, remains unsure, thus making its management challenging. (Doherty, 2011)



Picture2: Camptocormic posture (reference: <http://en.wikipedia.org>)

Nevertheless, the ultimate confirm of the diagnosis will be possible only postmortem, by observation of the pathological signs such as the presence of alpha-synuclein positive Lewy bodies and the loss of pigmented neurons, particularly in the substantia nigra pars compacta (SNpc). These motor hallmarks however, which, on average, will start to be evident only after about 50% of the dopaminergic neurons in the SNpc have been lost, are often the main target in PD treatment. The therapy for PD, in fact, mostly consists in replacing the lack of dopamine, due to the degeneration of those neurons responsible for its production, at first throughout dopamine agonist drugs and, later on, by adding Levodopa (L-dopa), a precursor of dopamine. Levodopa will act on those motor hallmarks, but it will not affect other important common features often present in PD, such as freezing of gait, autonomic, cognitive, behavioral and affective dysfunctions: on the opposite, besides other side effects, Levodopa, more likely, will trigger or exacerbate some of them. (Sethi, 2008)

3.7 Non motor symptoms

Despite PD is diagnosed by the presence of clinical motor signs listed above, the “non-motor” deficits are just as important as the first ones, and just as well they can influence the quality of life of the patient and his/her family or caregivers, besides being one of the main reasons for a PD patient institutionalization. Under the term

non-motor symptoms is collected a heterogeneous group of dysfunctions, in particular related to cognitive, memory, attention, executive, visuospatial, autonomic and behavioral areas. It has been observed that patients exhibiting non-motor symptoms of Parkinson's disease tend to be particularly more affected in one of these domains. (Litvan, 2011)

3.7.1 Cognitive impairments

Throughout the years, studies on both animal and human subjects have brought the scientific community to the observation that basal ganglia dysfunctions are one of the causes of cognitive and behavioral dysregulations.

Concerning the cognitive domain, the main consequences from basal ganglia dysfunctions include a general slowing down in the processing of all the information retrieved from the environment, an inefficient retrieval of memories (sometimes more than actual memory loss), an impaired executive capacity and behavioral symptoms such as inertia, apathy and depressed mood (Jankovic, 2002).

Put together, these signs make up what are the most recurrent observation and complaints made by the family or the caregiver of the patient: forgetfulness, difficulty to concentrate (or "set maintenance") and the difficulty in following conversations with more than one interlocutor (Jankovic, 2002).

In the following paragraphs, the main cognitive areas, found to be most commonly impaired at some level in individuals suffering from PD, have been illustrated; as it shows, cognitive impairment in PD, although very common (up to 93% of the clinical PD population, according to Pillon, 2001) and present from the very early stages of the disease, is more likely to interests very specific domains of cognition, these being memory, executive and visuospatial capacities.

3.7.2 Memory impairments

Memory is not a uniform one-way process. Research in the years has only been able to partially clarify the mechanisms behind it. In PD patients, both the "working memory" and the "long term memory" can result impaired. Working memory, that part of memory with the function of retaining newly acquired piece of information

waiting to be “filtered” and manipulated before being stored by the long term one, can result impaired by PD, also due to the incapacity or inefficiency of repressing secondary, interfering stimuli. This can be proved, for example, by poor results in short term recall tasks (eg. remembering as many items from a list) (Jankovic, 2002).

Long term memory, on the other hand, can result impaired as well; the temporal-lobe controlled “strategies” aimed at storing the information, do not result particularly affected in this category of patients, while, on the other hand, the organization, either temporal or according to other different associative conditions, can result impaired. Further inefficiencies can be recognized in the procedural learning, at variable extents, and in the internal control of attention, which also contributes to the inefficiency at maintaining the attention to given stimuli. (Jankovic, 2002)

3.7.3 Attention impairments

Attention can be defined as the voluntary decision to select one particular information, whether of the visual, auditory or any other sensory type, while ignoring as not important other stimuli occurring at the same time, in the same circumstance. Attention should not be confused with the concept of “arousal”, which, however, can be affected in Parkinson’s disease patients: while arousal describes a global attentiveness and readiness, which can be opposed to apathy, with “attention” clinicians refer usually to the conscious and voluntary choice to focus on a particular subject. (Selzer & Clarke, 2006). The psychologist William James wrote, back in 1890, that attention requires “withdrawal from some things in order to deal effectively with others...”.

Similarly, attention may play a relevant role in the learning process by helping addressing the subject’s mind on the task or notion that needs to be acquired (Selzer & Clarke, 2006). Cognitive impairment, including the attention functions, is not influenced by dopamine levels alone, but more likely, by a precise equilibrium between dopamine, noradrenaline, serotonin and acetylcholine: this translates into the fact that the dopaminergic treatment addressed at the motor symptoms will be of no effect in addressing the non-motor ones (Solari, 2013).

3.7.4 Executive dysfunction

Executive function can be regarded as an “umbrella” term, comprehensive of different cognitive processes, such as setting the attention on a specific thing, maintaining this attention as long as it is necessary, flexible thinking, necessary to adapt ourselves efficiently to the ever-changing situations and also, once set a goal, the capacity of the individual to act and behave according to that outcome requirements. This being said, it is clear how many different cognitive functions are necessary to maintain an efficient executive capacity. As a consequence of this quantity of different facets of cognition, many different specific tests will be needed (some of which will be further illustrated in appendix one), in order to conduct a satisfactory assessment of this sphere of cognition. The evidence we obtain from clinical settings (tests, scans, fmri,...) has stressed the importance of the frontal lobes in the ambit of disturbances and impairments of the executive area of cognition: this mainly because of the vast network of reciprocal links between cortical and subcortical strata in this specific area of the brain, which would act as “supervisor” and “modulator” of the myriads of connections existing. Eventual frontal lobe damages are seen more in the everyday life than in the results coming from the most commonly used intelligence tests; in particular, some difficulties and impairments are observed more often in these individuals’ daily lives. Firstly, the patient is not able or has anyway difficulties in modifying his behavior accordingly to changing situations/stimuli, as it can be evidenced by the “Wisconsin Cards Sorting out Test”. Secondly, in his daily life, the patient encounters difficulties in carrying out tasks composed by more than one finite action: the problem in these circumstances is not represented by the single “steps” making up the task as a whole, the difficulty resides instead in the capacity from him of planning and handling the “steps” as a sequence. Thirdly, the patient may result unable to sort out from a group of concomitant stimuli the single, most important one, and focus on that the response; this incapacity of telling the important stimulus from the secondary distractors can be assessed by the “Stroop Test”; it is also a primary cause of what is defined “Environmental Dependency Syndrome”, a condition in which the subject feels composedly forced to take and use any object he may see in a given setting, although not asked to do so. Fourthly, the perseveration of a behavior, whether vocal or motor and even if as response of a previous stimulus is an indicator of possible dysexecutive syndrome, causing the patient to be unable to voluntarily suppress

that behavior. Lastly, an impairment that can be added as part of the dysexecutive “spectrum” is memory dysfunction: in PD patients this impairment does not affect directly the working memory itself, rather the problem resides more in attention deficits and/or inefficient retrieval strategies of these memories. Retrieval, in particular, requires a conscious effort, a strategy, and it is this organizational aspect that the PD patient is inefficient at, with the result of appearing forgetful to family and caregivers. (Jankovic, 2002)

The tests (see “Appendix 1” for some of current use), generally adopted for these reasons in clinical settings, are all evaluating the frontal lobe functions, in particular the formation of concepts, the individuation of implicit rules (“Wisconsin card sorting” test and “Spatial delayed response” task), problem solving skills (“Tower Task”-like tests), the capacity of set shifting (“Trail making” and “Odd man out” tests) and, on the opposite, the ability to maintain a given mind set and therefore inhibiting interferences (“Verbal fluency” and “Stroop” tests). However, dysexecutive syndrome, as it is observed in PD, is a condition which can have different presentations, accordingly to the area of prefrontal cortex of major (or exclusive) affection. In particular, a major dorsolateral prefrontal cortex damage will cause the most severe cognitive deficits, while a major or exclusive disruption in the orbitofrontal cortex, having connections to the limbic region, will be reflected more as an impairment in the affective and social capacities. (Jankovic, 2002)

3.7.5 Visuospatial impairments

Despite clinical evidence (Tachibana, 2013; Aarsland, 2011) stated some connection between PD and visuospatial dysfunction, the main belief is that this impairment may be due primarily to the high cognitive demand that the tests used to ascertain it requires the patient: in these occasions, in fact, the patient is asked to perform tasks that also require a cognitive level that the syndrome may already make difficult to reach (for example, the capacity of centrally processing the various stimuli presented at the same time, or set shifting). Always in the field of visuospatial impairments, further impairments have been detected in the preattentive visual processing system, the unconscious collection of all the concomitant environmental stimuli destined to be filtered by importance by the brain. (Jankovic, 2002)

3.7.6 Behavioural deficits

Mood and behavioral changes are often reported as features of PD: introversion, obsession with control of any life aspects, hypervigilance and caution, especially when finding himself in unusual situations, repression of strong emotions leading to apathy are the most commonly reported ones. Depression may also develop, together with and not as a consequence of the disease, since it is not strictly related to the stages of PD. However, the development of depression should require further attention, since evidence suggest this state may trigger, at first, attention and memory impairments, and then depressive mood can contribute to the development of dysexecutive syndrome. (Jankovic, 2002)

3.7.7 Sleeping dysfunctions

The disturbances in the sleeping REM phase, defined as “REM sleep behavior disorder” (RBD) have been already identified as one of the anticipating signs of a diagnosis of Parkinson’s disease, as well as other synucleinopathies. Other sleeping dysfunction, including insomnia and excessive drowsiness during the daytime are being investigated as other possible warning signs of a future diagnosis of Parkinson’s disease. (Manni, 2007)

The REM sleep behavior disorder has also been observed to accompany PD throughout its course, particularly those forms characterized by a quicker progression of the cognitive aspects, often into PD-specific dementia. In addition, RBD is associated with a significant likelihood of the patient presenting with concurrent visual hallucinations. Furthermore, the breathing pattern throughout the whole sleeping cycle, both REM and non REM phases, could result dysfunctional, with temporary, often periodical events such as sleeping apneas and/or hypopneas (this latter one indicating significant reduction in the amplitude of the breathing pattern): this phenomena, defined as “Sleep Disordered Breathing” (SDB), have been shown to further make the patient prone to neuropsychological and cognitive impairments, including memory (both short and long term), logical functions and frontal activities. (Manni, 2007)

3.7.8 Sensory dysfunctions

Parkinson's disease patients may present either with hyposmia or anosmia. Olfactory functions (smell detection, its source identification and the ability to discriminate one smell from the other) result impaired very early in the course of the disease, preceding by years the degeneration of the Substantia Nigra and the consequential motor signs and symptoms. (Antonini, 2012)

Furthermore, the high recurrence at which this category of impairments occurs (at least 90%) makes it a significant contributor in differentiating idiopathic Parkinson's disease patients from those suffering from other forms of parkinsonisms (Doty, 2012).

In the recent years, dysfunction of other sensory systems have been taken into consideration in the ambit of Parkinson's disease. Visual functions can result impaired in PD at different levels, either due to the increased risk of developing glaucomas, or as a consequence of the depletion of dopamine, which has been found to play a role in the organization of receptive fields and of the photoreceptors. These impairments can result in reduced visual acuity, in particular in contrast discrimination, colors recognition, as well as abnormalities in the eye movement, as in smooth pursuit movements, particularly along the vertical direction, together with a general reduction and jerkiness of eye movements; it has also been noted PD patients tend to exhibit a reduced blinking rate, this in turn contributing to the "expressionless" mask-face, together with dry eyes and generally a reduced vision; however, given the overlapping results between PD patients and healthy controls of the same age, further research is auspicious before considering them as possible biomarkers. (Armstrong, 2008)

Hearing could be also involved in the evolution of this condition, as suggested by a study reporting a major frequency of hearing impairment in this category of patients when compared with healthy controls of the same age (Vitale, 2012). Studies concerning this subject, though, are still limited in number, thus not providing yet a clear evidence on the possible link between Parkinson's disease and hearing impairments.

3.8 Mild cognitive impairments anticipating dementia?

These deficits will ultimately develop in dementia, though only a small percentage of the cases (about 25%) will be clinically recognized as such (Svenningsson, 2012).

Despite the onset time of dementia can be extremely variable from one patient to the other (it can either be few years after Parkinson's disease has been clinically diagnosed, to decades after), it has been observed that after dementia has set in, the Parkinson's syndrome will progress to its terminal stage in a typical average timing of three years. This being said, since early cognitive impairments can be the prodromes of dementia in Parkinson's patients, it is important not only to establish better criteria to define mild cognitive impairments, but also to draw an optimal therapy that can enable the patient to at least slow down this decline. Exercise has drawn attention as a possible side effects-free way. (Svenningsson, 2012)

3.9 Dementia in Parkinson's disease

As already stated, cognitive decline in Parkinson's disease follows the motor symptoms (on the opposite, in Dementia with Lewy Bodies, the cognitive deficits precedes the motor ones) and with a rate which is slower in the earlier stages of the disease; nevertheless, once dementia sets in, the progression will follow a rather regular course: both physical and cognitive decline will progress into the terminal stage for about three years, with patient's death.

The time of onset of dementia can vary a lot: some patients will develop dementia few years after PD has been diagnosed, while for others it may take decades.

It has been observed that a faster cognitive impairment (meaning a quicker development into dementia) occurs:

- in patients whose PD has been diagnosed in later age;
- in patients whose motor symptoms are mostly of the non-tremor type (in particular relevant postural instability and disturbed gait);
- in patients whose non-motor symptoms include hallucinations, behavioral and REM sleep phase disturbances and pronounced olfactory dysfunction.

One of the challenges relies right in the difficulty of adopting clear and unified standards to define and diagnose mild cognitive impairment in PD: for this reason,

the Movement Disorder Society has been the first to propose the criteria that have received clinical consensus. (Litvan, 2011)

4 EXERCISE IN PARKINSON'S DISEASE

4.1 Aerobic exercise

The definition of "Aerobic Exercise" applies to any intentional physical activity "using large muscle groups and maintained continuously with rhythmic pattern" (Hanson, 1988).

Also, aerobic physical exercise can be differentiated in three main typologies; "Group 1" includes those physical activities which provide a constant bout of intensity - and the consequential energy consumption – independently from the individual's skills in that very activity: examples of "Group 1" activities would be brisk walking, cycling and even jogging. "Group 2" activities would be those which energy costs can register significant variations depending on the skills of the performer, as, for example, swimming or dancing. Wide variations in energy consumption from one performance to the other, instead, will be observed in those activities and sports such as football or tennis. (Kravitz & Vella, 2002)

4.2 Low, medium or high intensity, what is better?

Despite the studies carried out on this subject, the terminology concerning the physical exercise intensity level is still cause of imprecisions and misunderstandings; in order to provide the patients, especially those with limited experience in the sport field, a clear indication of the intensity of physical activity that would best suit their specific status, thus avoiding both under and over training, some standardization of the basic terminology for physical activity should be achieved.

The basal metabolism, the minimum amount of energy an individual's body requires in order to carry out its life functions in a physiological fashion is increased, at different levels, by any activity taken up by the subject; this increment occurs with any

activity of the living, from the very basic sleeping, up to the highest level of physical activity, that of the elite athletes. This increment in energy needs has been divided by Norton (2010) into five major ranges: sedentary, light, moderate, vigorous and high intensity. Activities can be classified into one of those categories according to either objective, subjective and descriptive measures. Objective measures are those expressed through METS (metabolic equivalents, 1 MET = 3,5ml O₂/kg/min), HR_{max} (which can be either measured or more, quickly, though less precisely calculated with the formula: 220 – age), HRR_{max} (where HRR, heart rate reserve, is calculated: HR_{max} – HR_{rest}), a safer threshold for calculating exercise intensity with less fit patients, or, finally, VO₂max (which is the maximum quantity, volume, of oxygen consumption, a very specific amount for each individual, not likely to change even with physical conditioning). Subjective measures, though less precise, are often used because considered more accessible to the patient, in particular when this is not so acquainted with physical exercise. One form of subjective measurement is that provided by the use of the Borg RPE (Rated Perceived Exertion) scale: throughout it, the patient can indicate his level of fatigue, with 6 (zero) being the lowest level (corresponding to the same fatigue that lying in bed would cause) and 20 being the highest (the same fatigue of a maximal, “all out” exercise) anytime during the activity/exercise session. Finally, the same “Position Statement” indicated a third category of measuring the level of exercise intensity, that of descriptive measures: these take into account some common reactions that can be observed at a given exercise intensity, like changes in breathing path, the capacity of maintaining the same intensity for 1’ or less, the capacity to hold a conversation at the same time without running out of breath, etc). (Norton, 2010)

Despite the arguable choice of selecting overlapping limits for all the objective measures, the following table summarizes in an efficient visual way the results of the review conducted by Norton and colleagues on the terminology and categorization of aerobic exercise adopted in the scientific literature.

Table 1. Categories of exercise intensity and the objective, subjective and descriptive measures accompanying each category. (Adapted from Norton, 2010)

<u>Intensity Category</u>	<u>Objective Measures</u>	<u>Subjective Measures</u>	<u>Descriptive Measures</u>
SEDENTARY	<1,6 METs <40% HR max <20% HRR <20% VO2 max	RPE < 8	activities: sitting, lying with little additional movement and low energy requirement
LIGHT	1,6 < 3 METs 40 < 55% HRmax 20 < 40% HRR 20 < 40% VO2max	RPE 8-10	- an aerobic activity that does not cause noticeable change in breathing rate - an intensity that can be sustained for at least 60 minutes
MODERATE	3 < 6 METs 55 < 70% HRmax 40 < 60% HRR 40 < 60% VO2max	RPE 11-13	- an aerobic activity that is able to be conducted whilst maintaining a conversation uninterrupted - an intensity that may last between 30 and 60 minutes
VIGOROUS	6 < 9 METs 70 < 90% HRmax 60 < 85% HRR 60 < 85% VO2max	RPE 14-16	- an aerobic activity in which a conversation generally cannot be maintained uninterrupted - an intensity that may last up to about 30 minutes
HIGH	≥ 9 METs ≥ 90% HRmax ≥ 85% HRR ≥ 85% VO2max	RPE ≥ 17	- an intensity that generally cannot be sustained for longer than about 10 minutes

4.3 Effects of aerobic exercise on brain – how can aerobic exercise influence cognition?

In these last decades many studies (Erickson, 2009; Bass, 2013) have been undertaken in order to assess the correlation between physical activity and cognitive functions: across all the ages, from children to the elderly, healthy or already affected by cognitive dysfunctions (often age related), the results have proved this correlation to exist and to be particularly strong.

What still have not been fully understood and documented is the causal relationship: how this beneficial documented effect of increased physical activity on specific areas of cognition is reached? Four main hypotheses have been individuated, these being:

cardiovascular, immunological, trophic factors (and their modulators) and fourthly, the neuroendocrine effect. (Phillips, 2014)

4.3.1 Cardiovascular aspect

Concerning the relationship between cardiovascular effects of increased physical activity and cognitive functions, the improved hemodynamics, particularly that of those vessel supplying the brain area with oxygen and nutrients (and taking the “wastes” such as reactive oxygen species, or ROS, for example), consequential to higher levels of physical activity was associated with an inferior rate of gray and white matter loss. (Colcombe, 2003)

All this evidence appears to be of particular strong relevance in the elderly population (while the connection cardiovascular fitness improvement and cognition is not as clear cut in average, in the younger populations). (Lautenschlager, 2008)

4.3.2 Immunological aspect

The extent of the immunological effect will depend on the duration as well as the intensity of the physical activity carried out by the individual; these beneficial effects will often include a general boost of immune function and increase in anti-inflammatory factors. This immunological enhancement is fundamental, as evidence proved that inflammation, when reaches chronic levels can be a cofactor to neurodegenerative conditions (Parkinson’s disease included) as well as to cognitive impairments. (Gleeson, 2011)

4.3.3 Trophic factors action

Neurotrophins are among the possible reasons explaining the beneficial effect physical activity can promote in terms of cognitive functions. Different polypeptides belong to the category of neurotrophins, and among these, the brain-derived neurotrophic factor, or BDNF, is the most spread within the brain, particularly in the hippocampal region, which role is fundamental in learning and memory functions

(Phillips, 2014). Furthermore, BDNF retains a fundamental role in the survival of neurons, by influencing growth, differentiation and maintenance in general (Reichardt, 2006). It has also been observed that BDNF is fundamental in preventing hippocampal neuronal cells death and its plasma levels have proved to be a valid biomarker when assessing memory impairments (Pringle, 1996; Komulainen, 2008). Evidence shows that physical activity, when in moderate intensity, is positively and significantly linked to raised BDNF serum levels, and this increase has been observed to persist for up to seven days after the physical activity session. (Coelho, 2014; Berchtold, 2005). However, the specific causes of this increment have not, so far, been clearly recognized. On the other hand, as scientific studies (Taverniers, 2010) have shown, high intensity levels of physical exercise lead more to damages than benefits; this can occur in two ways: either by lowering the anti-oxidant factors count or by increasing the levels of the hormone cortisol. The brain, in fact, is responsible for at least the 20% of the whole oxygen consumption and this, together with brain low anti-oxidants levels already under physiological conditions, makes the central nervous system particularly vulnerable to the consequences of oxidative stress and their byproducts, as the so called “Reactive Oxygen Species” or ROS (Utara, 2009).

5 STUDIES SELECTED

5.1 Research history

In June 2014 the search of studies for this thesis was carried out accessing PubMed database. An “advanced search” was chosen by inserting the terms "Parkinson's" [Title/Abstract] AND "exercise" [Title/Abstract] AND "cognition" [Title/Abstract]. Search resulted in 17 articles. The following restrictions were applied at first: studies dating back to the last ten years, their subjects being “humans” and the studies being available in English and in free full text. Out of the initial 17 articles, 11 passed this first selection; then, the author reviewed all the abstracts of these 11 results in order to assess the ones that complied with the PICOS principles established beforehand and listed above: it resulted that four studies could be included in this thesis. In this

second phase of the search, reviews concerning the topic were excluded from the thesis material: however, these were kept into consideration as an eventual source of other articles that for any reason had been not included in PubMed. In an analogue fashion, Cochrane Library and PeDro databases were searched, leaving out of the results eventual duplicates, already included from the PubMed search. This being said, a total of seven studies had been selected for this thesis; these will be summarized in the following paragraph.

5.2 Studies included

The seven studies selected have been collected in the following two tables. In the first table (Table 2), the type of study, PEDro rating, intervention and the different treatment plans administered in the sample and control group had been summed up. In the second one (Table 3), the modalities of assessment, the final results and the eventual causes of bias have been described.

Table 2. Intervention plan, PEDro grading, sample group and control group implementations.

Title, Authors and Type of Study	PEDro Grade	Intervention	Sample Group	Control Group
1) "Benefits of physical exercise on executive functions in older people with Parkinson's Disease" (Tanaka, 2009) Study	7	Multimodal exercise program VS same daily routine. Participants qualified for the study when: •Clinical PD from 1 to 3 in Hoehn & Yahr scale. •No signs of dementia. •Haven't taken part to any exercise program. •Attending min. 70% of the program they are assigned to.	5 women, 5 men. Multimodal exercise program for elderly with PD: basic aerobics. 60' sessions, 3/week. The program consisted of six parts of increasing load, each made of 12 sessions, lasting one month/each. Each session was divided in 5 parts (warm-up; pre-exercise stretching; exercise session; cool down; post exercise stretching). HR: 60-80% HRmax (only one participant/session had a HR monitor)	6 women, 4 men; CG participated already as control group in another study in the same structure. This control group (CG) was asked to maintain the same daily routines, without joining any exercise program
2) "Phase I/II randomized trial of aerobic exercise in Parkinson's disease in a community setting" (Uc, 2014)	6	Four different training methods: 1_individual and continuous training; 2_group continuous training; 3_individual interval training; 4_group interval training;	The study was conducted throughout three years. Initially, during the first two years, participants were randomized into 4 different training methods: 1_individual and continuous training; 2_group continuous training (only in	No control group.

Randomized trial			<p>the first year); 3_individual interval training; 4_group interval training (only in the first year).</p> <p>Then, on the third year, the study focused only on continuous, individual training.</p>	
<p>3) “The effects of adapted tango on spatial cognition and disease severity in Parkinson’s disease”</p> <p>(McKee, 2013)</p> <p>Study</p>	7	<ul style="list-style-type: none"> Adapted Argentinian Tango. Patient education in the form of seminar. 	<p>n pts = 24 H&Y: I-III</p> <p>2x90 min./wk for a total of 20 sessions of adapted tango.</p> <p>Each class: 20’ standing warm up and practice of the steps already learnt; then new steps were added, strictly according to the manual, and after that those were integrated with the older ones.</p> <p>During the partnering phase, each pt both conducted and followed, though always paired with non PD partner.</p>	<p>n pts = 9 H&Y: I-III</p> <p>2x90 min./wk educational sessions for a total of 20 sessions.</p> <p>Health-related topics with medical students and professors. 1hr+30’ discussion.</p>
<p>4) “Exercise and Parkinson’s: benefits for cognition and quality of life”</p> <p>(Cruise, 2011)</p> <p>Study</p>	4	<ul style="list-style-type: none"> Exercise Intervention Program (EIP, n=15) Control group (n=13) 	<p>n pts =15, 2/wk for 12 wks.</p> <p>Each session (60’) always included both aerobic and strength training. Each session included:</p> <ul style="list-style-type: none"> 5’ warm up (low intensity aerobic activity such as walking, stationary cycling and stretching). Resistance training: 6 exercises for 	<p>n pts =13, maintained its usual lifestyle for 2/wk for 12 wks.</p> <p>Baseline and follow-ups carried out always during the “on” phase.</p>

			<p>both upper and lower body major groups.</p> <ul style="list-style-type: none"> • 25-30' aerobic training: stationary cycling, rowing, treadmill at 60-85% HRmax. <p>The intensity of the exercises was increased gradually throughout the sessions.</p>	
<p>5) "Can exercise improve language and cognition in Parkinson's disease? A case report"</p> <p>(Nocera, 2010)</p> <p>Single Case Report</p>	(4)*	<p>8 weeks of aerobic exercise as single and dual task.</p> <p>Intensity: starting from 50% HRRmax, increased by 5% every week up to 75% HRRmax.</p>	<p>Subject of the study: woman idiopathic PD for 11yrs 66 y.o. H&Y: 2 UPDRS: 31/106 dx-handed</p> <p>Aerobic Exercise in the form of stationary ergometer in single and cognitive dual task.</p> <p>Therapy delivered for 8 wks, 3times/wk, for a duration of 20' each.</p>	No control group
<p>6) "Efficacy of a multimodal cognitive rehabilitation including psychomotor and endurance training in Parkinson's disease"</p> <p>(Reuter, 2012)</p> <p>Clinical Study</p>	8	<p>Random allocation to group A, B or C, (C being the "sample group") with different combination of cognitive, transfer, psychomotor training, plus occupational therapy and relaxation sessions to reach the same amount of therapeutic interventions in each group.</p> <p>The study was structured in 2 phases: Period 1: 4wks, at the rehabilitation unit. Physiotherapists, occupational</p>	<p>240 pts</p> <p>male and female</p> <p>Age: 50-80 y.o. (average 64±4 yrs)</p> <p>Diagnosed w/ PD (average diagnosed 8 before)</p> <p>Mild Cognitive Impairment (MCI) inclusion criteria</p> <p>Patients did not differ demographically</p>	<p>Two control groups, group A and group B.</p> <p>Group A: exclusive cognitive training (plus to reach same amount of training time of group C, relaxation and occupational training)</p> <p>Group B: cognitive training, transfer training (Plus to reach same amount of training time of group C, relaxation and occupational training).</p>

<p>therapists and neuropsychologists. Period2: 6mo, with family/caregiver collaboration (after receiving education), training programmes adapted to individual home settings.</p> <p>More specifically: COGNITIVE TRAINING:</p> <ul style="list-style-type: none"> • 60' lessons • 4 times/wk • individual sessions • min. 14 sessions/pt • cognitive program individually tailored on pt's needs. <p>TRANSFER TRAINING:</p> <ul style="list-style-type: none"> • ADLs in different settings, • 3 times/wk, • total 10 sessions • 90' duration each. <p>MOTOR TRAINING:</p> <ul style="list-style-type: none"> • 60' sessions • 10-12 sessions • games and tasks (e.g. orientation); • dual tasks (walk and bounce or throw a ball); • parcours w/obstacles; • Aerobic activities including treadmill walking in winter and Nordic walking in summer • during the 2nd phase at home, caregiver received instructions how 	<p>from one group to the other.</p> <p>Group C: cognitive training, transfer training, psychomotor training.</p>	
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		<p>to organize the sessions, so that 40% outdoor and 60% gym</p> <p>All the training programs were carried out having the patients in the “on” stage.</p>		
<p>7) ”Intensive Rehabilitation Increases BDNF Serum Levels in Parkinsonian Patients: a Randomized Study”</p> <p>(Frazzitta, 2014)</p> <p>Randomized Study</p>	9	<p>SUBJECTS:</p> <ul style="list-style-type: none"> • Average age 67±5 • Idiopathic PD. similar duration (approx. 8 yrs) • H&Y 1-1,5. • Rasagiline treatment. • No other neurological comorbidity. • Mini mental state examination >26. • Vision and hearing sufficient to understand the instructions. • Walking w/out physical assistance. <p>METHODS:</p> <ul style="list-style-type: none"> • 2 groups, treatment group and non-treatment/control group. • 4 weeks therapy. • 3 daily sessions (2 in the morning, 1 in the afternoon). • 1 hour duration/session. • 5 days/week. 	<ul style="list-style-type: none"> • 3 session/day, 1 hour each. <p>SESSION 1: Cardiovascular warm up, ROM spinal, pelvic and scapular joints, strengthening abdominal wall, postural changes from supine, stretching, relax.</p> <p>SESSION 2:</p> <ul style="list-style-type: none"> • balance training on stabilometric platform + visual cue; • gait training on treadmill plus (visual and auditory cue), HRreserve ≥60% for 30’ every day for 4wks. <p>SESSION 3: Occupational therapy for ADL: transfers, rolling in bed, dressing, tool usage, hand skills.</p>	No treatment.

(*) = This article, being a single case report, is not particularly suitable to be graded according to the PEDro scale.

Table 3. Assessment tests, study results and eventual reasons of bias.

Study (Title, Authors and Year)	Assessment	Results	Bias/Discussion
<p>1) "Benefits of physical exercise on executive functions in older people with Parkinson's Disease"</p> <p>(Tanaka, 2009)</p>	<ul style="list-style-type: none"> • Wisconsin card sorting test (executive functions). • Wechsler adult intelligence scale III (concentrated attention). • State trait anxiety inventory (anxiety). • Hospital anxiety and depression scale (depressive symptoms, not the anxiety part) 	<p>As shown by the Wisconsin card sorting test, the study group improved in the executive functions, particularly in the variables:</p> <ul style="list-style-type: none"> • "Categories completed" (telling about the ability to concentrate on specific aspect and ignore others) • "Perseverative errors" (index of mental flexibility). This was not the case of the control group. <p>Both the groups showed no significant improvement in the "Confounding variables" (concentrated attention, state anxiety and depressive symptoms) = the improvement in the Executive Functions registered in the sample group was not due to a change in confounding variables, but strictly to the exercise regimen.</p>	<p>I. Procedure was not purely random.</p> <p>II. Not enough HR monitors for the control group sessions.</p> <p>III. Although further explanation of the exercise sessions is available in the article, still the very exercises instructed are not illustrated.</p>
<p>2) "Phase I/II randomized trial of aerobic exercise in Parkinson's disease in a community setting"</p> <p>(Uc, 2014)</p>	<ul style="list-style-type: none"> • Eriksen flanker task (primary cognitive measurement) • Stroop test (inhibition of secondary stimuli). • Wisconsin Card Sorting test (set shifting). • Trail making test (set shifting). • Judgement of line orientation (visual perception). • Complex figure test-copy (visual perception). • Rey auditory verbal learning test (verbal memory). 	<p>Improvements in different categories have been reported:</p> <ol style="list-style-type: none"> 1. Aerobic fitness and motor function; 2. Cognition (flanker test); 3. Quality of life and other non-motor functions. <p>Concerning cognitive improvements, those were mostly in the area of inhibition (selective cognitive improvement).</p>	<p>I. NO control group: efficacy of the implementation cannot be proven; still, the authors claimed that this phase of their on-going study provided indications more on safety, tolerability and general feasibility for a future phase three of this study.</p> <p>II. The study design was partially modified throughout the years, in particular:</p> <ul style="list-style-type: none"> • "Group setting": no randomization was possible, due to logistical factors (rural residence of the patients); for this reason, the "group setting" was abandoned after the first year of

<p>3) “The effects of adapted tango on spatial cognition and disease severity in Parkinson’s disease” (McKee, 2013)</p>	<ul style="list-style-type: none"> • Complex figure test-recall (visual memory). • Controlled oral word association test (language). • Montreal cognitive assessment (general cognition). • Geriatric depression scale (depression). • PD quality of life scale PDQUALIF (quality of life) 		<p>study.</p> <ul style="list-style-type: none"> • “Interval exercise modality”: abandoned as well in the third year, due to safety issues.
	<ul style="list-style-type: none"> • MoCA - Montreal Cognitive Assessment (general cognition). • Reverse Corsi Blocks (visuospatial memory). • Brooks Spatial Task (spatial cognition). • UPDRS-III • FAB - Fullerton Advanced Balance Scale. • Four-Square Step Test. • TUG – Time Up and Go (single task, dual cognitive task and dual manual task). • PDQ-39 – PD Questionnaire 39. • FOGQ – Freezing of Gait Questionnaire. • Short Form Health Survey-12 (physical PCS and mental composite MCS). 	<p>The adapted tango intervention was found to enhance cognition, mainly evidenced in the MoCA test.</p> <p>A positive trend has been observed also in the Reverse Corsi Blocks test.</p> <p>These results were maintained at the 12th week follow up.</p> <p>Other main results included the improvements reported in the tango group in the FAB and the Four-Square Step tests.</p> <p>These results were maintained in the postop.</p> <p>No main effects were reported concerning the TUG.</p>	<p>I. Small sample size (particularly the control group).</p> <p>II. Slight age difference between the two groups.</p> <p>III. Participants knew their group assignment.</p> <p>IV. Some raters were not blinded.</p> <p>V. Treatments administered in two different centers.</p> <p>VI. Education group began one week earlier.</p> <p>VII. Places for the control group were filled before passing to the tango group.</p> <p>VIII. Participants took part to the interventions only when in “on” phase.</p> <p>IX. No distinction made between dx and sin. side dominant disease.</p>
<p>4) “Exercise and Parkinson’s: benefits for cognition and</p>	<ul style="list-style-type: none"> • Verbal Fluency (words starting with F, A and S for 1’ each). 	<p>Concerning the neuropsychological results, a 10% change has been considered to be clinically meaningful.</p>	<p>I. Small sample (28 individuals completed the study).</p>

<p>quality of life” (Cruise, 2011)</p>	<ul style="list-style-type: none"> • Semantic Fluency (for animals in 1’ period). • Pattern Recognition Memory test. • Spatial Recognition Memory test. • Spatial Working Memory test. • Stockings of Cambridge (working memory and spatial planning). • Geriatric Depression Scale (GDS – level of depressed mood). • Parkinson’s Disease Questionnaire (PDQ-39). 	<p>This said, the conclusions were:</p> <ul style="list-style-type: none"> • Exercise is “likely beneficial” for improving verbal fluency and spatial working memory (SWM). • Exercise is “possibly beneficial” for semantic fluency for animals. • Both EIP and control had conditions “possibly beneficial” for the Stockings of Cambridge. • No clinical benefits came from pattern/spatial recognition (neither for EIP and control groups). • Exercise was reported not to have any negative effect. 	<p>II. Participants’ depression level was in the normal ranges and none of the pts reported poor disease-specific QoL at the beginning of the study; this could have affected the post intervention relative measurements.</p> <p>III. Participants selected only from support groups: these may be more self-motivated and active at looking for support than other parkinsonians.</p> <p>IV. Treatment of the control group: some benefits in the EIP could be due more to social interaction than to the exercise intervention itself.</p>
<p>5) “Can exercise improve language and cognition in Parkinson’s disease? A case re-port” (Nocera, 2010)</p>	<p><u>Only single task:</u></p> <ul style="list-style-type: none"> • Mini-Mental Status Examination. • Stroop test (color X’s and color words). <p><u>Both single and dual task:</u></p> <ul style="list-style-type: none"> • Verbal fluency-animals. • Verbal fluency-letters (F; A; S). • Digit span forward and backward. • Picture description task (language function). 	<p>Major improvements were observed in:</p> <ul style="list-style-type: none"> • Stroop Color X’s test; • Stroop Color Words; • Verbal Fluency-Animals (single task). • Only a minimal improvement was seen in Verbal Fluency- Letters. • “Picture Description”: improvements in conciseness, grammar and contained less extraneous comments. 	<p>I. The motor tasks for assessment and training were the same: difficult to distinguish the improvement due to practice of the task and those due to cognitive improvement.</p> <p>II. One case only under study, low representativeness.</p> <p>III. Lack of a control group as comparison.</p>
<p>6) “Efficacy of a multimodal cognitive rehabilitation includ-</p>	<p>Blinded assessors. Assessment Tests: • UPDRS</p>	<p>Neuropsychological assessment: at screening session, no differences between the groups, all of them with deficits particularly in the EF.</p>	<p>Motor Training: Pts had difficulties solve some tasks by themselves, e.g parcours with obstacles; it was not</p>

ing psycho-motor and endurance training in Parkinson’s dis-ease”

(Reuter, 2012)

<ul style="list-style-type: none"> • GAS <p>The following tests were administrated at the beginning (baseline), after 4wks of the “period 1” (second assessment) and 6mo later, at the end of “period 2” of the study (final assessment):</p> <ul style="list-style-type: none"> • PANDA • MMSE • ADAS-COG • SCOPA-COG <p>As for health-related QoL:</p> <ul style="list-style-type: none"> • PDQ-39 <p>Additional tests for Executive Function (baseline, second assessment, final assessment):</p> <ul style="list-style-type: none"> • PASAT-Paced Auditory Serial Addition Test (processing information speed). • BADS-Behavioral Assessment of the Dysexecutive Syndrome. •MWT-B (Mehrfach-Wortschatz-Test) for premorbid performance. • Multiple choice word test. • Hospital anxiety and depression scale. 	<p>EF-BADS scale, did not differ at the baseline. The difference was relevant after period 1 ($p<0,03$) and at the final assessment ($p<0,01$). An even more significant difference of improvement between sample group and the control ones was observed ($p 0,001$ at the final assessment). Also, only the group C maintained the levels of improvement after the 6 months.</p> <p>PASAT Test: only group B and C showed improvements.</p> <p>GAS scale is indicative as well. When, at the last assessment, the goals were reviewed to check whether they had been reached, subject from the C group showed a major tendency to meet their objective ($p<0,001$). The goals did not differ particularly from one group to the other, gravitating all around the spectrum of EF.</p> <p>PDQ-39. Group C tended to rate their QoL higher than the controls, while the UPDRS showed at the final assessment a mild improvement in all the groups (meaning that the reported selective cognitive improvement in EF is not only part of a general benefit of the therapy to the whole condition).</p>	<p>possible to hold group lessons.</p> <p>I. Three different treatments combinations were under study, no real “control” group (“No treatment”).</p> <p>II. No evidence based for what transfer-exercises are the most effective: the selection of the exercises used in this section is based only on therapists’ and medical staff’s.</p> <p>III. ADAS-COG and SCOPA-COG may be considered not clinically relevant.</p> <p>IV. Short follow up, only 6 months (long term effects from the different exercise regimes cannot be reported).</p> <p>V. Physical exercise was paired with other modalities of exercise: not possible to completely isolate the benefit coming from the first exclusively.</p>
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7) "Intensive Rehabilitation Increases BDNF Serum Levels in Parkinsonian Patients: a Randomized Study"

(Frazzitta, 2014)

<ul style="list-style-type: none"> • Blind assessors and observer. • Measurements could be taken in 4 occasions: T0 = baseline T1 = 10 days after T2 = 20 days after T3 = 28 days after <p>Primary outcomes were serum BDNF and UPDRS III, assessed in both groups.</p> <p>UPDRS II, UPDRS tot, BERG balance scale, 6MWT only in the treatment group.</p>	<p>The sample group showed improvements in motor factors (balance and gait).</p> <p>The sample group also showed significant and persistent increases in serum BDNF levels (average increment of 14%), whose role has been proved to be fundamental in cognitive functions.</p>	<p>I. Group tested relatively small.</p> <p>II. Durability of the results unknown.</p> <p>III. Eventual correlation BDNF serum levels and motor performance not established.</p> <p>IV. Efficacy, feasibility and costs of the treatment of the study should be assessed outside the clinical settings, before establishing eventual validity.</p>
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6 CONCLUSIONS FROM STUDIES REVIEWED

What this review put into evidence, as well as other studies in the previous years did, is that the endurance/aerobic type of physical activity may be beneficial to the different cognitive functions of individuals suffering from PD; moreover, there are added benefits when the intensity of the exercise rises to medium or medium-high. More in particular, the aspects of cognition which have been seen to benefit (either by means of maintenance or, more often, enhancement of a specific cognitive domain) of the new aerobic regimes are: concentration (or the ability to sustain attention on a given stimulus), inhibition of unnecessary stimuli, mental flexibility (or the ability to shift the attention from one stimulus to the other), visuospatial memory, verbal fluency (more for semantic animal, minimal for letters) and velocity of processing the available information and stimuli.

Furthermore, Frazzitta (2014) reported a significant increase in the serum BDNF, which has been proved to act on the growth and/or maintenance of neural brain cells (particularly of the hippocampus) and, consequently, be a relevant contributor of the cognitive functions.

However, being the cognition itself a term underlying more than one specific function, the studies which, so far, had been carried out on this subject have been focusing on, and addressing the assessment batteries to, one or more of these subcategories, inevitably ignoring others. This being said, any comparison of one study to another, though all belonging to the same area of the interventions addressed to the cognitive deficits in Parkinson's disease, should be done taking into account their efficacy had been evidence proven strictly regarding some of the cognitive demands. Therefore, in order to determine an eventual most effective form of aerobic physical activity, the author believes future studies should take into consideration, and destine an appropriate assessment measurement, to each and every feature of cognition.

The duration of the interventions were variable, both if considering the overall extent of the studies, ranging from a minimum of four weeks to the maximum of three years, but also regarding that of the single sessions, from a minimum of 20 minutes to a maximum of 90 minutes. The frequency of the implementations varied from

twice a week up to everyday sessions; also, the same study which required daily sessions was the only one having them divided in three parts throughout the day, accordingly to the modalities of the activity.

However, although all these studies give a hint of eventual potential benefits that physical activity, specifically the aerobic one, retains on the cognitive functions of individuals suffering from Parkinson's disease in the mild stages, not all of them indicated, explicitly, a description and specific dosage of the activities taken into consideration. Synthesizing the whole activity with the name of "cardiovascular" or "aerobic" exercise contributes to make these studies difficult to be compared to one another and to be evaluated in terms of time spent, intensity and outcomes; the same lack of specificity make it difficult to actually assess what could be, if possible, the best option available. In addition, the same vagueness renders the studies interested of little use from the perspective of making the results more easily accessible by the population not belonging to the specialized field: Parkinson's disease patients in first person, their caregivers, but also those individuals interested in taking the available preventive actions as they age.

7 DISCUSSION

The topic of this thesis was chosen by the author consequently to a personal interest that rose in the context of a clinical placement in a neurological ward. However, what was the original idea of systematic review following the PRISMA statement (Website of the PRISMA Statement) could only be followed partially and the meta-analysis was not feasible, given the lack of formation and experience of the author in this specific area of research: this would have probably addressed the set questions more accurately. Furthermore, the restricted amount of time, this being necessary to present this thesis in the agreed amount of time, and the fact that the author was carrying out this review by herself also acted as limiting factor to the possibility to acquire the necessary skills right in advance, before starting writing the review. A further limitation was that, once the results were retrieved and visualized from the different search engines, only those articles, the visualization of those required either no charge or a minimum one (inferior to ten euros), were taken into consideration when

selecting the studies to be included in the review. This condition, summed to the fact that, originally, only few articles matched the requirements of this review, determined the small number of articles selected (seven). In order to provide a spectrum as wide as possible of alternative forms of aerobic physical activity, which, at the same time, had been proven to be accessible to those individuals diagnosed with Parkinson's disease from a mild to a moderate stage, different types of study design were included in the review: even when they were not paired with a control group, what the author retained of main importance was providing a "compendium" of what the available alternatives are, in terms of aerobic exercise and concerning this very specific class of subjects. This being said, it can be easily argued that the quality level of the different studies taken into account may be varying, when voices, such as the presence of any control group, or the methods of randomization adopted throughout the course of the study, are found to be not completely satisfactory, when compared to the highest standards auspicated by the instructions for systematic reviews; nevertheless, as already stated, it must be taken into account that the main objective of this thesis was that of providing multiple options of exercise to any eventual Parkinson's disease patient, falling into the first three stages of the disease, who is willing to actively take charge, at least in part, of his/her condition also from the cognitive perspective.

Coming to the studies themselves, the variety of implementation modalities, as well as the different outcome measures, made the possibility of a reliable comparison between one study and the other rather unlikely, since this would require, to begin with, dealing with the same variants (for example the same activity and assessment test) in each and every study. It should be noticed, however, that any of these studies was reported to be beneficial for at least one of the dominions of cognition: this, in the author's opinion, is indicative of the fact that, although it may still not be possible to determine the optimal exercise regime when it comes to protecting and enhancing the cognitive functions of individuals affected by mild to moderate Parkinson's Disease, any of the offered modalities of aerobic physical activity, perhaps together with new proposals, could potentially be the best solution in this clinical context, provided that all the cognitive areas have been assessed and the results compared with those of the other modalities.

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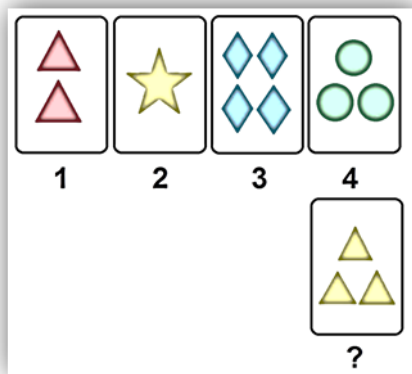
Zigmond M.J. & Burke R.E. 2002. Pathophysiology of Parkinson's disease. In: Davis K. L., Charney D., Coyle J.T. & Nemeroff C. (eds) *Neuropsychopharmacology: The Fifth Generation of Progress*. Lippincott, Williams, & Wilkins, Philadelphia, Pennsylvania 1781-1793

APPENDIX 1

TESTS GENERALLY EMPLOYED TO ASSESS DYSEXECUTIVE SYNDROME

Wisconsin Card Sorting Test (Wcst)

During this test, the stimuli are given to the patient in the form of cards (see picture 3), all of them presenting some colored shapes on them. The cards are differentiated by shape, color and quantity of shapes pictured on each of them.



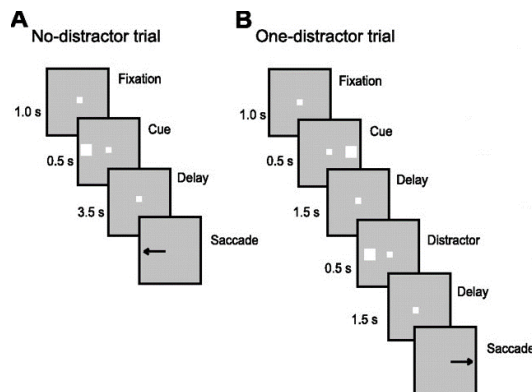
Picture 3. Example of WCST (source: <http://en.wikipedia.org>).

The participant to the test is asked to sort the cards into piles (the number of piles can vary from one version to the other of this test) according to some principle. The participant, though, is not told what principle is the correct one: the requirement of the test is for the participant to guess it out, with the only indications given from the test administrator being whether each trial of the patient follows or not the chosen principle. Moreover, throughout the test, the sorting principle will be changed, unbeknownst to the patient, and the test taker will have to discover the new rules as well, in order to pass the test.

Spatial Delayed Response Task (Sdr)

This test assesses the patient's spatial working memory. The patient is asked to look at a monitor and focus on the fixation point; while the test taker is still looking at the fixation point, another one, a cue, appears for milliseconds in another position towards the edge of the screen (32 locations are possible). Then, a delay interval is then

imposed, showing only the fixation point at the center of the screen (during this interval, different geometrical shapes can be shown in place of the original one: in this case the patient, in order to prosecute to the next phase, is asked to press the spacebar of the computer only when a diamond shape will appear as fixation point). In the following phase, the participant must indicate where the cue had appeared on the screen. (<http://www.cognitiveatlas.org/>)

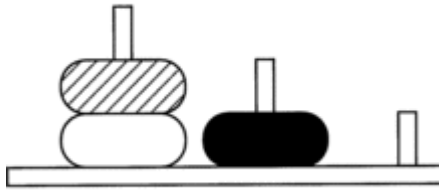


Picture 4. Example of SDR, no-distractor and one-distractor trial (source: <http://jn.physiology.org>).

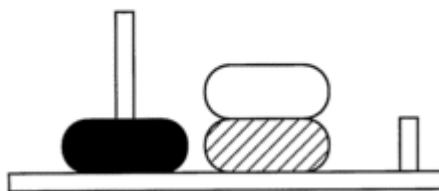
Tower of London test (and variations)

Tower of London is a version of the traditional puzzle Tower of Hanoi; different versions of this test have been developed, both manual and multimedial. The Tower of London is a tool to evaluate the problem-solving capacities of an individual. More specifically, it assesses the planning capacities, fundamental in order to accomplish everyday tasks, which may result impaired by different neurological conditions, including Parkinson's disease. The patient is first showed a model where beads of different colors and/or dimensions (depending of the version of this test) are inserted on two or more rods. The testee is then asked to rearrange the beads of his/her station (see picture 5) from the starting position in order to match the position of the beads in the model, this following some rules he/she has been made aware of beforehand (e.g. smaller and light colored beads cannot be placed below bigger or darker colored ones) . (Tower of London – Sanzen Neuropsychological Assessment Tests LLC, 2012 <https://neuropsychological-assessment->

Initial State



Goal State

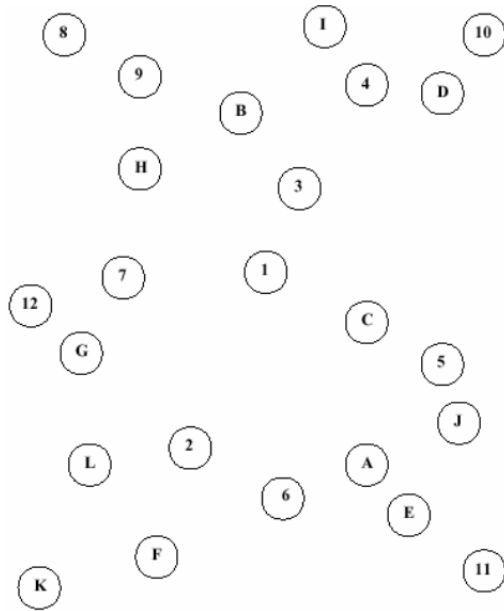


Picture 5. Example of Tower of London Stations (reference: <http://cbs-neuromarketing.wikispaces.com/Decision+making>)

Trail Making Test

It is a neuropsychological test of visual attention and task switching. Trail making test is made up of two parts, A and B, in which the patient is asked to connect a set of 25 dots as fast as possible, but, at the same time, maintaining the accuracy necessary to keep the pen, or pencil, in contact with the surface of the paper. The test can be administered either by paper or on a computer; the test is divided into two phases, A and B: in both of them, the patient is instructed to connect with a line 25 dots, but, while in the A-phase the targets are all numbers, to be ordered from 1 to 25, in the B-phase, the patient has to alternate between numbers and letters of the alphabet, both to be ordered in a crescent way (e.g.: 1, A, 2, B, 3, C,...)(see picture 6); in case the testee commits a mistake, the tester is entitled to correct him/her before passing to the next dot. The goal of the test is to complete the whole test, parts A and B, as quickly as possible; eventual mistakes in the tracking will not be taken into account in the paper version of the task, also due to the fact that these errors would anyway have an influence on the time of completion of the task. The main scores are given by measuring in seconds how much time will it take for the patient to complete each phase of the test (therefore giving two different times, usually the one relative to the

B-phase being longer, due to the more complex nature of this part of the test); While part A of this test mostly measures the processing speed of the individual, part B takes into account also the executive capacity of the testee; visual search and mental flexibility are considered to be involved as well in the completion of Trail Making Test. (Tombaugh, 2004)



Picture 5. Example of phase B of Trail Making Test

(source: http://doa.alaska.gov/dmv/akol/pdfs/uiowa_trailmaking.pdf)

Odd Man Out Test

The Odd Man Out is a test measuring a subject's reaction time in telling, given three stimuli, which one between the first and the second is the furthest from the second, central one. The "Odd man out" will then be the stimulus recognized to be the more distant from the central, second, stimulus. (Diascro & Brody, 1994). One version commonly used is the one making use of an adaptation of the so called "Jensen Box", with three lights being turned on at each trial and the patient being required to sort out the furthest light as the Odd Man Out stimulus. (Mackintosh, 2011). The main outcome that this test assess is the speed of the subject to understand the eventual relationships existing among different stimuli; it is, moreover a tool to assess the ability of the individual to process a given information, in particular the speed of inspection and the subsequent making of an appropriate decision. (Mackintosh, 2011)

Verbal Fluency Test

In the verbal fluency test, the patient is asked to list as many words as possible of a given category (established beforehand by the tester) within a given amount of time (usually 60 seconds). The category can either be semantic (e.g. animals, food...) or phonemic (e.g. words beginning with a given letter). (Lezak, 1995). Although the main outcome is the total number of words told by the testee, other important information can be drawn by taking into consideration eventual repeated words, the words belonging to a same subcategory ("clustering"), their number and length, as well as the number of switches to other subcategories ("cluster switching"). (Tombaugh, 2004). Throughout studies based on voxel-based lesion symptom maps it has been evidenced that the deficits in semantic and phonemic fluency are originated by lesions in different brain areas, more precisely in the temporal and frontal cortices, respectively. (Baldo, 2006).

Stroop Test

Also called the "Stroop color word test", it is a neuropsychological test measuring the ability to set shift and ignore/repress, as quickly as possible, the interfering information, which are of no use for the completion of the task proposed. Based on the effect described by the American neurologist John Ridley Stroop back in 1935, this test can be administered in many versions, each including some subtasks; one of the most common is divided in three subparts: the first one, "Word-task" requires the patient to simply read a set of words indicating colors; then, in the second part, the "Color-task", the subject will have to tell the color of a series of "Xs"; finally, as third task, the "Color-Word-task" consists of a panel on which the names of different colors have been written in different inks, which, however do not match with the name of the color indicated (Picture 7). The patient is then asked to name the color of the ink the word is written in. As already mentioned, further different variants of this test are available, their main difference being the number and type of subtasks. Similarly, the score can be calculated either as the number of words read in a given amount of time, or as the amount of time necessary to carry over the single subparts as well as the whole task. (Homack, 2004).

BLUE **GREEN** **YELLOW**
PINK **RED** **ORANGE**
GREY **BLACK** **PURPLE**

Picture 7. Example of Stroop Test panel (source: <https://faculty.washington.edu/chudler/sout2.html>).

Eriksen Flanker Task

The Eriksen Flanker Task is a test employed to assess the ability of a subject to inhibit unnecessary stimuli presented in a given situation. Diverse studies had proven that the response to a stimulus tends to be slower when distracting items are presented together with the stimulus: this observation applies to the whole population and has been seen to persist even in the case the testee is aware he/she has to ignore those extra stimuli (Davelaar, 2013). Although this test may present in some variants, the very basic idea is that of presenting the testee with a central stimulus, that has been put next to secondary stimuli and to which he/she will have to give an appropriate response to; these secondary, non-target stimuli can be of three different types: they can be “congruent”, meaning they trigger the same response of the central, target stimulus and can even present identical to this last one in shape; the non-target object can be “incongruent”, prompting a response in the subject that would be the opposite of the one associated with the central stimulus; third and last, the flanking stimuli can be of a “neutral” type, generating neither the same, nor the opposite response of the one triggered by the target stimulus. (Davelaar, 2009)

Originally, in the 1974 version of this test, the stimuli were constituted by letters, usually grouped in batches of seven items, then, later on, other variants were introduced, presenting arrows, numbers, colors and even setting the stimuli along directions other than the horizontal one. This being said, examples of incongruent stimulus could be HHHSHHH or >>><>>>, while congruent ones could be CCCCCC or >>>>>>>. An example of neutral stimulus would be, instead □□□>□□□, where target and secondary signals do not belong to the same category and, thus, are not comparable to one another. (Lamers, 2011). Despite this test is administered with the intention to assess the ability of a subject to respond to a central stimulus meanwhile inhibiting the coexisting unnecessary ones, still no clear explanation has been formu-

lated concerning how an individual manages to operate the selection between the target and unnecessary stimuli (Davelaar, 2013).

Montreal Cognitive Assessment

The Montreal Cognitive Assessment, or MoCA, was developed with the purpose of promptly recognize those individuals exhibiting “signs” of a possible mild cognitive decline in both physiological and pathological aging settings. It is considered a quick assessment tool since it allows, in approximately ten minutes, to screen different areas of cognition, also given the fact that the tasks making up the test may be indicative of more than one domain (Picture 8).

Executive functions are assessed in three parts: first, through a modified version of the B-phase of the “Trail making test”, then with a “Letter fluency test” and thirdly, using an abstraction task, requiring, for instance, to find out the similarities between two given items. Visuospatial skills are assessed with two tasks, the first one requiring to draw a clock indicating a given time, the second implying the copy drawing of a tridimensional cube (Nasreddine, 2010). Other domains of cognition which are being assessed throughout this test are attention, concentration, memory, language, conceptual thinking, calculations, and orientation.

Although the maximum score is 30, reaching 26 points is considered enough for average, healthy subjects; furthermore, according to the official website, a score from 18 to 26 indicate a mild cognitive impairment, one from 10 to 17 a moderate cognitive impairment while less than 10 suggests a severe cognitive impairment. It should be kept into consideration, however, that this division of the scorings is not officially set yet, as the official MoCA webpage states (Nasreddine, 2003).

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME: _____
Education: _____ Date of birth: _____
Sex: _____ DATE: _____

VISUOSPATIAL / EXECUTIVE							POINTS	
		Copy cube []	Draw CLOCK (Ten past eleven) (3 points)			[] /5		
NAMING							POINTS	
						[] /3		
MEMORY		Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.					No points	
		FACE	VELVET	CHURCH	DAISY	RED		
	1st trial							
	2nd trial							
ATTENTION		Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [] 2 1 8 5 4 Subject has to repeat them in the backward order [] 7 4 2					___/2	
ATTENTION		Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [] FBACMNAAJKLBAFAKDEAAAJAMOF AAB					___/1	
ATTENTION		Serial 7 subtraction starting at 100 [] 93 [] 86 [] 79 [] 72 [] 65 4 or 5 correct subtractions: 3 pts , 2 or 3 correct: 2 pts , 1 correct: 1 pt , 0 correct: 0 pt					___/3	
LANGUAGE		Repeat : I only know that John is the one to help today. [] The cat always hid under the couch when dogs were in the room. []					___/2	
LANGUAGE		Fluency / Name maximum number of words in one minute that begin with the letter F [] ____ (N ≥ 11 words)					___/1	
ABSTRACTION		Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler					___/2	
DELAYED RECALL		Has to recall words WITH NO CUE	FACE []	VELVET []	CHURCH []	DAISY []	RED []	POINTS for UNCUED recall only
Optional		Category cue						
Optional		Multiple choice cue						
ORIENTATION		[] Date	[] Month	[] Year	[] Day	[] Place	[] City	___/6
© Z.Nasreddine MD		www.mocatest.org		Normal ≥ 26 / 30		TOTAL		___/30

Picture 8. Example of Montreal Cognitive Assessment test (source: www.mocatest.org).

APPENDIX 2

ARTICLES GRADING ACCORDING TO PEDro SCALING SYSTEM

The author of this thesis used the PEDro scale system in order to give an indication of the methodological quality (more precisely, the “internal validity” and the “generalizability”) of the studies that had been included in this work (<http://www.pedro.org.au/english/faq/>). However, although a useful instrument, it should not be considered a measurement tool measuring the absolute validity of a study, as the same PEDro website suggests.

PEDro Scale items	1)	2)	3)	4)	5)*	6)	7)
1. Eligibility criteria were specified.	yes	yes	yes	yes	yes	yes	yes
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received).	no	no	no	no	no	yes	yes
3. Allocation was concealed.	no	no	no	no	no	no	yes
4. The groups were similar at baseline regarding the most important prognostic indicators.	yes	yes	yes	yes	no	yes	yes
5. There was blinding of all subjects.	no	no	no	no	no	no	no
6. There was blinding of all therapists who administered the therapy.	no	no	no	no	no	no	no
7. There was blinding of all assessors who measured at least one key outcome.	yes	yes	yes	no	no	yes	yes
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.	yes	yes	yes	no	yes	yes	yes
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by “intention to treat”.	yes	no	yes	no	yes	yes	yes

10. The results of between-group statistical comparisons are reported for at least one key outcome.	yes	yes	yes	yes	no	yes	yes
11. The study provides both point measures and measures of variability for at least one key outcome.	yes	yes	yes	yes	yes	yes	yes
TOTAL SCORE	7	6	7	4	4*	8	9

(*) = This article, being a single case report, is not particularly suitable to be graded according to the PEDro scale.

Where:

- 1) "Benefits of physical exercise on executive functions in older people with Parkinson's Disease" (Tanaka, 2009).
- 2) "Phase I/II randomized trial of aerobic exercise in Parkinson's disease in a community setting" (Uc, 2014).
- 3) "The effects of adapted tango on spatial cognition and disease severity in Parkinson's disease" (McKee, 2013).
- 4) "Exercise and Parkinson's: benefits for cognition and quality of life" (Cruise, 2011).
- 5) "Can exercise improve language and cognition in Parkinson's disease? A case report" (Nocera, 2010).
- 6) "Efficacy of a multimodal cognitive rehabilitation including psychomotor and endurance training in Parkinson's disease" (Reuter, 2012).
- 7) "Intensive Rehabilitation Increases BDNF Serum Levels in Parkinsonian Patients: a Randomized Study" (Frazzitta, 2014).