Pontifícia Universidade Católica
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Eduarda Naidel Barboza e Barbosa

Parkinson's Disease: Innovative Perspectives in Diagnosis and Treatment

Tese de Doutorado

Thesis presented to the Programa de Pós-gradução em Psicologia of PUC-Rio in partial fulfillment of the requirements for the degree of Doutor em Psicologia Clínica.

Advisor Prof(a) Helenice Charchat-Fichman

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Abstract

Barbosa, Eduarda Naidel Barboza e; Charchat-Fichman, Helenice (Advisor). **Parkinson´s Disease: Innovative Perspectives in Diagnosis and Treatment**. Rio de Janeiro, 2020. 102p. Tese de Doutorado – Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

Parkinson's disease (PD) is considered the second most common neurodegenerative disease and its motor characteristics are much better known than non-motor ones, but functional impairment is present in almost all cases. Deep Brain Stimulation (DBS), which consists of electrical stimulation of subcortical structures to decrease or stop motor symptoms, has been used as a tool for greater control of motor symptoms and is gaining ground in studies with non-motor symptoms. It is for this reason that a systematic review was carried out to find out the instruments used in the neuropsychological assessment of people with PD who underwent DBS surgery in subtalamic nuclei (STN) and to investigate whether cognitive effects would arise after surgery. In addition, a computerized neuropsychological battery, the CompCog, was validated for people with PD from a public hospital in the Rio de Janeiro city and was also used to compare ON and OFF stages of 9 patients, from a private clinic, who did the implementation of the DBS-STN. With systematic reviews, it was possible to develop a neuropsychological assessment protocol, later used in empirical studies and to verify that verbal fluency was the aspect that showed the greatest difference between the ON and OFF stages of patients with ECP-NST. In the clinical validation study of CompCog it was possible to establish cutoff points for people with PD and in the comparison study between ON and OFF stages of people with PD and ECP-NST it was possible to identify that the time variables such as mean reaction time and total time, were able to differentiate the two stages, ON and OFF, of the sample of 9 people in the subtests of incidental memory, episodic memory and inhibitory control, in addition to showing a tendency to differentiate in attention, processing speed and episodic memory.

Keywords

Parkinson's Disease; Cognition; Deep Brain Stimulation; Validation of a computerized neuropsychological battery

Resumo

Barbosa, Eduarda Naidel Barboza e; Charchat-Fichman, Helenice. **Doença de Parkinson: Perspectivas Inovadoras em Diagnóstico e Tratamento.** Rio de Janeiro, 2020. 102p. Tese de Doutorado – Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

A doença de Parkinson (DP) é considerada a segunda doença neurodegenerativa mais comum e suas características motoras são muito mais conhecidas que as não motoras, mas o comprometimento funcional está presente em quase todos os casos. A Estimulação Cerebral Profunda (ECP), que consiste na estimulação elétrica de estruturas subcorticais para diminuir ou cessar os sintomas motores, tem sido usada como uma ferramenta para maior controle dos sintomas motores e está ganhando terreno em estudos com sintomas não motores. É por esse motivo que foi realizada uma revisão sistemática para conhecer os instrumentos utilizados na avaliação neuropsicológica de pessoas com DP submetidas à cirurgia ECP nos núcleus subtalâmicos (NST), além de investigar também se surgiriam efeitos cognitivos após a cirurgia. Além disso, uma bateria neuropsicológica computadorizada, a CompCog, foi validada para pessoas com DP de um hospital público da cidade do Rio de Janeiro e também foi usada para comparar os estágios ON e OFF de 9 pacientes, de uma clínica privada, que fizeram a implantação da ECP-NST. Com as revisões sistemáticas foi possível elaborar um protocolo de avaliação neuropsicológica, posteriormente utilizado nos estudos empíricos e verificar que a fluência verbal foi o aspecto que apresentou maior diferença entre os estágios ON e OFF dos pacientes com ECP-NST. No estudo de validação clínica da CompCog foi possível estabelecer pontos de corte para as pessoas com DP e no estudo de comparação entre estágios ON e OFF de pessoas com DP e ECP-NST foi possível identificar que as variáveis de tempo como tempo médio de reação e tempo total, foram capazes de diferenciar os dois estágios, ON e OFF, da amostra de 9 pessoas nos subtestes de memória incidental, memória episódica e controle inibitório, além de apresentar uma tendência à diferenciação na atenção, velocidade de processamento e memória episódica.

Palavras-chave

Doença de Parkinson, Cognição, Estimulação Cerebral Profunda, Validação de Bateria Neuropsicológica Computadorizada

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I. BACKGROUND

Parkinson's disease (PD) was first described in 1817 by James Parkinson, and, just 47 years later, was called Parkinson's disease. It is considered the second most common neurodegenerative disease, preceded only by Alzheimer's Disease (AD) (Pavão, 2007; Rita, 2012; de Paixão et al, 2016). Its motor characteristics are much better known than non-motor ones, but functional impairment is present in practically all cases (Machado & Reppold, 2015; Pavão, 2007; Werneck, 2010; Heluani, 2014). Patients with PD present, in addition to motor impairments, non-motor impairments, such as a variety of neuropsychiatric symptoms (depression and psychotic symptoms) (Aarsland et al, 2009; Navarro-Peternella & Marcon, 2012). When it was described, it was believed that cognition was preserved in PD, but current research (Nombela et al, 2014; Ding et al, 2015) brings reports of cognitive decline.

The PD diagnosis is made through clinical criteria by trained professionals, such as neurologists. These criteria are based on the identification of clinical manifestations, pure motor symptoms. The definitive diagnosis can only be made with necropsy. The most widely used criteria are those of the UK Parkinson's Society Brain Bank (Litvan et al, 2012) and in 2015 the Movement Disorders Society launched new criteria (MDS, 2015).

The pathological marker of this disease is deterioration in the substantia nigra *pars reticulata* in addition to Lewy bodies accumulation - protein aggregates (Melo et al, 2007). PD is considered the result from the degeneration of dopaminergic neurons, resulting in a consequent reduction of dopamine levels in the substantia nigra, a region located in the upper part of the brain stem, impairing the functioning of motor circuits and - implicit procedural learning (Pavão, 2007; Rita, 2012; de Paixão et al, 2016). Pathological changes take an upward path, from the brain stem to neurons of the substantia nigra and from there to cortical areas (Melo et al, 2007). The reduction in the primary motor activation, pre-motor and supplementary area are also possible causes of PD symptoms. This occurs due to an excessive excitatory discharge from the subthalamic nucleus that promotes hyperactivity of the internal pale globe and/or *pars reticulata* substantia nigra (Nasser, 2002).

The occurrence of PD is more frequent in individuals aged between 85 and 90 (Driver et al, 2009), but it is also observed below 40 and above 70 years old (Silva and Nakamura, 2013), with the degenerative and the silent development start long before reaching these age groups. Silva and Nakamura (2013) estimate 1.5 to 2 individuals for every 1000 over 60 years of age will have the disease. Studies (de Lau & Breteler, 2006; Toulouse & Sullivan, 2008) claim that the number of cases tends to double by 2050. As a result, it is necessary as soon as possible to develop a neuropsychological assessment protocol to establish a profile of commitment within PD.

Losses in cognitive functions such as implicit memory, executive function, visuospatial skills and language are increasingly attracting attention in the current literature (Rita, 2012). One in three PD patients has cognitive impairment at or shortly after diagnosis, with progressive worsening or even causing dementia in the later stages (Nombela et al, 2014), but cognitive changes are common in non-demented PD patients (Schneider, Sendek and Yang, 2015).

In addition to pharmacological and therapeutic treatment, there may be an indication for surgical intervention. One of these methods is deep brain stimulation (DBS), targeting the subthalamic nucleus (STN) or globus pallidus (GPi), which consists of electrical stimulation of subcortical structures. The main objective of the DBS is to control motor function (Aguilar, Soto & Esguerra, 2011). The reason why STN is chosen is due to the possibility of decreasing the dose of medications and, consequently, reducing adverse effects, but there is controversy in the literature. A macro electrode is implanted in the STN and then a microelectrode operated by a neurostimulator that creates a closed circuit by sending electrical stimulation to specific areas of the brain that control movement, blocking the abnormal nerve signals that cause the tremor and the symptoms of PD. The DBS circuit has 3 components: the electrode that is inserted through a small opening in the skull and implanted in the brain, the extension that is a wire that runs from the stimulation area in the brain to the shoulder, under the skin, connecting to the neurostimulator that is implanted near the collarbone or, in some cases, in the abdomen. DBS works by inhibiting or blocking GPi or STN activity - the latter being more advantageous - due to its high frequency, reversing its

abnormal functionality, but without the risks and complications of bilateral ablation (Nasser, 2002).

The literature points to an evident motor and quality of life improvement after DBS in patients with PD, however studies dedicated to the relationship between STN-DBS and cognitive functioning are divergent - generating the motivation for this investigation. In this context, it becomes propitious to validate an instrument that allows a more specific neuropsychological assessment of aspects not considered for this population.

II. OBJECTIVES

According to the background presented, first this study wants to investigate the use of certain instruments in studies with PD patients with STN-DBS to propose a protocol that addresses the cognitive functions involved in the disease, also wants to analyze the effects on cognition in people with PD and STN-DBS. The second part of this thesis is composed of two studies: the first seeks to validate a computerized neuropsychological battery, CompCog, for people with PD and the second one wants to compare ON and OF stages in cognitive performance on STN-DBS patients using the protocol proposed previously and CompCog.

ARTICLES SECTION

ARTICLE 1

Barbosa E. N. B., Charchat-Fichman H. Systematic review of neuropsychological instruments used in subthalamic nucleus deep brain stimulation in Parkinson´s disease patients. **Dementia and Neuropsychologia**, 2019, v. 13, n. 2, p. 162-171.

ABSTRACT

Introduction: In addition to drug treatment, surgical intervention represents an alternative to PD patients with motor deficits. The most common intervention is subthalamic nucleus deep brain stimulation (STN-DBS). It is extremely important to perform a neuropsychological assessment in patients with STN-DBS, not only to identify losses related to the disease, but also to compare influence on cognition both pre and postoperatively. **Objective:** the objective of this systematic review was to investigate the instruments frequently used in studies related to STN-DBS in PD patients. Methods: articles were retrieved from Medline/ PubMed databases published in the 2007-2017 period using PRISMA criteria. **Results:** after analyzing 27 articles, the absence of a specific evaluation protocol for PD with STN-DBS was evident. **Conclusion:** non-motor symptoms are not given due importance in neuropsychological assessments. It is crucial to acknowledge that these symptoms have a major impact on the quality of life of patients. Greater engagement in assessing these aspects is required, in order to bridge the gaps in research.

Keywords: Parkinson's disease, deep brain stimulation, neuropsychological instruments, neuropsychological assessment.

Systematic review of neuropsychological instruments used in subthalamic nucleus deep brain stimulation in Parkinson´s disease patients

1. INTRODUCTION

Parkinson's disease (PD) is considered to be the second most common neurodegenerative disease, preceded only by Alzheimer's disease (AD)[1,2]. PD's motor characteristics are much better known than non-motor ones, but the patient also presents functional impairment[1,3-5]. When PD was described, it was believed that cognition was preserved, but current research[6, 7] brings reports of cognitive decline.

Besides drug treatment, it is possible to use surgical intervention in some cases. One of these methods is deep brain stimulation (DBS) consisting of the electrical stimulation of subcortical structures. The main objective of DBS is motor control of symptoms; however, the stimulated areas are also potentially able to stimulate some cognitive functions secondarily[8].

Studies usually promote cognitive screening in patients to characterize the sample and identify the impairments to be analyzed. However, comparing cognitive data from different populations and through different tests can produce some conflicts in the literature, mainly because it is used screening instruments that do not have the sensitivity to detail cognitive functioning sufficiently[5] and some of them provide different versions of the same test or use nonstandard tasks.

The objective of this review is to learn and understand the use of certain instruments in studies with PD patients with STN-DBS and to relate those findings with the literature in general. The search included articles published from January 2007 to January 2017, based on The Preferred Reporting Items for Systematic Review and Meta-Analyzes (PRISMA) criteria.

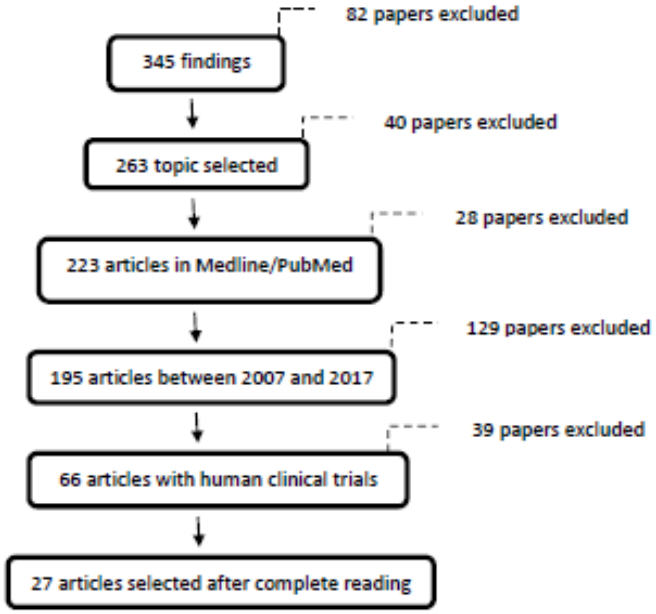
2. METHODOLOGY

The systematic review is a type of scientific research that aims to gather, critically evaluate and conduct a synthesis of multiple primary studies[9].

2.1 Bibliographic Survey We projected a systematic review of the literature according to the Preferred Reporting Items for Systematic Review and Meta-Analyzes (PRISMA) criteria. The following terms were used: "Deep Brain Stimulation", "DBS", "Cognitive Functions" and "Parkinson Disease" with the Boolean operator "and". We selected scientific papers published in English between January 2007 and January 2017, with comparative clinical trials in humans, in Medline / PubMed databases. Articles published before 2007, systematic reviews, case studies, books chapters and studies using animals were excluded.

2.2 Studies selection Initially, this method identified 345 responses (Figure 1). To refine the research, the following topics were selected: "Parkinson's Disease", "Subthalamic Nucleus", "Deep Brain Stimulation", "DBS", "Cognition" (263), published in the Medline / PubMed database (223) between 2007 and 2017 (195). From the material collected, we observed titles and summaries to consider studies with human clinical trials exclusively (66). Literature reviews and case studies were excluded, as well as articles containing problems in the methodology, such as not inclusion of (a) inclusion and exclusion criteria, (b) complete assessment protocol and (c) lack of pre or post-surgery assessment fulfillment (27). The researchers selected the articles independently: they considered suitable studies that (a) evaluated PD patient's cognition with STN-DBS; (b) presented the instruments and domains evaluated; and (c) presented pre and post-surgical results.

Figure 1. Articles research fluxogram



3. RESULTS

Following are the final list of articles that were included by the research criteria in ascending order of year, with objectives and results (Table 1), a list of instruments with quantity, separated by domains (Table 2) and a list of instruments used before and after DBS implantation to assess the cognitive aspects of the patients (Table 3).

Table 1. List of articles included in the systematic review criteria.

	Authors and Name	Year	Used instruments
1	*Cilia et al.* Brain networks underlining verbal fluency decline during STN-DBS in Parkinson's disease: An ECD-SPECT study.	2007	Mini-Mental State Exam (MMSE), Phonemic and Semantic Verbal Fluency Tasks, Wisconsin Card Sorting Test (WCST), Raven´s Progressive Matrices (RPM)
2	*Klempírová et al.* Deep brain stimulation of the subthalamic nucleus and cognitive functions in Parkinson's disease.	2007	Mattis Dementia Rating Scale (MDRS), Weschler Memory Scale-III (WMS), Stroop Test, VFT
3	*Castelli et al.* Apathy and verbal fluency in STN-stimulated PD patients.	2007	RPM, Bi-Syllabic Words Repetition test (BWR), Corsi´s Block Tapping test (CBTT), WMS, Trail Making Test (TMT), Nelson Modified Card Sorting test (MCST), VTF, Beck Depression Inventory (BDI), Apathy Evaluation Scale (AES)
4	*Heo et al.* The effects of bilateral Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) on cognition in Parkinson disease.	2008	TMT, Korean Boston Naming test (K-BNT), Rey-Kim Memory Battery, Grooved pegboard test, WCST, Stroop test, VFT, Korean Mini-Mental Status Examination (K-MMSE), BDI
5	*Witt et al.* Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study.	2008	UPDRS-I MDRS, German Rey´s Auditory Verbal Learning Test (G-RAVLT), Weschler Adult Intelligence Scale (WAIS), Benton Visual Retention Test, Stroop test, VFT, BDI, Montgomery-Asberg Depression Rating Scale (MADRS), Beck Anxiety Inventory (BAI), Parkinson´s Disease Questionnaire (PDQ-39)
6	*Alberts et al.* Bilateral subthalamic stimulation impairs cognitive–motor performance in Parkinson's disease patients.	2008	n-back task, dual task
7	*Lueken et al.* Impaired performance on the Wisconsin Card Sorting Test under left- when compared to right-sided deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease.	2008	MMSE, WCST, German Hospital Anxiety and Depression Scale (HADS-D), German Apathy Evaluation Scale (AES) *

8	*Zangaglia et al.* Deep brain stimulation and cognitive functions in Parkinson's disease: A three-year controlled study	2009	MMSE, long memory task, verbal span, digit span, CBTT, WCST, RPM, FVT
9	*York et al.* Relationship between neuropsychological outcome and DBS surgical trajectory and electrode location	2009	MMSE, RAVLT, VFT, MDRS, BDI, State-Trait Anxiety Inventory (STAI)
10	*Williams et al.* Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease.	2009	UPDRS-I, PDQ-39, MDRS, Delis-Kaplan executive function system (D-KEFS), Weschler Abbreviate Scale Intelligence (WASI)
11	*Daniels et al.* Risk factors for executive dysfunction after subthalamic nucleus stimulation in Parkinson's disease	2010	MDRS, RAVLT, WAIS, BVRT, Stroop test, VFT
12	*Castelli et al.* Neuropsychological changes 1-year after subthalamic DBS in PD patients: A prospective controlled study	2010	RPM, Bi-Syllabix Words Repetition Test, Corsi´s Block Tapping test, Paired Associate Learning, Trail Maling Test, MCST, VFT
13	*Fasano et al.* Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants	2010	MMSE, Corsi´s Block Tapping Test, digit span forward, digit span backward, RAVLT, RPM, MWCST, VFT, Zung´s depression Scale, Zung´s Anxiety Scale
14	*Van Wouwe et al.* Deep Brain Stimulation of the Subthalamic Nucleus Improves Reward-Based Decision-Learning in Parkinson's Disease	2011	Haruno and Kawato Task, MMSE
15	*Israeli-Korn et al.* Subthalamic Nucleus Deep Brain Stimulation Does Not Improve Visuo-Motor Impairment in Parkinsons Disease	2013	MMSE, BDI, VFT, Frontal Assessment Battery (FAB), Visual Analog Mood Scale, Digit Span Forward and Digit Span Backward, Finger Tapping Test, Visual-motor Coordination Task
16	*Kim et al.* Initial cognitive dip after subthalamic deep brain stimulation in Parkinson disease	2013	MMSE, TMT, K-BNT, Rey-Kim Memory Battery, Stroop Test, VFT, BDI

17	*Yágüez et al.* Cognitive predictors of cognitive change following bilateral subthalamic nucleus deep brain stimulation in Parkinson's disease	2014	WAIS-III, Recognition Memory Test, Birt Memory and Information Processing Battery, Graded Naming Test, Visual Object and Space Perception Battery, Hayling Sentence Completion Test, Brixton Spatial Anticipation Test, VFT
18	*Asahi et al.* Impact of bilateral subthalamic stimulation on motor/cognitive functions in Parkinson's disease	2014	MMSE, Japanese Adult Reading Test (JART), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), WAIS-Revised
19	*Rizzone et al.* Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: From the advanced phase towards the late stage of the disease?	2014	UPDRS-I, MMSE, RPM, Digit Span Forward, Corsi´s Block Test, MWCST, VFT, RAVLT, TMT, Paired Associated Learning, Attentive Matrices, Zung´s Depression Scale, Zung´s Anxiety Scale, BDI, State-Trait Anxiety Inventory (STAI)
20	*Houvenaghel et al.* Reduced Verbal Fluency following Subthalamic Deep Brain Stimulation: A Frontal-Related Cognitive Deficit?	2015	MDRS, VFT, Stroop Test, TMT, MCST, MADRS, Apathy Evaluation Scale (AES)
21	*Markser et al.* Deep brain stimulation and cognitive decline in Parkinson's disease: The predictive value of electroencephalography	2015	MMSE, MDRS, Dem-Tech
22	*Pham et al.* Self-Reported Executive Functioning in Everyday Life in Parkinson's Disease after Three Months of Subthalamic Deep Brain Stimulation	2015	MDRS, Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A), Symptom Checklist 90- Revised (SCL-90-R), AES
23	*Tang et al.* Evidence of improved immediate verbal memory and diminished category fluency following STN-DBS in Chinese-Cantonese patients with idiopathic Parkinson's disease	2015	Montreal Cognitive Assessment Hong Kong version (HK-MoCA), Chinese Auditory Verbal Learning Test (CAVLT), BVRT, Chinese modified version of BNT, Hooper Visual Organization Test (HVOT), Stroop Test Chinese victoria version, VFT (semantic), BDI-II, BAI
24	*Tremblay et al.* The effects of subthalamic deep brain stimulation on metaphor comprehension and language abilities in Parkinson's disease	2015	MoCA, Metaphor Comprehension Task, VFT (semantic), Alternation VFT, Lexical Decision Test, Word Association Test, BDI version IA

25	*Krishnan et al.* The decade after subthalamic stimulation in advanced Parkinson's disease: A balancing act.	2016	UPDRS-I, MMSE, Addenbrooke´s Cognitive Examination, BDI, Parkinson´s Disease Quality of Life (PDQL) Questionnaire
26	*Vonberg et al. Fabian.* Deep Brain Stimulation of the Subthalamic Nucleus Improves Lexical Switching in Parkinson's Disease Patients	2016	Parkinson Neuropsychometric Dementia Assessment (PANDA), German VFT
27	*Ventre-Dominey et al.* Distinct effects of dopamine vs STN stimulation therapies in associative learning and retention in Parkinson disease	2016	Conditional Associative Learning (CAL), Visual spatial Working Memory Task, Non-spatial Working Memory Task

Table 2. List and Quantity of Instruments used separated by Domains

Nº	Assessed Domains	Instruments	Nº of articles
1	Daily Life Activities	UPDRS-I Non-Motor Experiences	3
2	PD Quality of Life	Parkinson´s Disease Questionnaire (PDQ-39)	2
		Parkinson´s Disease Quality of Life (PDQL)	1
3	Global Functioning	Mini-Mental State Exam (MMSE)*	14
		Mattis Dementia Rating Scale (MDRS)	8
		Raven´s Progressive Matrices (RPM)	6
		Weschler Adult Intelligence Scale (WAIS-III)*	4
		Montreal Cognitive Assessment (MoCA)*	2
		Addenbrooke´s Cognitive Examination	1
		Japanese Adult Reading Test (JART)	1
		Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	1
		Dem-Tech	1
		Parkinson Neuropsychometric Dementia Assessment (PANDA)	1
4	Psychiatry Symptoms	Brief Psychiatric Rating Scale (BPRS)	1
		Visual Analogue Mood Scale	1
		Symptom Checklist 90- Revised (SCL-90-R)	1
		Verbal Fluency Tasks - Semantic*	19
		Verbal Fluency Tasks - Fonemic*	17

		Wisconsin Cards Sorting Test (WCST)*	9
		Stroop Test*	7
		Trail Making Test (TMT)*	6
		Digit Span Forward and Backward	5
		Frontal Assessment Battery (FAB)	1
5	Executive Functioning	Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A)	1
		Hayling Sentence Completion Test	1
		Brixton Spatial Anticipation Test	1
		Haruno e Kawato Task (2006)**	1
		Delis-Kaplan Executive Function System (D-KEFS)	1
		N-back and dual task	1
		Visual Spatial and Non-spatial Working Memory Task	1
		Rey´s Auditory Verbal Learning Test (RAVLT)*	6
		Corsi´s Block Tapping test (CBTT)	5
		Paired Associate Learning (Wechsler Memory Scale)	4
		Bi-Syllabic Words Repetition test (BWR)	2
6	Memory	Rey-Kim Memory Battery	2
		Recognition Memory Test	1
		Birt Memory and Information Processing Battery	1
		Long Memory Task and Verbal Span	1
		Conditional Associative Learning (CAL)**	1

		Boston Naming Test (BNT)*	3
		Graded Naming Test	1
7	Language	Metaphor Comprehension Task	1
		Lexical Decision Test	1
		Word Association Test	1
8	Attention	Attentive Matrices	1
9	Perception	Incomplete Letters and Object Decision tasks (Visual Object and Space Perception Battery)	1
10	Visuospatials Skills	Benton Visual Retention Test	3
		Hooper Visual Organization Test (HVOT)	1
		Beck Depression Inventory (BDI)	10
		Apathy Evaluation Scale (AES)*	4
		State-Trait Anxiety Inventory (STAI)	2
		Zung´s Anxiety Scale	2
		Beck Anxiety Inventory (BAI)	2
11	Mood	Zung´s Depression Scale	2
		Montgomery-Asberg Depression Rating Scale (MADRS)	2
		Hospital Anxiety and Depression Scale (HADS-D)*	1
		Snaith-Hamilton Pleasure Scale	1
		Bech-Rafaelsen Mania Scale	1
		Grooved Pegboard Test	1
12	Sensory-Motor Coordination	Visual-motor Coordination Task	1
		Finger Tapping Test	1

Table 3. Instruments most used pre and post DBS

Instruments
Parkinson´s Disease Questionnaire (PDQ-39) Parkinson´s Disease Quality of Life (PDQL)
Mini-Mental State Exam (MMSE)*
Mattis Dementia Rating Scale (MDRS) Raven´s Progressive Matrices (RPM)
Symptom Checklist 90- Revised (SCL-90-R)
Verbal Fluency Tasks - Semantic*
Verbal Fluency Tasks - Fonemic*
Wisconsin Cards Sorting Test (WCST)*
Stroop Test*
Trail Making Test (TMT)*
Digit Span Forward and Backward
Rey´s Auditory Verbal Learning test (RAVLT)*
Corsi´s Block Tapping test (CBTT)
Rey-Kim Memory Battery
Boston Naming Test (BNT)*
Attentive Matrices
Incomplete Letters and Object Decision tasks (Visual Object and Space Perception Battery)
Benton Visual Retention Test
Beck Depression Inventory (BDI)
Apathy Evaluation Scale (AES)*
State-Trait Anxiety Inventory (STAI)
Beck Anxiety Inventory (BAI)
Grooved Pegboard Test

4. DISCUSSION

As observed in Table 2, 61 (sixty-one) instruments were used to evaluate several aspects of patients, considering batteries, subtests, scales and tasks. They can be

ordered from the most evaluated and least contemplated: executive functions (14), global cognitive functioning (10) and mood (10), memory (9), language (5), psychiatric symptoms (3) and sensory-motor coordination (3), patients' quality of life (2) and visuoconstructive skills (2) and attention (1), perception (1) and activities of daily living (1). Early in the onset of symptoms, 24% of the patients present cognitive impairment, especially memory problems, and executive function disorders: selective attention, flexibility in reasoning and planning capacity, visuoconstructive skills and naming ability[9].

What justifies the most evaluated domains in the selected articles? PD patients with mild cognitive impairment (MCI), compared with PD patients without MCI show significantly impoverished performance in almost all cognitive domains: executive functions, attention, memory, and language[7]. One in three patients with PD presents cognitive impairment at the time or shortly after diagnosis, progressively worsening or even causing dementia in the advanced stages[6]. However, cognitive alterations are common even in non-PD patients[10]. The cognitive impairment increases the risk of dementia, ranging from 1.7 to 5.9 and its early detection and identification of dementia risk is a major challenge due to the heterogeneity of patients' profile[6]. The prevalence of dementia in PD is 24 to 31%[11], thus, evaluating the PD patient in a global and continuous way is the best path for monitoring the evolution of the effects of the disease. Comorbidity with dementia can be justified when we consider the ascending involvement of the brainstem to the cortical area. Microscopic modifications may be incorporated into its pathophysiology, including losses of neurons, gliosis and the surviving neurons may contain Lewy bodies. The loss of neurons markedly reaches the substantia nigra, though it is not restricted to it. The damage also affects the aminergic nuclei of the brainstem, Meynert's basal nucleus, hypothalamic nuclei and olfactory bulb[12]. For this reason, it is essential to investigate the effects of surgery such as STN-DBS on the different aspects of a subject with PD.

The MMSE was the most used instrument[13-25] for the global cognitive functioning assessment among the selected studies. It was followed by MDRS[17, 24, 26-31] and RPM[13, 16, 18, 32]. MMSE has some qualities such as fast administration, easy interpretation to be used during medical consultation; patient acceptability; cultural independence; and both language and schooling, which makes it easier to reproduce in different studies and similar performance among examiners. In

contrast, this instrument is influenced by the application and interpretation often subjective or non-standardized by the professionals. Screening tests, such as these, known and widely used, are highly dependent on a minimal educational level and has low sensitivity and specificity[33]. Thus, an evaluation protocol containing only this instrument to evaluate the global cognitive functioning would have little range regarding to the patient cognitive loss.

Several instruments assessed patients EF with PD and STN-DBS, but the most recurrent were verbal fluency tasks, both semantic and phonemic [13, 14, 16-18, 20, 21, 23, 26, 27, 29, 30, 32, 34, 35, 37, 38], followed by WCST[13-16, 18, 23, 30, 32, 34]. These tasks, in particular, presented different adaptations in each article. Evaluating EFs is a great challenge, as well as defining this concept. In general, it is understood as abilities that involve planning, organization, flexibility, monitoring and inhibitory control[39], presenting an adaptive value for the subject, since their performance in activities related to personal, professional and other domains also become impaired[40]. Executive dysfunction is not always associated with memory, language, visuospatial skills impairment, among others, but rather a functional decline that can often be assessed from the self-report or from a caregiver and / or family member. In patients with PD, it is a predictor of impairment, leading to ADL deficits[8].

A few studies[14, 16-18, 21, 23, 27, 29, 32, 34, 35, 36, 41] used 9 different types of tests to evaluate the memory and the most used ones were RAVLT (memory and verbal learning) and CBTT (memory and visual learning). The neocortex and the striatum are structures involved in implicit memory processing and dopamine is the neurotransmitter involved in the formation of these memories[2, 42]. Therefore, with the dopaminergic deficit and the degeneration of the nuclei of the base in the PD pathology, this processing and the pre-activation of the priming and learning procedures are impaired. In the early stages of PD, there are deficits in the implicit learning of new tasks. Implicit learning is the process through which we become sensitive to certain regularities in the environment, in the absence of the intention to learn about these same regularities and in such a way that the resulting knowledge is difficult to express. In other words, implicit learning refers to the incidental or casual, and sometimes seemingly small, acquisition of a given event. It can generate significant future consequences[42].

Few articles were used to assess Language[14, 35, 37], Attention [23], Perception [35] and Visuospatial Skills[27, 36]. A study[43] showed patients with PD without dementia which exhibited impairment in verbal comprehension, grammatically complex sentences identification, repetitive speech, decreased abstraction capacity, slow processing speed and attention deficit[44]. There is a greater impairment in naming ability and verbal fluency[8]. Language difficulties may be related to EF that play an important role in language. We also found difficulties in understanding grammatically complex sentences, disorders involving communication and repetitive speech[44]. Attention is impaired in PD, causing reduction of latency in the simple and choice reaction time. After dopaminergic replacement, there is an improvement in the identification of stimuli [40]. Regarding Visuospatial and Perception skills, they require the involvement of certain subcortical structures, in addition to the occipital, parietal and frontal lobes[45]. Deficits in this function in PD correlate with postural instability and gait difficulty[44]. Sensory-motor coordination also had only 2 instruments for its evaluation[14, 20].

Only 3 articles[20, 31, 38] used instruments to assess psychiatric symptoms in PD (PANDA, BPRS and Visual Analogue Mood Scale). Some authors[46] investigated the existence of some information on various psychiatric conditions in patients with PD and found that more than 50% of non-motor symptoms are not identified in clinical practice. They observed the prevalence in depression (2% - 31%), psychosis (15% - 75%), anxiety (19% - 67%), sleep disorder (15% - 87%) and cognitive deficits (MCI 18% - 55% and dementia reaching 31%), among others. Psychiatric symptoms were associated with the stage of PD and cognitive impairment of the patient, but not with age, duration of illness, levodopa dose or 'ON' or 'OFF' stage. Although common, psychiatric changes in PD are not criteria for clinical diagnosis[47]. They may become more disabling than the motor and may be a consequence of complications of the pharmacological treatment for the motor symptoms of the disease or as an integral part of the PD clinical manifestations[48].

Only 2 scales were used for PD Quality of Life (QoL): PDQ-39[49] and PDQL[50]. Regarding mood, several scales were used, having an inventory for depression appeared more often[14, 20, 21, 23, 25, 27, 32, 36, 37]. Together with the QoL scales, these instruments enable a more in-depth look at the individual and the impacts of the disease on his life.

Some of the limitations of the study were the instruments used in different moments of the research, being in the inclusion and/or exclusion criteria and in the pre and postoperative evaluation of the patients. We can observe that, besides the great diversity of instruments, other aspects such as version, validation and cut points were heterogeneous as well.

As shown in Table 3, these are the instruments used before and after DBS implantation to assess the cognitive aspects of the patients. In a generic way, we could consider them as a possible battery to evaluate the effects of surgery. The literature has shown that most of the authors consider these instruments as sufficient to identify the patient's diagnostic profile. These aspects are extremely relevant to analyze the results of a study. Differences in each of them may engender results that differ from those expected. These changes range from severely compromised to slightly compromised. Another example is the use of tailored tasks, Verbal Fluency Tasks[13, 14, 16-18, 20, 21, 23, 26, 27, 29, 30, 32, 34-36, 38] n-back task and dual task[51] rather than standardized tests, such as Weschler Adult Intelligence Scale[27, 35] and Hooper Visual Organization Test[36].

The results of this review point to the absence of a specific assessment protocol for PD with STN-DBS, they display an extensive variability of instruments used in different studies. However, after analyzing each of the methodologies, we may get to a possible battery to investigate the effects of surgery from the frequency of certain instruments in the studies. The feasibility of using this battery and its findings is a suggestion for future studies that perhaps establish a standard of assessment.

Authors contributions. Eduarda Naidel Barboza e Barbosa: study concept and design, literature search, drafting and revising the manuscript; Helenice Charchat Fichman: contribution during the writing process with suggestions and corrections.

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ARTICLE 2

Barbosa E.N.B., Charchat-Fichman H. How Is Cognition on Subthalamic Nucleus Deep Brain Stimulation Parkinson´s Disease Patients? A 2007 to 2017 Systematic Review. **Dementia and Neuropsychologia**, 2019, v. 13, n. 4, p. 367-377.

ABSTRACT

Introduction: The impairments in cognitive functions such as memory, executive function, visuospatial skills and language in Parkinson´s Disease (PD) are increasingly drawing attention in current literature. Studies investigaying the relationship between deep brain stimulation of the subthalamic nucleus (ECP-NST) and cognitive functioning are contradictory. **Objective:** This systematic review aims to analyze the impact on the cognitive functioning of patients with PD and NPS-STD. **Method:** The articles were collected in the Medline / PubMed databases published in the 2007-2017 period, using PRISMA criteria. **Results:** After analyzing 27 articles, many opposite results were observed. **Conclusion:** It was not possible to agree on a cognitive functioning standard, which makes it difficult to establish a neuropsychological profile for patients with this disease who underwent surgery, so further studies are needed.

Keywords: Parkinson Disease, Deep Brain Stimulation, Cognitive Functions, Cognition

How Is Cognition on Subthalamic Nucleus Deep Brain Stimulation Parkinson´s Disease Patients? A 2007 to 2017 Systematic Review.

INTRODUCTION

The diagnosis of PD is performed through clinical criteria by trained professionals such as neurologists. These criteria are based on the identification of clinical manifestations, pure motor symptoms. Patients with PD present, in addition to motor impairments, non-motor impairments, as a variety of neuropsychiatric symptoms[1,2] changes in sleep, behavior and cognition[3,4] , which may lead to dementia[5,6].

The impairments in cognitive functions such as memory, executive function, visuospatial skills and language in PD are increasingly drawing attention in current literature[6]. One in three patients with PD presents cognitive impairment at the time or soon after diagnosis, progressively worsening or even causing dementia in the later stages[7].

Since 1940, surgical treatment of PD has been performed and, since 1998, ablation has given rise to deep brain stimulation (ECP), targeting the subthalamic nucleus (STN) or globuspalildus (GPi)[5,8]. The most chosen target by the centers that perform the surgery is in the STN due to the possibility of decreasing the doses of the drugs and, consequently, reducing the adverse effects.

The literature points to evident motor and QoL improvement after DBS in patients with PD, however, studies dedicated to investigating the relationship between STN-DBS and cognitive functioning are controversial, and further studies are needed to investigate this relationship.

In this context, the investigation of the cognitive effects of STN-DBS in PD becomes fundamental. The objective of this study is to analyze the effects of subthalamic nucleus (STN) DBS on cognition of PD patients through a systematic review. The Preferred Reporting Items for Systematic Review and Meta-Analyzes (PRISMA) Checklist was employed.

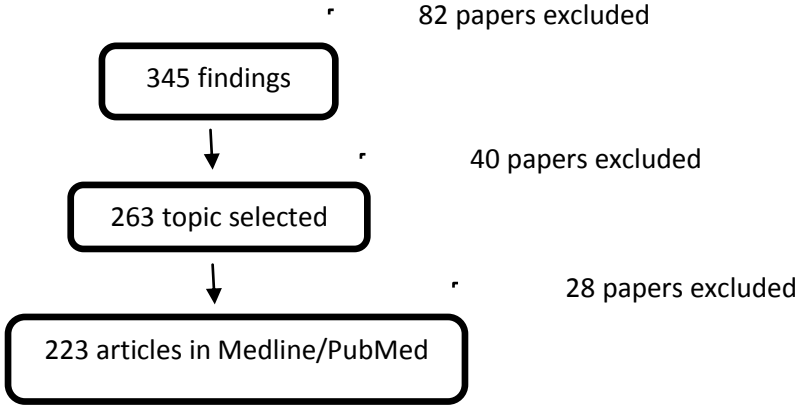
METHODOLOGY

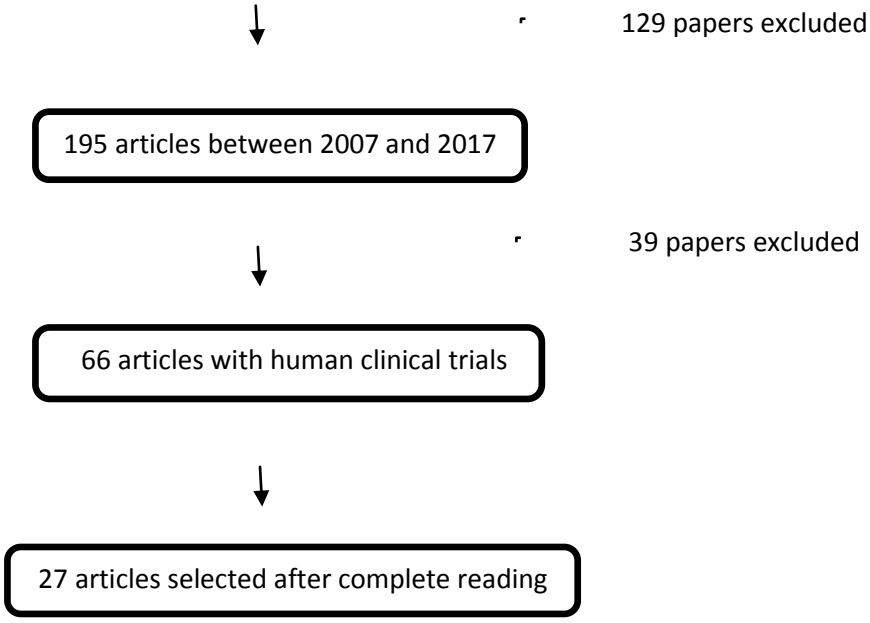
The systematic review is a type of scientific research that aims to gather, critically evaluate and conduct a synthesis of multiple primary studies[10].

Bibliographic Survey We projected a systematic review of the literature according to the Preferred Reporting Items for Systematic Review and Meta-Analyzes (PRISMA) criteria. The following terms were used: "Deep Brain Stimulation", "DBS", "Cognitive Functions" and "Parkinson Disease" with the Boolean operator "and". We selected scientific papers published in English between January 2007 and January 2017, with comparative clinical trials in humans, in Medline/PubMed databases. Articles published before 2007, systematic reviews, case studies, books chapters and studies using animals were excluded.

Studies selection Initially, this method identified 345 responses (Figure 1). To refine the research, the following topics were selected: "Parkinson's Disease", "Subthalamic Nuclei", "Deep Brain Stimulation", "DBS", "Cognition" (263), published in the Medline/PubMed database (223) between 2007 and 2017 (195). From this, a title and summary analysis was performed manually to consider only the work with human clinical trials (66). Literature reviews and case studies were excluded, as well as articles containing problems in the methodology, such as not inclusion of (a) inclusion and exclusion criteria, (b) complete assessment protocol and (c) lack of pre or post-surgery assessment fulfillment (27). The researchers selected the articles independently: they considered suitable studies that (a) evaluated PD patients cognition with STN-DBS; (b) presented the instruments and domains evaluated; and (c) presented pre and post-surgical results. of articles was carried out independently by the researchers.

Figure 1. Articles research fluxogram.





RESULTS

Following are the final list of articles that were included by the research criteria in ascending order of year, with objectives and results (Table 1) and a list of studies grouped according to the effects of DBS on specific cognitive domains with neuropsychological tasks (carried out in each of the studies taken into account) (Table 2).

There were 27 studies with a total of 832 patients with STN-DBS and 458 patients with DP and / or healthy subjects in the control group who did not undergo surgery. The age ranged from 51 to 67 years, the disease duration ranged between 9.7 and 15.75 years, schooling (when mentioned) ranged between 1.9 and 14.5 years and the pre-surgical evaluation occurred 2 weeks before surgery and postoperative up to 132 months (11 years).

Table 1. List of articles included in the systematic review criteria.

	Name	Year	Objective	Result
1	*Cilia et al.* Brain networks underlining verbal fluency decline during STN-DBS in Parkinson's disease: An ECD-SPECT study.	2007	To evaluate changes of evaluation after a DBS-STN and its possible correlation with the cognitive result related to the frontal lobe.	Patients with STN-DBS improved motor symptoms and reduced medications, but they selectively decreased the fluency of the categories.
2	*Klempírová et al.* Deep brain stimulation of the subthalamic nucleus and cognitive functions in Parkinson's disease.	2007	To evaluate how STN-DBS affects cognitive functions.	Patients treated by STN-DBS tend to worsen executive functions and logical memory.
3	*Castelli et al.* Apathy and verbal fluency in STN-stimulated PD patients.	2007	To evaluate apathy and its relationship with verbal fluency tasks in patients with PD who underwent STN-DBS.	The results suggest that STN-DBS does not necessarily induce apathy, even if individual patients show moderate postoperative worsening of apathetic symptoms.
4	*Heo et al.* The effects of bilateral Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) on cognition in Parkinson disease.	2008	Research the STN-DBS effects on cognition and mood.	Bilateral STN-DBS did not lead to a significant overall deterioration in cognitive function. However, it has small, long-term detrimental impacts on the memory and function of the frontal lobe.
5	*Witt et al.* Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomized, multicenter study.	2008	To evaluate the DBS neuropsychiatric consequences in patients with PD.	STN-DBS does not reduce cognition or general affectivity, although there is a selective decrease in frontal cognitive functions and an improvement in anxiety in patients after treatment, but not influencing improvements in quality of life.
6	*Alberts et al.* Bilateral subthalamic stimulation impairs cognitive–motor performance in Parkinson's disease patients.	2008	To determine the effects of unilateral and bilateral STN-DBS on upper extremity motor function and cognitive performance in single and double task conditions in patients with advanced PD.	Significant decreases in cognitive and motor function in modest dual-task conditions with bilateral STN-DBS, but not unilateral.

7	*Lueken et al.* Impaired performance on the Wisconsin Card Sorting Test under left- when compared to right-sided deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease.	2008	To evaluate whether changes in performance of executive tasks after chronic ECP may be predominantly associated with stimulation of only one hemisphere.	STN-DBS is not only involved in motor control, but also participates in functions of the cognitive domain. All patients had a significant improvement in postoperative motor symptoms. Selected aspects of executive task performance were compromised under the left - when compared to right side pacing.
8	*Zangaglia et al.* Deep brain stimulation and cognitive functions in Parkinson's disease: A three-year controlled study	2009	To evaluate the DBS cognitive and behavioral effects.	Verbal fluency worsening after DBS, but relatively safe surgery from the cognitive point of view, since the short-term worsening of the front-executive functions was transient.
9	*York et al.* Relationship between neuropsychological outcome and DBS surgical trajectory and electrode location	2009	Evaluate whether surgery and the best medical therapy have improved a self-reported quality of life better than advanced medicine.	After 1 year, surgery and improved medical therapy improved patient self-reported quality of life, rather than the best medical therapy in patients with advanced PD - clinically significant differences.
10	*Williams et al.* Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease.	2009	To observe if the differences in the position of the electrode and in the surgical trajectory of the ECP can lead to a differential neuropsychological outcome.	Cognitive and emotional changes after 6 months of bilateral STN-DBS may be related to the surgical trajectory and to the positioning of the electrodes.
11	*Daniels et al.* Risk factors for executive dysfunction after subthalamic nucleus stimulation in Parkinson's disease	2010	To evaluate the baseline parameters that contribute to the deterioration of cognitive functioning after DBS.	Surgical procedure, exact electrode placement or postoperative administration may be more relevant for a decline in executive functioning after STN-DBS, in addition to factors such as age, high levodopa dosages and high scores in the UPDRS III axial subset in OFF stage.
12	*Castelli et al.* Neuropsychological changes 1-year after subthalamic DBS in PD patients: A prospective controlled study	2010	To investigate the STN-DBS neuropsychological effect in patients with advanced PD.	Phonemic verbal fluency decreased one year after STN-DBS, while the other cognitive domains did not change significantly. Only 4 subjects had significant cognitive decline 1 year after surgery.

13	*Fasano et al.* Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants	2010	To assess long-term PD patients undergoing STN-DBS 8 years previously: long-term motor outcome of symptoms that improve in the short and medium term with STN-DBS; identification of predictors of long-term motor outcome; and long-term cognitive and behavioral outcome.	STN-DBS is a safe procedure for cognitive and behavioral morbidity in relation to long-term follow-up. However, the overall benefit decreases later in the course of the disease due to the progression of PD and to the appearance of stimulant-resistant medications and symptoms.
14	*Van Wouwe et al.* Deep Brain Stimulation of the Subthalamic Nucleus Improves Reward-Based Decision-Learning in Parkinson's Disease	2011	To investigate the effect of STN-DBS on reward-based learning in patients diagnosed with PD.	The DBS cognitive effects have benefited a subset of relatively younger patients with relatively less disease duration in daily association learning situations.
15	*Israeli-Korn et al.* Subthalamic Nucleus Deep Brain Stimulation Does Not Improve Visuo-Motor Impairment in Parkinsons Disease	2013	To evaluate how STN-DBS affects visuomotor coordination in patients with PD.	Clinically measured "low-level" motor function responds to STN-DBS, but cognitive and "high-level" functions related to VMC may not respond to STN-DBS.
16	*Kim et al.* Initial cognitive dip after subthalamic deep brain stimulation in Parkinson disease	2013	To examine whether the rate of change in overall cognitive functioning during the initial 6 months after STN-DBS was different from the mean change of 6 months that occurred between 6 and 36 months after surgery.	The decline in overall cognitive function was faster in the first 6 months after surgery, compared to 6 months between 6 and 36 months post surgery.
17	*Yágüez et al.* Cognitive predictors of cognitive change following bilateral subthalamic nucleus deep brain stimulation in Parkinson's disease	2014	Specifically establish a detailed neuropsychological profile before and after STN-DBS and identify any pre-surgical cognitive profile that can predict cognitive outcomes after stimulation.	Non-dementia patients with mild impairment, both in general intellectual functions and in list learning, may be at a greater risk of decline in other aspects of verbal memory after STN-DBS.
18	*Asahi et al.* Impact of bilateral subthalamic stimulation on motor/cognitive functions in Parkinson's disease	2014	Systemically assess the impact of bilateral STN-DBS on motor and cognitive functions in patients with PD.	Bilateral NST-DBS can significantly improve cognitive function in a given subgroup of patients whose therapeutic effects on motor function are prominent.

19	*Rizzone et al.* Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: From the advanced phase towards the late stage of the disease?	2014	To report the results of a long-term follow-up of patients implanted with DBS bilaterally in two centers.	Despite the NST-DBS long-term safety and efficacy in PD, the patients functionality worsened over time, mainly for the onset and progression of levodopa and non-motor-resistant symptoms.
20	*Houvenaghel et al.* Reduced Verbal Fluency following Subthalamic Deep Brain Stimulation: A Frontal-Related Cognitive Deficit?	2015	Explore the mechanisms underlying DBS.	Cognitive deceleration and apathy seem to have a more decisive influence on the impairment of phonemic verbal fluency after DBS.
21	*Markser et al.* Deep brain stimulation and cognitive decline in Parkinson's disease: The predictive value of electroencephalography	2015	To examine whether clinical recordings of EEG can be used to predict cognitive impairment in PD patients undergoing STN-DBS.	The GTE preoperative score can be used to identify patients with PD who are at high risk of developing cognitive impairment after STN-DBS surgery even though their preoperative cognitive status is normal.
22	*Pham et al.* Self-Reported Executive Functioning in Everyday Life in Parkinson's Disease after Three Months of Subthalamic Deep Brain Stimulation	2015	To compare self-reported daily executive functioning in patients with PD before and after three months of NTS-DBS.	Patients with PD showed significant improvement in executive functioning of daily life 3 months after surgery, anxiety indexes decreased significantly and psychiatric symptoms, including apathy, remained unchanged. Only the preoperative depressive mood presented predictive value for the improvement of the executive function and seems to prevent potentially favorable results of the NST-DBS in some aspects of the executive function.
23	*Tang et al.* Evidence of improved immediate verbal memory and diminished category fluency following STN-DBS in Chinese-Cantonese patients with idiopathic Parkinson's disease	2015	To investigate the STN-DBS neuropsychological effects in Chinese-Cantonese patients with PD.	A diminished performance of verbal fluency was observed, on the other hand, an improvement of the immediate verbal memory, besides anxiety level
24	*Tremblay et al.* The effects of subthalamic deep brain stimulation on metaphor comprehension and language abilities in Parkinson's disease	2015	To determine the STN-DBS effects on the comprehension of metaphor and linguistic abilities such as lexical and semantic abilities.	STN-DBS had a significant beneficial effect on motor symptoms in PD, but such stimulation had no effect on the understanding of the metaphor or any other cognitive ability assessed in this study.

25	*Krishnan et al.* The decade after subthalamic stimulation in advanced Parkinson's disease: A balancing act.	2016	To we examined the long-term quality of life, motor and cognitive outcomes of bilateral subthalamic nucleus STN DBS and the pre-DBS factors that predict sustained motor benefits at or beyond 7 years from surgery.	Improvements in severity of motor fluctuations, stiffness, and tremor are the long-lasting STN-DBS benefits, which can last for a decade. However, these are compensated by the higher levodopa requirement, worsening of cognitive and axial functions, such as bradykinesia and dyskinesias.
26	*Vonberg et al. Fabian.* Deep Brain Stimulation of the Subthalamic Nucleus Improves Lexical Switching in Parkinson's Disease Patients.	2016	Outline the nature of verbal fluency dysfunction.	The STN-DBS group tasks performance was lower than that of healthy controls. In addition to affecting motor symptoms, surgery seems to influence the dynamics of cognitive procedures.
27	*Ventre-Dominey et al.* Distinct effects of dopamine vs STN stimulation therapies in associative learning and retention in Parkinson disease.	2016	To investigate and to compare the results of the treatment with dopamine versus DBS in the capacity of the patient with PD to acquire and to maintain over the successive days their performance in the visual work memory.	While STN-DBS patients demonstrate more accurate and faster responses in the ON stage than in the OFF stage, regardless of the day of the test, patients with dopamine replacement therapy had a more accurate and faster ON response compared to OFF during the first day of learning and then maintained or even improved their performance on the second day after consolidation in both the OFF and ON stages.

Table 2. Domains evaluated and effects found in each article.

Domain	STN DBS cognitive effects	Articles by
Global Cognitive Functioning / Reasoning	↑ (MMSE)	Lueken et al, 2008; Wouwe et al, 2011
	↑ (DemTect)	Markser et al, 2015
	↑ Addenbrooke	Krishnan et al, 2016
	= (MDRS)	Klempírova et al, 2007; Witt et al, 2008;
	= (MMSE)	Daniels et al, 2010
	= (Repeatable Battery For The Assessment of Neuropsychological Status)	Cilia et al, 2007; Heo et al, 2008; Zanglagia et al, 2009; Israeli-Korn et al,
	= (Wechsler Adult Inteligence Scale)	2013; Asahi et al, 2014
	= (Japanese Adult Reading Test)	Asahi et al, 2014
	= abstract reasoning (Raven Colour Matrices)	Asahi et al, 2014
	= (MoCA*)	Asahi et al, 2014
	↓ MMSE	Castelli et al, 2007; Castelli et al, 2010; Rizzone et al, 2014
	↓ MDRS	Tang et al, 2015; Tremblay et al, 2015
	↓ Raven	York et al, 2009; Kim et al, 2013; Markser et al, 2015; Krishnan et al, 2016
		Williams et al, 2010; York et al, 2009; Markser et al, 2015
		Fasano et al, 2010

Memory	↑ episodic verbal memory (RAVLT* immediate recall)	Tang et al, 2015
	= verbal memory (RKMB)	Heo et al, 2008
	= verbal memory (Benton)	Tang et al, 2015
	= verbal memory (RAVLT*)	Witt et al, 2008; Daniels et al, 2010
	= verbal memory (Bi-sillabic Words Repetition test)	Castelli et al, 2007; Castelli et al, 2010
	= short-term spatial memory (Corsi´s Block Tapping Test)	Castelli et al, 2007; Castelli et al, 2010
	= verbal learning (WMS Paired Associate Learning)	Castelli et al, 2007; Castelli et al, 2010
	= memory (Verbal and Digits Span)	Zanglagia et al, 2009
	= memory (MDRS)	Witt et al, 2008
	= memory recognition (verbal and visual Recognition Test)	Yagüez et al, 2014
	↓ immediate, late and recognition memory (WMS logic memory)	Klempírova et al, 2007
	↓ late memory (RBANS)	Asahi et al, 2014
	↓ episodic verbal memory (RAVLT* immediate and late recall)	Fasano et al, 2010; Rizzone et al, 2014
	↓ verbal memory recall (BMPI immediate and late memory and learning)	Yagüez et al, 2014
	↓ verbal recognition memory and late memory (RKMB)	Heo et al, 2008

Executive Functions	↑ (WCST right categories, right answers, errors nº and non perseveratives errors)	Lueken et al, 2008
	↑ (Stroop effect)	Houvenaghel et al, 2015
	↑ executive functioning (BRIEF-A)	Pham et al, 2015
	↑ visuoespacial working memory (working memory tasks)	Ventre-Dominey et al, 2016
	↑ stimulus-action-reward association (Haruno and Kawato task)	Wouwe et al, 2011
	= regulation behavior (BRIEF-A)	Pham et al, 2015
	= semantic verbal fluency (tasks)	Castelli et al, 2007; Castelli et al, 2010; Tremblay et al, 2015
	= fonemic verbal fluency (tasks)	
	= cognitive flexibility (alternate verbal fluency tasks)	Cilia et al, 2007
	= cognitive flexibility (Trail Test B)	Tremblay et al, 2015
	= abstracts concepts development and cognitive flexibility (WCST*)	Castelli et al, 2007
	= abstracts concepts development (metaphor comprehension)	Cilia et al, 2007; Castelli et al, 2007; Castelli et al, 2010; Houvenaghel et al, 2015
	= response initiation and response inhibition (Hayling Sentence Completion Test)	
	= working memory (Span Dígitos)	Tremblay et al, 2015
	= (Stroop effect)	Yagüez et al, 2014
	= executive functions (Frontal Assessment Battery)	Daniels et al, 2010; Tang et al, 2015
	= processing of outcome errors (Haruno e Kawato task)	Tang et al, 2015
	= working memory (n-back DBS STN unilateral task)	Israeli-Korn et al, 2013
	↓ logic executive functions (WCST* e Raven)	Wouwe et al, 2011
	↓ semantic verbal fluency (category task)	Alberts et al, 2008 Zanglagia et al, 2009
	↓ fonemic verbal fluency (initial recall tasks)	Cilia et al, 2007; Witt et al, 2008; York et al, 2009; Daniels et al, 2010; Houvenaghel et al, 2015; Tang et al, 2015; Vonberg et al, 2016
	↓ fonemic and semantic verbal fluency (Delis-Kaplan executive function system)	Castelli et al, 2007; Klempírova et al, 2007; Witt et al, 2008; Zanglagia et al, 2009; York et al, 2009; Daniels et al, 2010; Castelli et al, 2010; Fasano et al, 2010; Kim et al, 2013; Yagüez et al, 2014; Houvenaghel et al, 2015; Vonberg
	↓ verbal fluency (MDRS Initiative/Perseveration)	
	↓ working memory (Span Digits)	
	↓ cognitive flexibility (WCST* perseverative responses and errors)	

	↓ (Stroop effect)	et al, 2016
	↓ interference (Trail Test B form)	Williams et al, 2010
		Witt et al, 2008
	↓ planning skills (London Tower)	Witt et al, 2008
	↓ working memory (n-back DBS STN bilateral tasks)	Heo et al, 2008; Lueken et al, 2008; Fasano et al, 2010; Rizzone et al, 2014
		Klempírova et al, 2007; Heo et al, 2008; Kim et al, 2013
		Klempírova et al, 2007; Kim et al, 2013; Rizzone et al, 2014; Houvenaghel et al, 2015
		Klempírova et al, 2007
		Alberts et al, 2008

Attention	= (Trail Test A and B forms) = (Stroop) = (MDRS attention) = (WCST*) = (Span Digits) ↓ (WCST*) ↓ (RBANS)	Heo et al, 2008; Castelli et al, 2010; Houvenaghel et al, 2015 Witt et al, 2008; Daniels et al, 2010; Tang et al, 2015 Witt et al, 2008; Castelli et al, 2010 Tang et al, 2015 Rizzone et al, 2014 Asahi et al, 2014
Perception	= (Visual Object and Space Perception Battery Object Decision task) = (Visual Object and Space Perception Incomplete Letters task)	Yagüez et al, 2014 Yagüez et al, 2014
Language	↑ lexical changing and word production = (Boston Naming Test*) = (Graded Naming Test) = (lexical decision task and words association task) ↓ word production ↓ Vocabulary (WASI) ↓ fluency tasks (Fonemic and Semantic Verbal Fluency Test)	Vonberg et al, 2016 Heo et al, 2008; Tang et al, 2015 Yagüez et al, 2014 Tremblay et al, 2015 Cilia et al, 2007 Williams et al, 2010 Rizzone et al, 2014
Visuoconstructive and visuospacial skills	= (MDRS) = visuoespacial reasoning (Raven) = (Benton) = visuospacial organization capacity (Hooper Test) ↓ (Corsi´s Block Tappint Test forward and backward) ↓ visuoconstructive skills (RBANS)	Witt et al, 2008 Cilia et al, 2007 Witt et al, 2008 Tang et al, 2015 Rizzone et al, 2014 Asahi et al, 2014

Motor and sensory coordination	↑ fine motor dexterity and speed (Purdue Pegboard Test)	Wouwe et al, 2011
	= motor and sensory coordination (Purdue Pegboard Test)	Heo et al, 2008
	= (Trail Test A)	Klempírova et al, 2007
	= (Stroop Test)	Klempírova et al, 2007

* Indicates different types of versions; ↑ indicates "improvement"; = indicates "no changes"; ↓ indicates "impairment"; Mini-Mental Scale Exam (MMSE); Mattis Dementia Rating Scale (MDRS); Raven Colour Matrices (Raven); Montreal Cognitive Assessment (MoCA); Rey Auditory Verbal Learning Test (RAVLT); Weschler Memory Scale (WMS); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); Birt Memory and Information Processing Battery (BMPI); Rey–Kim Memory Battery (RKMB); Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A); subtalamic nucleus Deep Brain Stimulation (STN-DBS); Weschler Abbreviated Scale of Intelligence (WASI).

Global cognitive functioning Most studies[9-21] evaluated global cognitive functioning with 3 different instruments and did not observe a significant change in subjects performance. Only 3 articles[22-24] presented impairment in the overall cognitive functioning on their sample.

Memory Memory[10, 14], as well as specific aspects such as verbal memory[10, 11, 13, 20, 17, 18], verbal learning[17,18], recognition[27] and spatial memory[17,18] didn´t show significant difference before and after surgery. Although there was a decline in specific aspects in 6 articles[9, 13, 16, 19, 23, 27].

Executive function Several EFs aspects were evaluated: visuoespacial working memory, stimulus-action-reward association, behavior regulation, semantic and phonemic verbal fluency, cognitive flexibility, abstracts concepts development, initiation and inhibition responses and working memory. Thirteen articles[11, 12, 15, 17, 18, 20, 21, 25-30] presented stability or improvement in their result. However, the most part of articles[9-14, 17-19, 22-25, 27, 28, 31-35] presented opposite results to those observed above in verbal semantic and phonemic verbal fluency, working memory, planning and cognitive flexibility.

Perception and Attention In these two cognitive functions, only two articles[16, 19] presented cognitive decline after STN DBS in attention, in 7 other articles[10, 11, 13, 18, 20, 27, 28] there were no significant changes.

Language Five articles[13, 20, 21, 27, 33] showed a better or stable performance in language, in production of words[12], tasks of semantic and phonemic verbal fluency[19] and vocabulary subtest from Weschler Abbreviated Scale[24] worse postoperative performance.

Visuoconstructive and visuospacial skills Two articles[16,19] presented decline in Visuoconstructive and visuospacial skills, while 3 articles[10, 12, 20] didn´t show any difference pre and postoperative.

Motor and sensory coordination There was no decline[9, 13, 26.]

DISCUSSION

This systematic review wanted to investigate the cognitive functions most affected by STN-DBS according to studies published in the last 10 years.

After analyzing the results of all 27 articles, it was observed that there was no consensus among studies on the effect of this surgery on patients. In most articles that evaluated global cognitive functioning, it was noticed that it improved or did not worsen, which is a good finding, since it does not have a direct purpose in non-motor symptoms. However, it can exert an improvement in cognition indirectly: once the subject has reduced or eliminated motor symptoms, his quality of life (QoL) improves, allowing him to return to previously abandoned tasks and habits. This behavior change can bring both cognitive and mood benefits. To confirm this hypothesis, it would be interesting to carry out a study comparing mood (anxiety, depression) before and after stimulation.

In general, we can relate this variance of results due to several factors that will be discussed below. The aggravation of cognitive disorders can be strongly predicted by neuropsychological tests in the early stage of the disease, with or without timely medical treatment. On average, 25-50% of PD patients develop MCI or dementia or progress from MCI to dementia within 5 years of diagnosis[36]. Thus, the selection of instruments is of paramount importance and needs to be accompanied by certain precautions. There is no specific protocol established with the most appropriate instruments for this evaluation, but knowing which functions are influenced by PD, choosing the tests becomes easier. By establishing a protocol to be used by different studies and research centers, it would be easier to access, understand and compare results, leading to further investigation of the impaired aspects[37]. Any change indicated by the tests becomes subtle, as cognitive impairment detected in specialized tests is not commonly reported by patients, caregivers or health professionals. As stated above, QoL assessments in these patients show improvement, even when cognitive impairment is detected. In memory impairment, for example, there are several associated factors, such as the subject's age, duration of illness, and even executive functioning. In the case of the articles, the recognition memory[9,13] and recall[18,19,27,28] were impaired and this is observed in the literature, indicating a possible evolution to dementia in PD[36]. EFs are an umbrella concept that cover several aspects and, consequently, appear as the most evaluated functions and with the most discrepant results. Commonly,

it appears to be impaired functions earlier in the disease and are directly associated with daily activities, which interferes with patients' QoL[38]. Verbal fluency has worsened in many articles[9-12,14-16,22-24,27,28,31,35] In fact, the worsening in the fluency task category is the most frequent cognitive sequela reported after DBS-STN. This is in accordance with recent evidence suggesting that STN is a potent regulator of basal ganglia and talamocortical limbic and associative circuits. Frontal lobe-related cognitive changes after DBS may be determined by the modulation of these distinct neural networks[39]. Impairment of visuospatial skills, in which motor involvement is the main criteria, even in the early stages of the disease, is already expected in PD and this contrasts with the fact that only 5 articles evaluated this function[10,12,16,19,20].

One of the inclusion criteria was surgery to STN target and this was one of the limitations found in the studies. STNs are considered to produce more cognitive side effects in patients than when electrodes are implanted in the GPi[39]. Patients' ages ranged from 51 to 67 years at the time of surgery and the literature indicates a higher risk of cognitive decline associated with older age. The medication or stimulation parameters in the studies participants were not controlled, and there may be influence of a reduction in postoperative medication or the difference in DBS parameters. Added to this, we have the variation regarding follow-ups, making it difficult to understand and establish "specific milestones", in which we could predict an improvement or worsening of effects over the months / years. Thus, while certain articles had follow-up effects of 36[22,24], 84[22,26] or up to 132[19] months, others had data of 12[24.26], 6[13,15,20,24] and up to 3[17,22,31] months. This discrepancy makes a fair comparison and reliable analysis of the data unfeasible. Using the same battery of tests at such varying time intervals may give the impression of an improvement simply by the learning effect of a short-term reassessment and a marked worsening as the disease progresses naturally over a long-term reassessment[37].

There was an absence of records of the daily cognitive decline subjective impact of the subjects associated with the motor symptoms[28] and preoperative follow-up on cognitive function[33]. There was no further evaluation of impairments of daily life activities associated with the disease, which interfere with the subjective perspective of patients' abilities. These aspects are directly influenced when the

motor improvement occurs. Thus, from the recovery of skills, new perspectives are idealized, which can have a repercussion on non-motor symptoms, such as cognitive ones. The angle of the surgical trajectory and the proximity of the STN-DBS electrodes greatly influence the results that will be seen after the surgery: these aspects may be related to the changes in the cognitive and emotional functioning of the patients[12,33]. Therefore, the results are expected to vary from each other - as it has been seen, mainly due to variations in the characteristics of patients selected for surgery between different centers (age[21,26], preoperative state[10,24] and comorbidity with other conditions such as psychiatric disorders[11,12]) and, therefore, the conclusions are difficult to compare and to be analyzed.

Thus, it was not possible to establish a neuropsychological profile of the patient with PD and STN-DBS. This is quite worrying since patients with MCI in PD are more likely to progress to dementia as the disease progresses and it is necessary to understand which cognitive functions become impaired in this disease after DBS implantation to avoid miscalculating normal with worsening evolution. Much of this also occurs due to the lack of a specific PD assessment protocol[37].

From the results of this review it became clear the need to establish a neuropsychological profile of PD patients to understand and investigate the effects on cognitive non-motor symptoms after the implantation of STN-DBS. In the next studies, it is intended to develop a neuropsychological battery and evaluate patients with PD and STN-DBS to discriminate the affected or not aspects of this subjects and to understand which factors contribute to the result.

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ARTICLE 3

Eduarda Naidel Barboza e Barbosa, Larissa Marques Francisco, Mariana Spitz and Helenice Charchat-Fichman. CompCog has high accuracy to identify cognitive symptoms in Parkinson´s Disease patients. (in preparation).

ABSTRACT

Introduction: Currently, we can observe the help of technology in the diagnosis and treatment of several diseases. In clinical neuropsychology, we have computerized neuropsychological batteries aimed at both neuropsychological assessment and rehabilitation. CompCog is one of those instruments that uses the iPad as an interface. **Objective:** The aim of this study is to investigate the accuracy of the CompCog to screen Parkinson Disease among patients assisted in a neurology outpatient clinic at a public hospital in Rio de Janeiro city and develop cutoff points for this disease. **Method:** There was 32 patients with PD from a public hospital in Rio de Janeiro city and 32 healthy subjects from a social program that is offered by the government of Rio de Janeiro city (Casas de Convivência e Lazer para Idosos). It was used several instruments (Brief Cognitive Screening Battery that includes Mini-Mental State Examination, Figure Memory Tests, Clock Drawing Test and Animal Verbal Fluency Test, besides Beck Depression Inventory) for the neuropsychological assessment and CompCog for clinical validation. **Results:** The results showed that time variables, like choice reaction time and total time, were good to discriminate the sample of healthy subjects from the sample of people with PD, mainly in tasks of choice of stimulus, implicit learning, visuospatial memory, memory and recognition of faces and inhibitory control. **Conclusion:** These findings suggest that time variables are good measures to evaluate PD patients and CompCog is a useful tool for screen PD cognitive impairments.

Keywords: Neuropsychological Assessment; Neuropsychology Computadorized Battery; CompCog; Parkinson Disease

CompCog has high accuracy to identify cognitive symptoms in Parkinson´s Disease patients

Parkinson's disease (PD), being the second most common neurodegenerative disease today, needs to have all its aspects well investigated, including non-motor symptoms: cognition. It is increasingly important to develop and clinically validate instruments that improve the neuropsychological assessment of these conditions. To characterize a sample and identify the compromises to be analyzed, a screening of the patient's cognitive functioning is performed. However, comparing cognitive data from different populations and using different tests generates conflicts in the literature, mainly because they use screening instruments that do not have the sensitivity to detail cognitive functioning sufficiently (Heluani, 2014). Computerized tests batteries have been applied in several clinical populations, helping in diagnoses, drug, and psych educative interventions. These studies appear in both international and national literature, however more frequently in international studies. This evidence corroborates the relevance regarding the validation of computerized batteries benefiting from the new technologies applied to Psychology (Charchat et al, 2001).

CompCog is a computerized neuropsychological battery consisting of 8 subtests (Simple Reaction Time, Choice Reaction Time, Implicit Learning Test, Visuospatial Short-Term Memory, Face Recognition and Memory, Stroop Test, Inhibitory Control and Survey), which assesses different cognitive domains: attention, memory, executive functions, perception and processing time information. It was initially called the *Bateria de Testes Neuropsicológicos Computadorizados* (BTNC) and evaluated visual perception, attention, anterograde episodic memory, short-term memory and processing time information in 6 subtests (Charchat, 1999). The MEL Professional version 2.0 program (Schneider, 1995) was used and Charchat et al (2001) carried out an initial study to investigate clinical markers of early Alzheimer's Disease (AD). It was found that both episodic memory, short-term memory, and choice reaction time substances were sensitive and specific to discriminate between groups of people with probable mild AD and healthy people. Subsequently, a screening

version called Computerized Cognitive Screening test (CompCogs) was created with the same characteristics as the initial version, but reducing the application time by 25 minutes, requiring only 15 minutes for its administration. Its validity for the early diagnosis of AD was investigated and proved to be highly sensitive and specific for this diagnosis (Fichman et al, 2008). Since 2011, CompCog has been administered via a portable computing device that operates on iOS operating system - iPad. The iPad is a small tablet and easily transported to different places, making its use even more practical. The use of tablets, especially the iPad, has increased considerably in recent years.

The validation of this neuropsychological instrument that assess the main cognitive functions (attention, memory, perception, speed of information processing) is a great achievement for PD patients who previously only had access to instruments that required capacities that were not compatible with impairments resulting from the disease, but not related to cognitive functioning - motor symptoms. This equipment uses only the touchscreen, which makes the automation of commands accessible to individuals who do not normally use traditional computers.

In the context of neuropsychology, especially in Brazil, the search for the validation of tests and computerized measures is essential for two main reasons: the scarcity of tests validated in Brazil (Atalaia-Silva and Lourenço, 2008) and the verification of the usefulness of computerized evaluation in investigation of cognitive impairments in neurological and psychiatric diseases (Johnson et al, 2008). In this study, it is administered in people with PD to allow this assessment to be capable, even with the motor losses inherent to the condition. This study aims to investigate the accuracy of the CompCog to screen PD among patients assisted in a neurology outpatient clinic at a public hospital in Rio de Janeiro city.

METHODOLOGY

Sample

The sample for this study consisted of neurology outpatients of a public hospital in Rio de Janeiro city. Thirty-two patients with PD diagnosis and 32 healthy subjects were investigated. The PD diagnosis was the gold standard

adopted by the medical staff based on the UK Parkinson's Society Brain Bank (Hughes et al, 1992; Litvan et al, 2012).

The patients were referred by the neuropsychologist, which performed a screening with an evaluation protocol established. The inclusion criteria to participate in the study was: a) be a user of the hospital's neurology service, b) have a PD diagnosis and c) be over than 45 years of age. Were excluded patients a) presenting serious systemic diseases (hormonal, brain disorders, among others that can cause cognitive decline) b) a recent history of alcohol or other drug dependence, c) use of psychotropics that affect cognition, such as benzodiazepines, d) existence of cardiovascular diseases, hypertension and diabetes no controlled, e) visual and/or hearing disorders without correction; f) presence of current or previous neurological diseases and g) fulfill dementia criteria, based on the clinical evaluation of the medical team.

The group of 32 healthy subjects was selected from a social program offered by the government of Rio de Janeiro city of the Special Secretariat for Healthy Aging and Quality of Life of Rio de Janeiro city. The inclusion criteria to participate in the study was: a) be a user of the Casas de Convivência, b) be over than 45 years of age, c) having no neurological and/or psychiatric illness. Were excluded people a) presenting serious systemic diseases (hormonal, brain disorders, among others that can cause cognitive decline), b) a recent history of alcohol or other drug dependence, c) use of psychotropics that affect cognition, such as benzodiazepines; d) existence of cardiovascular diseases, hypertension and diabetes no controlled, e) visual and/or hearing disorders without correction; f) presence of current or previous neurological diseases and g) fulfill dementia criteria, based on the clinical evaluation of the medical team.

Ethical aspects

This study was approved by the Research Ethics Committees of the the State Servers Federal Hospital from Rio de Janeiro city (3.271.273) and Catholic Pontifical University from Rio de Janeiro city (21/2019). People participated in this research by signing a term of informed consent, according to Resolution 466/12 of the National Health Council, which deals with the guidelines and standards for research involving humans.

Instruments

The following instruments were applied: a) structured interview (with questions regarding clinical and socio-demographic aspects), b) CompCog - IPad version (Table 1) and c) Brief Cognitive Screening Battery that includes the following tests: Mini-Mental State Examination (MMSE), Figure Memory Tests (FMT), Clock Drawing Test (TDR), Animal Verbal Fluency Test (AVFT) and Beck Depression Inventory (BDI).

Table 1. CompCog subtests, variables and description

Subtests	Variables	Description
Simple Reaction Time	Median reaction time	There is a white rectangle at the bottom of the screen. As soon as a white square appears in the middle of the screen, the person should touch the rectangle.
Choice Reaction Time	Median reaction time, correct answers and revised median reaction time (choice reaction time - simple reaction time)*	There are two rectangles, a white and an orange one, at the bottom of the screen. As a white or orange square appears in the middle of the screen, the person should touch the rectangle of the same color.
Implicit Learning Test	Median reaction time in each of five tasks and implicit learning (median reaction time in sequence 4 – median reaction time in sequence 1)*	There are 10 grey squares distributed on the screen. One square becomes white at a time and, as the person touches it, another one lights up. There is a fixed sequence of 25 squares that is repeated 4 times and one last random sequence of also 25 squares. The difference between reactions of subsequent sequences are used as an implicit learning measure.
Visual and Spatial Short-Term Memory	Correct answers, direct order SPAN, reaction time in direct order, inverse order SPAN and reaction time in direct order	There are, as there were in the last test, 10 grey squares distributed on the screen. One will become white at a time, making a sequence that must be reproduced. The sequence increases in number if the person gets two of four attempts right. The test starts with a message stating the type of sequence – first forward and then reverse - and the number of squares that will appear in sequence - from 2 to 8. When the forward sequences end, the reverse sequences starts. Results are measured by the span reached.
Face Recognition	Correct answers and	At first, 10 drawings of unknown

and Memory	median reaction time for each of the four tasks	faces are presented for 30 seconds on the screen with the instruction for memorizing the faces. After that the person should choose between 10 pairs of faces which one was among those initially shown for memorization. The task is repeated three times in a row and again after 20 minutes.
Inhibitory Control Test	Median reaction time, correct answers, correct answers median reaction time, errors median reaction time and errors	Squares of different colors will appear in the middle of the screen for one second each, the white ones should be avoided.
Stroop Test	Interference, median reaction time and errors for each of the three tasks	This test includes three tasks, like the original Stroop paradigm. All tasks have 4 rectangles (green, red, blue and yellow) located at the bottom of the screen. The person should touch the one matching the stimuli (first: a colored square, second: fruit names written in different colors than the actual color of the fruit, and third: color names that are written in another color) that appears in the middle of the screen considering its color.
Survey Test	Median reaction time, correct answers, reaction time of correct answers, errors and reaction time of errors for each of the three tasks	Squares of different colors will appear in the middle of the screen for one second each. Results are measured by reaction time and the percentage of errors and correct answers.

** possible variables to be calculated*

Procedures

The Neurology outpatient clinic of the Federal Hospital of the State Servers (FHSS) was the place where the research was carried out and the PD patient received a call scheduling the evaluation. Once in the hospital for his appointment, he signed the Free and Informed Consent (FIC) and, subsequently, the evaluation started with an anamnesis (interview), evaluating the inclusion and exclusion criteria of the project and starting the application of the instruments. For healthy subjects from the Casas de Convivência, neuropsychological assessments were carried out at the institution itself.

Data Analysis

Comparisons between means of demographic, clinical profile data and CompCog results were performed through the t-test or chi-square test. ROC curves were used to evaluate the accuracy of each test and define cutoff points for each variable. A diagnosis model using the short battery was proposed from the logistic regression analyses. That model generated an equation that determined the probability for each individual to present clinically probable diagnosis of PD. These results classified the subjects and defined the sensitivity and specificity of the computerized neuropsychological battery for the diagnosis of PD in the studied sample.

These data analyses were performed with the aid of statistical software Statistical Package for Social Sciences (SPSS) version 22.0. For all analysis the value of significance was set at $p<0.05$.

RESULTS

Below there is a description of the two groups, both the socio-demographic data (Table 2) and the neuropsychological profile (Table 3) based on the Brief Cognitive Screening Battery.

Table 2. Socio-demographic data

	Control group (n=32)	PD group (n=32)
Gender	25 W x 7 M	15 W x 17 M
Age	53-63y 6.3% 64-74y 25% Above 75y 18.8%	42-52y 9.4% 53-63y 12.5% 64-74y 21.9% Above 75y 6.3%
Schooling	Elementary school 3.2% High school 10.9% Graduation 10.9% Post-graduation 25%	Illiterate 3.1% Elementary school 18.7% High school 17.2% Graduation 7.8%

W: women, M: men, y: years.

The mean age of PD patients was 64 (± 10.18) years and 8.77 (± 4.10) years of schooling. The mean age of the control group was 71.48 (± 6.90) years and 14.32 (± 4.13) years of schooling.

Table 3. Neuropsychologic profile

	Control group (n=32)	PD group (n=32)
MMSE	27.48 (±1.98)	25.12 (±2.79)
MFT (Nomination)	10	10.33 (±2.10)
(Incidental Memory)	5.81 (±1.47)	5.33 (±1.73)
(Mem Imediata 1)	8.32 (±1.40)	7.55 (±1.30)
(Mem Imediata 2)	9.13 (±1.02)	8.39 (±1.25)
(Late Memory)	8.58 (±1.54)	7.67 (±1.78)
(Recognition)	9.90 (±0.30)	9.94 (±0.36)
Animals FVT	20.68 (±4.02)	17.21 (±3.86)
CDT	7.16 (±2.45)	4.42 (±1.07)

It was observed significant difference between groups only in CDT [t(55)=5.288, p<.01]. T test did not show difference between MMSE [t(62)=3.881, p=.087], Nomination [t(62)=-,883, p=.051], Incidental Memory [t(62)=1.177, p=.478], Late Memory [t(62)=2.188, p=.596], Recognition [t(60)=-.383, p=.505] and AVFT [t(62)=3.517, p=.919].

Below are presented and compared the results of the CompCog of each group (Table 4):

Table 4. Description and comparison of CompCog results of both groups

	Control group (n=32)	PD group (n=32)
Simple Reaction Time		
Median Time	468.32 (±307.03) ms	818.79 (±350.53) ms
Total Time	59.66 (±39.40) s	95.93 (±41.51) s
Choice Reaction Time		
Median Time	684.97 (±128.77) ms	1060.62 (±185.91) ms
Total Time	72.63 (±14.79) s	109.91 (±21.94) s
Correct Answers	98.19 (±1.89)	97.21 (±3.08)
Implicit Learning Test		
Reaction Median Time Seq 1	706.53 (±125.29) ms	994.36 (±196.28) ms
Total Time Seq 1	37.56 (±6.54) s	54.47 (±12.53) s
Reaction Median Time Seq 2	648.14 (±115.16) ms	944.63 (±161.38) ms
Total Time Seq 2	32.81 (±5.79) s	48.60 (±9.71) s
Reaction Median Time Seq 3	624.17 (±114.34) ms	934.67 (±172.13) ms
Total Time Seq 3	31.70 (±5.43) s	48.50 (±10.23) s
Reaction Median Time Seq 4	611.25 (±106.88) ms	913.52 (±159.88) ms
Total Time Seq 4	31.49 (±5.02) s	47.13 (±8.99) s
Reaction Median Time Seq 5	645.28 (±86.57) ms	941.86 (±192.13) ms
Total Time Seq 5	32.18 (±4.31) s	49.53 (±14.14) s
Implicit Learning	.793 (±.250)	.922 (±.093)
Short-Term Visuospatial Memory		

Reaction Median Time	679.81 (±248.88) ms	1148.41 (±785.98) ms
Total Time	150. 26 (±64.31) s	114.29 (±60.10) s
Correct Answers	67.84 (±14.07)	56.83 (±23.34)
Longest Direct Sequence	4.10 (±1.49)	3.36 (±1.55)
Longest Indirect Sequence	3.74 (±1.13)	2.64 (±1.31)
Face Recognition and Memory		
Reaction Median Time	1513.15 (±317.033) ms	2399.12 (±1456.15) ms
Total Time	72.58 (±19.58) s	108.37 (±55.06) s
Correct Answers	96.77 (±6.48)	84.57 (±19.75)
First Block Reaction Median Time	2088.03 (±764.47) ms	3302.71 (±2218.25) ms
First Block Correct Answers	92.71 (±12.50)	80 (±20.67)
Second Block Reaction Median Time	1530.03 (±362.89) ms	2402.51 (±1461.63) ms
Second Block Correct Answers	97.29 (±13.32)	86.52 (±25.34)
Third Block Reaction Median Time	1390.24 (±267.64) ms	2168.38 (±1271.39) ms
Third Block Correct Answers	99.38 (±2.45)	86.09 (±21.48)
Late Test Reaction Median Time	1389.74 (±324.29) ms	2035.81 (±1071.13) ms
Late Test Correct Answers	97.71 (±4.72)	85.65 (±17.01)
Inhibitory Control Test		
Reaction Median Time	627.08 (±93.82) ms	743.64 (±131.19) ms
Total Time	70.46 (±6.89) s	78.81 (±8.82) s
Correct Answers	94.96 (±14.29)	90.09 (±14.70)
Stroop Test		
Total Time	304.95(±62.14) s	396.14 (±141.96) s
First Block Reaction Median Time	844.80 (±133.47) ms	1061.73 (±269.45) ms
First Block Correct Answers	99.48 (±0.77)	95.45 (±16.68)
Second Block Reaction Median Time	934.39 (±174.44) ms	1177.28 (±338.92) ms
Second Block Correct Answers	98.06 (±4.34)	96.63 (±4.77)
Third Block Reaction Median Time	1054.12 (±249.00) ms	1299.80 (±395.23) ms
Third Block Correct Answers	92.42 (±19.24)	86.73 (±25.26)
Stroop Effect	1.30 (±.24)	1.20 (±.20)
Survey		
Total Time	124.07 (±7.76) s	135.70 (±8.90) s
First Block Reaction Median Time	663.65 (±87.62) ms	653.27 (±268.16) ms
First Block Correct Answers	96.04 (±12.72)	86.73 (±25.26)
Second Block Reaction Median Time	626.91 (±95.34) ms	682.21 (±237.25) ms
Second Block Correct Answers	97.36 (±5.58)	86.64 (±16.08)
Third Block Reaction Median Time	625.17 (±86.57) ms	680.17 (±231.16) ms
Third Block Correct Answers	94.21 (±6.57)	80.01 (±24.89)

After comparing the results of the healthy and PD groups, a significant difference was observed in the following variables: Choice Reaction Time (CRT) median reaction time (MRT) [t(47.451)=-8.931, p=.010], CRT total time (TT) [t(46.641)=-7.572, p=.004], Implicit Learning Test (ILT) first sequence MRT [t(45.040)=-6.634, p=.008], ILT first sequence TT [t(39.743)=-6.387, p=.001], ILT second sequence MRT [t(48.342)=-8.046, p=.003], ILT second sequence TT [t(43.107)=-7.487, p=.002], ILT third sequence MRT [t(46.205)=-8.071, p=.002], ILT third sequence TT [t(40.174)=-7.757, p<.001], ILT fourth sequence MRT [t(46.392)=-8.444, p=.004], ILT fourth sequence TT [t(41.407)=-8.129, p<.001],

ILT fifth sequence MRT [t(36.701)=-7.509, p<.001], ILT fifth sequence TT [t(31.530)=-6.237, p<.001], Visuospatial Short-Term Memory MRT direct sequence [t(31.877)=-3.021, p=.002], Face Recognition and Memory (FRM) MRT [t(29.313)=-3.153, p=.003], FRM TT [t(33.130)=-3.259,p=.004], FRM first block MRT [t(32.764)=-2.754, p=002], FRM second block MRT [t(30.007)=-3.074, p=.001], FRM third block MRT [t(29.163)=-3.176, p=.006], FRM late test MRT [t(30.151)=-3.016, p=.008), Control Inhibitory Test MRT [t(46.353)=-3.840, p=.025), Stroop Test (ST) TT [t(31.391)=-2.989, p=0.47], ST first block MRT [t(33.392)=-3.678, p=.042), Survey first block MRT [t(26.818)=-.520, p=.006], Survey second block MRT [t(28.765)=-1.076, p=0.19] and Survey third block MRT [t(28.012)=-1.107, p=.029].

The cutoff points, the sensibility, and specificity for each variable were generated by a Receiver Operating Characteristic (ROC) analysis and presented in Table 5. Only those variables with an area under the curve (AUC) > .8 and p-value < .05 were included in the table 5. Sensitivity was prioritized over specificity, and it´s preferable to find false positives during the neuropsychological assessment at first and, subsequently, investigate better if there is suspicion of cognitive impairment.

Table 5. Cut-off scores of the most discriminative significant variables

Subtests - Variable	Area under the curve, Range 95% confidence interval	p	Cut-off scores	Sensitivity (%)	Specificity (%)
Choice Reaction Time - MRT	.936, .879-.993	<.001	804.96 ms	100	83
Choice Reaction Time - TT	.912, .843-.981	<.001	81.25 s	100	78,7
ILT - Seq 1 - MRT	.906, .820-.993	<.001	751.04 ms	86.7	70.2
ILT - Seq 1 - TT	.899, .806-.992	<.001	39.80 s	86.7	74,5
ILT - Seq 2 - MRT	.939, .878-1.000	<.001	687.33 ms	100	74,5
ILT - Seq 2 - TT	.945, .888-1.000	<.001	34.62 s	100	78,7
ILT - Seq 3 - MRT	.932, .867-.997	<.001	655,77 ms	93.3	70.2
ILT - Seq 3 - TT	.942, .882-1.000	<.001	33,25 s	93,3	72.3
ILT - Seq 4 - MRT	.940, .878-1.000	<.001	640.70 ms	100	70,2
ILT - Seq 4 - TT	.950, . 891-1.000	<.001	33,17 s	93,2	72.3

ILT - Seq 5 - MRT	.919, .844-.994	<.001	671.35 ms	86.7	70.2
ILT - Seq 5 - TT	.915, .835-995	<.001	32.88 s	86,7	70,2
VSTM - MRT D	.833, .728-.938	<.001	675.00 ms	86.7	70.2
FRM - MRT	.835, .713-.958	<.001	1593.29 ms	80	70.2
FRM - TT	.821, .702-.941	<.001	76.90 s	73.3	70.2
FRM - BL2 - MRT	.813, .687-.939	<.001	1543.03 ms	73.3	70.2
FRM - BL3 -MRT	.871, .769-.973	<.001	1455.73 ms	86.7	70,2
FRM - Tardio - MRT	.828, 707-.950	<.001	1533.70 ms	80	70.2
STROOP - BL1 - MRT	.882, .799-.966	<.001	853.78 ms	93.3	70.2
STROOP - BL3 - MRT	.824, .713-.935	<.001	1155.60 ms	73.3	70.2
SUR - TT	.834, .716-.952	<.001	128.38 s	73.3	70.2

ms: millisseconds; s: seconds; MRT: Median Reaction Time; TT: Total Time; ILT: Implicit Learning Test; Seq: Sequence; VSTM: Visuospatial Short-Term Memory; FRM: Face Recognition and Memory; Stroop: Stroop Test; SUR: Survey.

It was demonstrated that, in general, time variables, like choice reaction time and total time, were good to discriminate the sample of healthy subjects from the sample of people with PD, mainly in tasks of choice of stimulus, implicit learning, visuospatial memory, memory and recognition of faces and inhibitory control.

The ROC curves (Figures 1, 2, 3 and 4) are presented below for PD versus CG.

Figure 1. ROC Curve - sensibility and specificity for Choice Reaction Time Median Reaction Time and Total Time for PD versus CG.

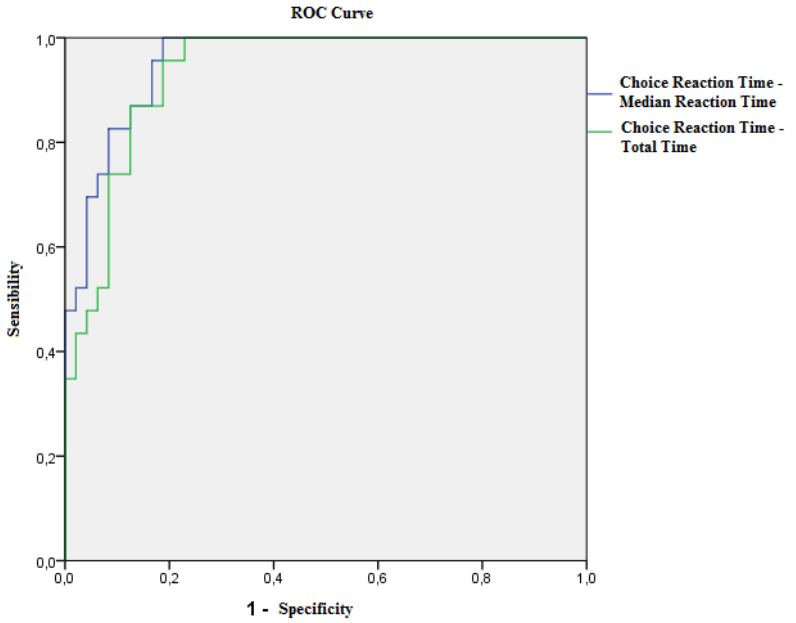


Figure 2. ROC Curve - sensibility and specificity for Implicit Learning Test Median Reaction Time and Total Time for PD versus CG.

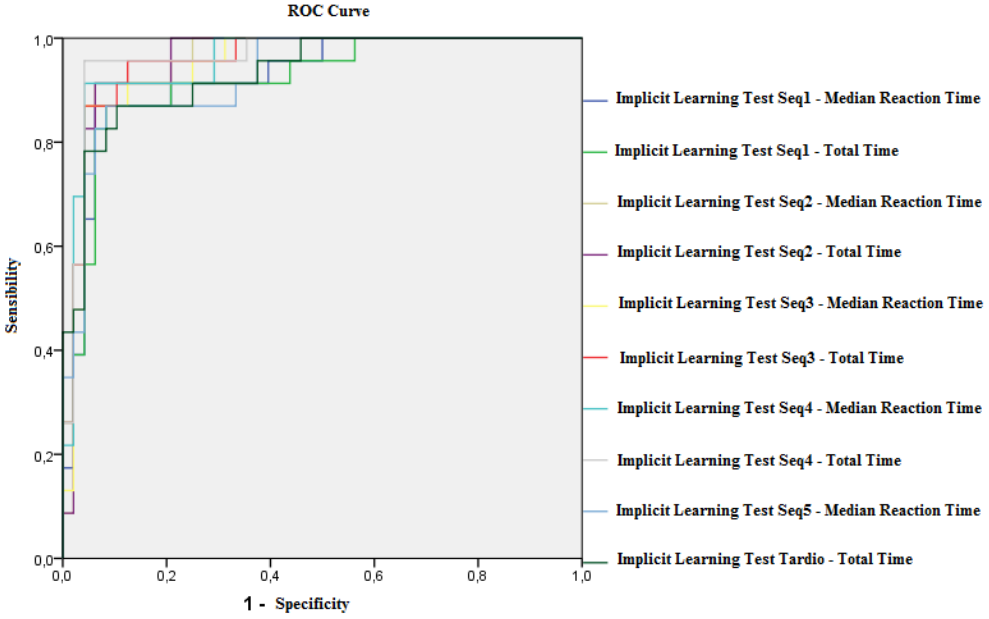


Figure 3. ROC Curve - sensibility and specificity for Visuospatial Short-Term Memory, Stroop Test and Survey Median Reaction Time and Total Time for PD versus CG.

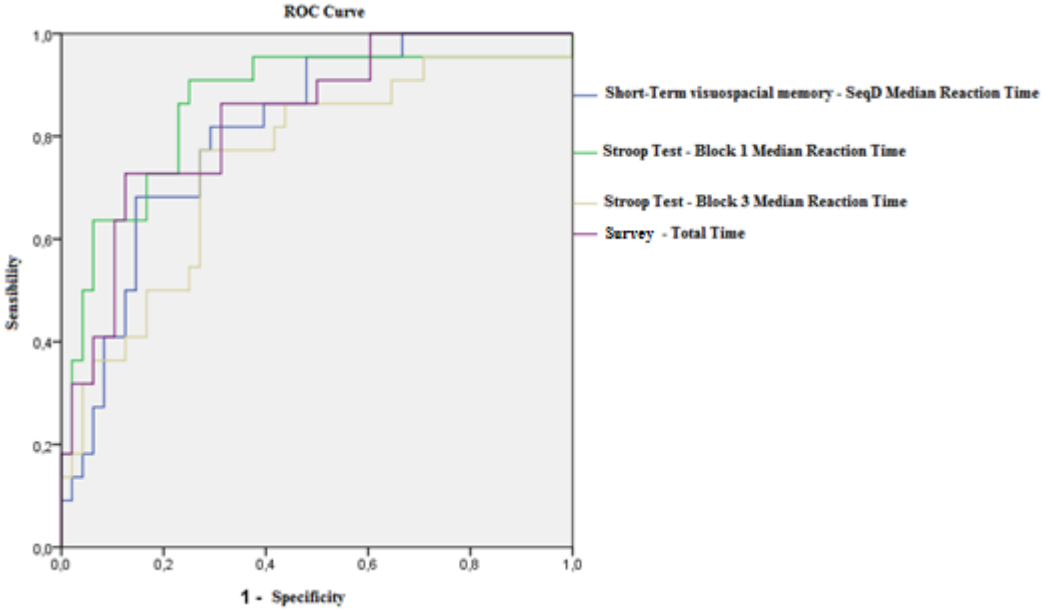
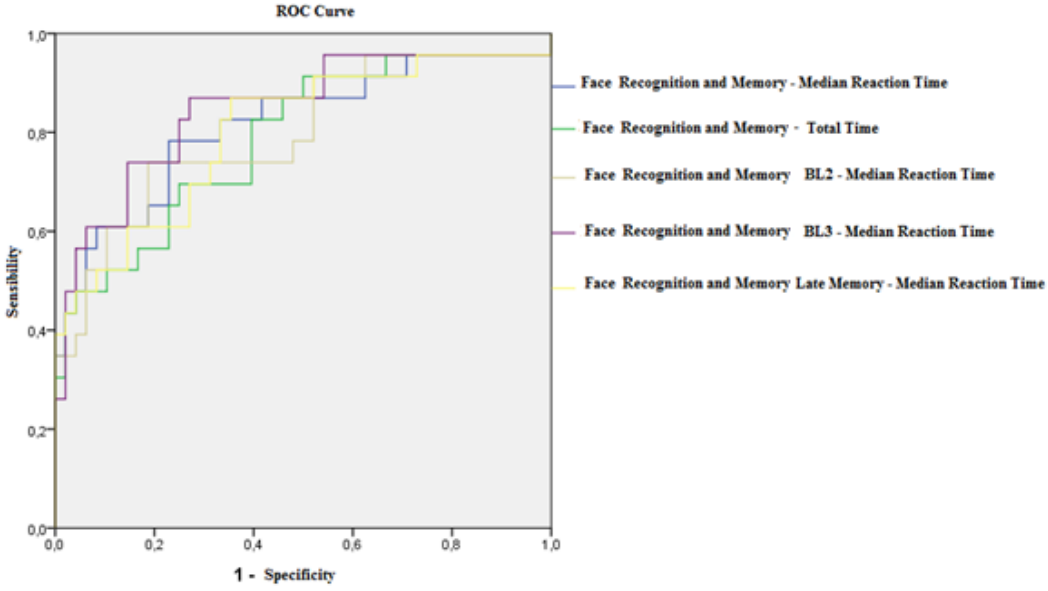


Figure 4. ROC Curve - sensibility and specificity for Face Recognition and Memory Median Reaction Time and Total Time for PD versus CG.



The Foward method was used during logistic regression analysis because we're looking for a simple model with as few variables as possible to promote faster tracking. The final model included 4 variables: Choice Reaction Time - Median Reaction Time, Implicit Learning Test - First Sequence Reaction Time, Implicit Learning Test - Fourth Sequence Total Time and Stroop Test - Block 2 Median Reaction Time. This model correctly classified 100% of cases, with 100% of specificity and 100% sensitivity. The final model had a chi-square value of

87.15 (4), p<..001. The -2 Log likelihood was <.001, with Cox & Snell R Square of 0.712 and 1.000 Nagelkerke R Square.

DISCUSSION

The screening of the patient's cognitive functioning is usually performed in studies to characterize the sample and identify the compromises to be analyzed. However, comparing cognitive data from different populations and using different tests generates conflicts in the literature, mainly because they use screening instruments that do not have the sensitivity to detail cognitive functioning sufficiently (Heluani, 2014). The batteries of computerized tests have been applied in several clinical populations, helping in diagnoses, drug and psychoeducative interventions. These evidences corroborate the relevance regarding the validation of computerized batteries benefiting from the new technologies applied to Psychology.

PD patients without dementia have impaired verbal comprehension, the identification of grammatically complex sentences, repetitive speech, decreased capacity for abstraction, slow processing speed and deficit in attention (Melo, Barbosa & Carameli, 2007). Regarding the processing speed, the slowing down of decision-making processes is a cognitive alteration that can arise early in the evolution of PD, without representing the installation of a dementia. This progressive decrease in processing is already expected over the years, being enhanced with the disease.

Memory impairment for non-verbal content, which is usually greater than for verbal content, is also present. In this regard, the difficulties in slowing down mental processing could corroborate the difficulty presented by the patient in non-verbal memory - represented here by the repetition of the 5 sequences of white squares arranged on the screen. PD patients show normal performance in several measures of explicit memory and recognition. CompCog was able to discriminate the performance of the two samples in these aspects.

Visual perception is divided into discriminative capacity (ability to analyze a new stimulus) and ability to recognize (ability to identify a familiar visual stimulus). The visual recognition task requires preserved memory for previously learned visual information and accurate visual perception for interpretation. Visual recognition is preserved in patients with PD. What was discriminated by

the computerized battery was not the successes or errors, but the difference in time for this identification and recognition. Parkinsonian patients also have difficulty in identifying specific figures involved in more complex patterns, which can be associated with the third task of Stroop, which in addition to attention also requires inhibitory control.

Levodopa acts on some aspects of cognition, such as flexibility and working memory without beneficial changes in other functions, such as visuospatial recognition, verbal ability or associative learning. Knowing this, it is necessary to emphasize that the executive function can worsen in the OFF phase, so it is the use of levodopa that is extremely important to occur before the neuropsychological assessment (Svenningsson et al, 2012; Yang et al, 2016) - which did not happen in all cases.

There are several advantages of using this computerized battery: the dynamic and colorful interface, the possibility of more accurately measuring response times discreetly throughout the evaluation process; control the time and order of presentation of stimuli; record latencies and response types; develop several forms of the same test; reduce financial costs by reducing the use of paper; reduce the examiner's effects and provide automatic performance correction, restricting the possibility of errors by the examiner (Cernich et al, 2007; Charchat et al, 2001; Schatz and Browndyke, 2002). Once explained and/or read, hardly any doubt or difficulty was presented by the subjects. Patients with visual difficulties could see the stimuli well, people with low education and/or who were not used to using technology were able to understand and respond to commands.

Other important issues are: the most standardized application format for computerized instruments; faster corrections, test scores and results are obtained, almost immediately (Ritsner et al, 2006). Allied to this, they reduce the time of administration and training of professionals when compared to traditional tests (Wild et al, 2008). What seems to stand out the most is the greater sensitivity to detect cognitive changes (Mattos, 1998; Wild et al, 2008). Among these measures, specific and complex variables stand out, such as reaction time (RT) in milliseconds. According to Charchat et al (2001), RT is a measure that allows a more detailed and refined assessment of cognitive functioning, as seen in that study.

It is interesting to think about why other variables did not differ. First, this sample had a very small number of participants due to difficulties already clarified in the methodology. A more robust sample would be needed to carry out a more forceful analysis. In addition, successes and errors were not enough to distinguish the stages, but rather time variables - be it the average reaction or the total completion of the task. That is, it is not enough to know the patient's final score to infer something about his performance, but it tells us much more how long it took him to react to the stimulus and to finish the task. PD patients constantly complain of generalized slowness, causing a longer delay to perform the usual tasks.

And in this way, we perceive the great contribution of the clinical validation of this instrument to this population, which has an impacting aspect on the time spent performing tasks, but which is not always considered in evaluations and, much less, measured. CompCog offers this measure for all subtests.

Some of the limitations of this study were that, despite being performed at the neurology outpatient clinic of a public hospital, the care for patients with PD was performed only one day a week - which prevented a much larger sample until the analysis was closed; for the same reason, all evaluations were performed by only one neuropsychologist, whereas if there were more space and days of attendance, simultaneous or alternate evaluations could be performed; despite being engaged, the patients were anxious for the neurologist's assistance and, sometimes, they did not completely disconnect from the outside; and the impossibility of increasing the sample due to not being able to recover the results of the patients evaluated at the end of the year.

For the future, the intention is to increase the samples to guarantee more reliable analyzes and more robust results.

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ARTICLE 4

Eduarda Naidel Barboza e Barbosa, Larissa Marques Francisco, Jose Augusto Nasser dos Santos and Helenice Charchat Fichman, What cognitive functions discriminate ON e OFF stages in people with Parkinson Disease after Subtalamic Nucleos Deep Brain Stimulation. (in preparation)

ABSTRACT

Introduction: In addition to drug treatment, surgical intervention represents an alternative for some PD patients with motor deficits. The most common intervention is deep brain stimulation of the subthalamic nucleus (STN-DBS). It is extremely important to carry out a neuropsychological assessment in patients with STN-DBS, not only to identify losses related to the disease, but also to compare the influence on cognition in the pre and postoperative period. **Objective:** The objective of this study was to compare the cognitive profile of PD patients who underwent STN-DBS implantation surgery in the ON and OFF stages, that is, with the stimulus on and off to check if there is any influence of the stimulus on the performance of cognitive tasks. **Method:** Nine patients with PD and STN-DBS were evaluated. Various instruments were used (Brief Cognitive Screening Battery that includes Mini Mental State Examination, Picture Memory Test, Clock Drawing Test and Animal Verbal Fluency Test, in addition to FAS Verbal Fluency Test, Verbal Rey Auditory Learning Test, Digits, Stroop Test, Visual Hooper Test Organization and Beck Depression Inventory) with the stimulation ON for the neuropsychological assessment and CompCog was used with the stimulation ON and OFF for comparison. **Results:** After analyzing the results of CompCog, a computerized neuropsychological battery, it was observed that time variables, such as reaction time of incidental and episodic memory and inhibitory control, were good for discriminating stages ON and OFF. In addition, CompCog showed a tendency to discriminate attention and processing speed reaction times and and total time in episodic memory. **Conclusion:** This discrete differentiation may be due to the small sample size, but provides data important factors to be considered in the search for discriminatory aspects at both stages and m PD patients with STN-DBS and perhaps PD with medication alone.

Keywords
Parkinson´s Disease; Neuropsychological Assessment; Deep Brain Stimulation; CompCog

RESUMO

Introdução: Além do tratamento medicamentoso, a intervenção cirúrgica representa uma alternativa para alguns pacientes com DP com déficits motores. A intervenção mais comum é a estimulação cerebral profunda do núcleo subtalâmico (STN-DBS). É extremamente importante a realização de uma avaliação neuropsicológica em pacientes com STN-DBS, não apenas para identificar perdas relacionadas à doença, mas também para comparar a influência na cognição no pré e pós-operatório. **Objetivo:** O objetivo deste estudo foi comparar o perfil cognitivo de 9 pacientes em DP submetidos à cirurgia de implantação de STN-DBS nos estágios ON e OFF, ou seja, com o estímulo ligado e desligado para verificar se há alguma influência do estímulo no estímulo. desempenho nas tarefas propostas. **Método:** Foram avaliados 9 pacientes com DP e STN-DBS. Foram utilizados vários instrumentos (Bateria Breve de Rastreio Cognitivo que inclui Mini Exame do Estado Mental, Teste de Memória de Figuras, Teste de Desenho de Relógio e Teste de Fluência Verbal Animal, além de Teste de Fluência Verbal FAS, Teste de Aprendizagem Auditiva Verbal Rey, Dígitos, Teste de Stroop, Organização Visual Hooper Teste e Inventário de Depressão de Beck) com a estimulação ligada para a avaliação neuropsicológica e o CompCog foi usado com a estimulação ligada e desligada para comparação. **Resultados:** Após analisar os resultados do CompCog, uma bateria neuropsicológica computadorizada, observou-se que variáveis de tempo, como tempo de reação da memória incidental e episódica e controle inibitório, eram boas para discriminar os estágios ON e OFF. Além disso, o CompCog mostrou uma tendência a discriminar os tempos de reação da atenção e da velocidade de processamento e o tempo total na memória episódica. **Conclusão:** Essa diferenciação discreta pode ser devida ao pequeno tamanho da amostra, mas fornece dados importantes a serem considerados na busca de aspectos discriminatórios em ambos os estágios em pacientes com DP com STN-DBS e, talvez, com DP apenas com medicação.

Palavras-Chave

Doença de Parkinson; Avaliação Neuropsicológica; Estimulação Cerebral Profunda; CompCog

What cognitive functions discriminate ON e OFF stages in people with Parkinson Disease after Subtalamic Nucleos Deep Brain Stimulation.

One of the most aggressive non-motor symptoms of Parkinson Disease (PD) is cognitive impairment, which occurs more quickly in attentional and visuospatial functions, as well as executive functions and skill learning (implicit) (Wang, 2018). In the early stages of the disease, cognitive impairment was found in memory (20%), in addition to executive functions (30%) and global cognitive functioning (50%) (Muslimovic et al, 2005). In the systematic review conducted by Barbosa and Charchat-Fichman (2019b) was demonstrated that the global cognitive functioning is quite assessed, as well as different aspects of executive functions and memory.

It is difficult to correlate neuropathology with cognitive decline in PD, but studies show that impairment of executive functions, visuospatial skills and global functioning are related to the APOE4 allele (Ding et al, 2015). Vasconcellos et al (2017) found structural abnormalities by observing MRI of both people with PD and controls with mild cognitive impairement (MCI) and attention, memory and executive function impairment were the functions more severe in amnestic PD-MCI group. In cases in which PD is associated with MCI, partial atrophy of the partial gray matter is observed in the frontal, temporal and parietal cortices, as well as in the regions of the hippocampus, amygdala and putamen. When compared with PD patients without MCI, they have significantly depleted performance in virtually all cognitive domains: executive functions, attention, memory and language (Ding et al, 2015). Deficits in executive funtions are the result of a change in dopaminergic transmission and visuospatial, language and memory deficits are the result of a change in cholinergic transmission.

The clinical presentation of PD is (motor symptoms) with rest tremor, stiffness, bradykinesia and postural instability, hypomimia, decreased eye blinking and hypophonia, micrograph, sialorrhea (non-motor symptoms) gastrointestinal, urinary and sexual disorders, sleep disorders and respiratory disorders and neuropsychiatric disorders, including cognitive deficits. The ON

and OFF stages appear in the intermediate stage of PD (between 3 and 5 years of the disease) and are related to the effect of the medication: at ON stage there is an improvement in parkinsonian symptoms and at OFF stage they reappear (Cardoso, 1995; de Paixão et al, 2016). After taking a dose of the medicine, the patient usually feels his symptoms controlled or ceased. With the end of the dose effect, the symptoms are noticed again. The amount of medication taken by patients with PD is around 5 or 4 doses a day.

Fifty-four por cent of PD patients do not adhere to drug treatment because forget and/or confuse the dose, the hour or even taking an extra dose. These difficulties affect the patient's clinical evolution and quality of life (Marchi et al, 2011). Over time, this maintenance becomes more and more complicated, with ON periods being shorter and needing medication replacement earlier and earlier.

Deep Brain Stimulation (DBS) consists in the application of low intensity electric current, generally high frequency and variable pulse width continuously or by intermittent cycles to previous selected nervous structures inside the brain. This neuromodulation relieves symptoms of various diseases, according to the target of the electrodes. In the case of PD, the targets are the subthalamic nuclei or globuspallidus (GPi) for motor symptoms control, effects on cognition - for example - may occur. While some studies show improvement in cognitive functions after DBS (Aguilar, Soto and Esguerra, 2011; Asahi et al, 2014; Vonberg et al, 2016), in visual working memory (Ventre-Dominey et al, 2016), in decision making (Boller et al, 2014), in executive functions (Pham et al, 2015), verbal memory (Tang et al, 2015). In others, the opposite effect is found, that is, worsening cognitive functions (Krishnan et al, 2016), verbal fluency (Houvenaghel et al, 2015; Tang et al, 2015). Massano & Garrett, (2012), Yilmaz et al (2015) and Tremblay et al (2015) did not observe changes in the assessed functions, in the understanding of metaphor and verbal fluency/visuospatial orientation, respectively. In assessing mood, anxiety levels decreased in Tang et al (2015) and Pham et al (2015) and that of apathy increased in Houvenaghel et al (2015).

The literature points to an evident motor and quality of life improvement after DBS in patients with PD, however studies dedicated to the investigation of

the relationship between DBS-STN and cognitive functioning are controversial, making further studies investigating this relationship necessary. Cognitive decline in PD is associated with an increased risk of developing dementia and affecting the functionality of patients, as well as promoting an increase in psychiatric comorbidities (Campos et al, 2014). In this context, the investigation of the cognitive effects of STN-DBS in PD becomes essential and here we are using, besides conventional neuropsychological battery to evaluate the neuropsychological patients profile, a neuropsychological computerized battery to promote more accurate information.

METHODOLOGY

Sample

The sample consisted of patients from a private clinic in Rio de Janeiro city, Neuroclínica, by neurosurgeon José Augusto Nasser dos Santos. Nine patients with PD diagnosis and STN-DBS were evaluated. The gold standard adopted was the diagnosis of PD performed by the neurosurgeon. Some of the criteria required for the diagnosis of PD, according to the UK PD Brain Society Bank (Litvan et al, 2009), are bradykinesia and at least one of the following symptoms: muscle stiffness, tremor at rest (clinically assessed) and non postural instability caused by vestibular, cerebellar or proprioceptive visual disturbances.

The patients were selected by the neurosurgeon for having already undergone implantation surgery. Patients who are selected for surgery are those with disabling motor complications. In addition, having been diagnosed with PD for at least 5 years, have a good response to levodopa and none or very mild cognitive impairment and absence of psychiatric or controlled disease - including dementia. Twenty-six patients referred by the neurosurgeon were evaluated, however not all met the inclusion criteria for this study, some were afraid to turn off the device (n=3), even in the presence of the physician, some would still have the surgery and the evaluation had another objective (n=6), there was still a problem with the computerized neuropsychological battery that prevented access to the data of some patients (n=4) and some had complications that impaired the assessment, whether motor or cognitive (n=4).

The patients were referred by the neuropsychologist, which performed a screening with an evaluation protocol established. The inclusion criteria to participate in the study was: a) be a patient selected by the neurosurgeon with PD diagnosis and STN-DBS and be over than 45 years of age. Were excluded patients a) presenting serious systemic diseases (hormonal, brain disorders, among others that can cause cognitive decline) b) a recent history of alcohol or other drug dependence, c) use of psychotropics that affect cognition, such as benzodiazepines, d) existence of cardiovascular diseases, hypertension and diabetes no controlled, e) visual and/or hearing disorders without correction; f) presence of current or previous neurological diseases and g) fulfill dementia criteria, based on the clinical evaluation of the physician.

Ethical aspects

This study was approved by the Research Ethics Committees of the Catholic Pontifical University (21/2019). People participated in this research by signing a term of informed consent, according to Resolution 466/12 of the National Health Council, which deals with the guidelines and standards for research involving humans.

Instruments

The following instruments were applied with the stimulation ON for establishing a neuropsychological profile: a) structured interview (with questions regarding clinical and socio-demographic aspects), b) CompCog - IPad version (Table 1) and c) Brief Cognitive Screening Battery that includes the following tests: Mini-Mental State Examination (MMSE), Figure Memory Tests (FMT), Clock Drawing Test (TDR), Animal Verbal Fluency Test (AVFT) and FAS Verbal Fluency Test (FAS), Rey Auditory Verbal Learning Test (RVALT), Digits, Stroop Test (Stroop), Visual Hooper Organization Test (Hooper) and Beck Depression Inventory (BDI). CompCog was applied with stimulation OFF to compare cognitive performance on both stages (table 1).

Table 1. CompCog subtests, variables and description

Subtests	Variables	Description
Simple Reaction Time	Median reaction time	There is a white rectangle at the bottom of the screen. As soon as a white square appears in the middle of the screen, the person should touch the rectangle.
Choice Reaction Time	Median reaction time, correct answers and revised median reaction time (choice reaction time - simple reaction time)*	There are two rectangles, a white and an orange one, at the bottom of the screen. As a white or orange square appears in the middle of the screen, the person should touch the rectangle of the same color.
Implicit Learning Test	Median reaction time in each of five tasks and implicit learning (median reaction time in sequence 4 – median reaction time in sequence 1)*	There are 10 grey squares distributed on the screen. One square becomes white at a time and, as the person touches it, another one lights up. There is a fixed sequence of 25 squares that is repeated 4 times and one last random sequence of also 25 squares. The difference between reactions of subsequent sequences are used as an implicit learning measure.
Visual and Spatial Short-Term Memory	Correct answers, direct order SPAN, reaction time in direct order, inverse order SPAN and reaction time in direct order	There are, as there were in the last test, 10 grey squares distributed on the screen. One will become white at a time, making a sequence that must be reproduced. The sequence increases in number if the person gets two of four attempts right. The test starts with a message stating the type of sequence – first forward and then reverse - and the number of squares that will appear in sequence - from 2 to 8. When the forward sequences end, the reverse sequences starts. Results are measured by the span reached.
Face Recognition and Memory	Correct answers and median reaction time for each of the four tasks	At first, 10 drawings of unknown faces are presented for 30 seconds on the screen with the instruction for memorizing the faces. After that the person should choose between 10 pairs of faces which one was among those initially shown for memorization. The task is repeated three times in a row and again after 20 minutes.
Inhibitory Control Test	Median reaction time, correct answers, correct answers median reaction	Squares of different colors will appear in the middle of the screen for one second each, the white ones

	time, errors median reaction time and errors	should be avoided.
Stroop Test	Interference, median reaction time and errors for each of the three tasks	This test includes three tasks, like the original Stroop paradigm. All tasks have 4 rectangles (green, red, blue and yellow) located at the bottom of the screen. The person should touch the one matching the stimuli (first: a colored square, second: fruit names written in different colors than the actual color of the fruit, and third: color names that are written in another color) that appears in the middle of the screen considering its color.
Survey Test	Median reaction time, correct answers, reaction time of correct answers, errors and reaction time of errors for each of the three tasks	Squares of different colors will appear in the middle of the screen for one second each. Results are measured by reaction time and the percentage of errors and correct answers.

** possible variables to be calculated*

Procedures

Two evaluations were performed on the same day: one with stimulation on, ON stage, comprising CompCog and the conventional tests (pencil and paper) and, then, with stimulation off, OFF stage, comprising only CompCog subtests. The duration of the CompCog tasks takes between half an hour and an hour, depending on the degree of motor or cognitive difficulty of the patient. In addition, the evaluations with the stimulation off were performed with the subject under the effect of levodopa, as it would be impracticable to carry out the tests without the medication. The neuropsychologist herself, previously trained to do so, turned off the device and turned it back on as needed. The assessments took place in the responsible neurosurgeon clinic Neuroclínica.

Data Analysis

Comparisons between means of demographic, clinical profile data and CompCog subtests results were performed through the t-test or chi-square test. In addition, the non-parametric test Wilcoxon 2 related samples, were used to

compare the performances of each subject in attention, processing speed, implicit learning, episodic and working memory and inhibitory control, checking if there are significant differences between their results in the two stages, ON and OFF. Cognitive data did not presented a normal distribution, so the non-parametric test were used.

These data analysis were performed with the aid of statistical software Statistical Package for Social Sciences (SPSS) version 22.0. For all analysis the value of significance was set at $p<0.05$.

RESULTS

The mean age of PD patients with STN-DBS was 60,56 (± 10.13) years and 12 (± 5.45) years of schooling. Table 2 shows patients social and clinical caractherists and table 3 shows the neuropsychological profile of the sample with the stimulation ON.

Table 2. Patients social and clinical caractheristics

Patients	Age	Schooling	Profession	Comorbidities	Medication
WMS	60	5	Merchant	High pressure	"for high pressure" name not informed*
HSB	79	14	Legal analyst	-	Prolopa, Sifrol and Entacapona
SLGS	52	15	Physiotherapist	Diabetes	Prolopa, Akington and Glifage
AOCS	62	11	Militar	-	Prolopa, Azilet and Contan
ESG	67	15	Lawyer	-	Levodopa, Sifrol, Niar and Aztec
VHSM	44	22	Physician and e acupuncturist	High pressure	Levodopa + Carbidopa, Amantatina, Rasagilina and Rotigotina
MSMO	53	11	Merchant	High pressure	Prolopa and Conversyl Plus
APM	66	4	Seller	High pressure and arthrosis	Prolopa, Rasagilina, Pinazan, Zytiga, Predinisona and

RFJ	62	11	Public agent	-	Natrilix Prolopa and Jumexil

* does not use any PD medication because he maintains the habit of drinking alcohol

Table 3. Patients neuropsychological profile on ON stage

Tests	Results (n=9)	Cut-off points
MMSE	25,89 (± 2,85)	1 to 4 y schooling - 24,8 Brucki et al (2003)
MFT		
(Nomination)	10,00 (0)	<10
(Incidental Memory)	6,33 (±1,73)	≤ 7
(Immediate Memory 1)	7,00 (±2,06)	≤ 7
(Immediate Memory 2)	7,67 (±1,66)	≤ 7
(Late Memory)	6,88 (±2,03)	≤ 5
(Recognition)	9,78 (±0,67)	≤ 7 (Nitrini, 1994)
Animals FVT	16,11 (±6,05)	1 to 4 y schooling - 10,73 (Silva et al, 2011)
FAS FVT	25.78 (±14.21)	
Clock Drawing Test	5.89 (±1.83)	≤ 9 (Sunderland et al, 1989; Fichman et al, 2013**)**
RAVLT		
(Learning A1A5)	37 (±14.20)	45.7 (±9.7)
Interference A6	4.44 (±3.00)	9.4 (±3.1)
Late Memory A7	4.56 (±3.94)	9.5 (±3.2)
Forgetting Speed	1.05 (±0.91)	1.02 (±0.19)
Proactive Interference	0.867 (±0.388)	0.82 (±0.29)
Retroactive Interference	0.396 (±0.228)	0.82 (±0.19) (de Paula and Malloy-Diniz, 2018)
Digit Span	11.11 (±3.33)	(Wechsler, 1997; Nascimento, 2005)
Stroop		
Stroop 1	20 (±8.0)	
Stroop 2	22.44 (±11.24)	
Stroop 3	45.63 (±13.63)	
Stroop Effect	2.37 (±0.63)	
Hooper	18.28 (±7.18)	10 to 19 - moderate (Malak et al, 2016)
Beck Depression Inventory	9.00 (±5.90)	0 to 11 - minimum symptoms (Cunha, 2001**)**

The patients had an average performance of 25.89 (± 2.85) in the MMSE, which, as suggested by Brucki et al (2003), is a result higher than expected for

subjects with schooling between 1 and 4 years (the lowest level of education was 4 years), both for the hospital and home context. There is no specific cutoff point for this group. It indicates preserved cognitive functioning in temporal and spatial orientation, attention and calculation, memory, language and constructive skills. In FMT, incidental and immediate memory were the ones impaired (Nitrini, 1994). The Animals FVT was generally preserved, while the CDT was compromised with concentrated numbers (Sunderland et al, 1989; Fichman et al, 2013). Regarding the BDI, it presented a minimum degree of depression (Cunha, 2001).

All patients had PD diagnosed for more than 5 years, had the electrodes implanted in the STN and Medtronic programmer and were evaluated in 2016.

Wilcoxon pairing was performed between the CompCog variables in the ON and OFF stages of PD patients. The variables with $p<0.05$ were considered and it was observed the following variables showing significantly difference between both stages: ON Face Recognition and Memory - Late MRT from OFF Face Recognition and Memory - Late MRT ($z = -2.310$, $p=.021$, $r = -.77$), ON Face Recognition and Memory - first block MRT from OFF Face Recognition and Memory - first block MRT ($z=-2.666$, $p=.008$, $r=-.889$), ON Stroop Test third block MRT from OFF Stroop Test third block MRT ($z=-2.666$, $p=.008$, $r=-.889$).

However, other variables showed a tendency for significantly difference between both stages: ON Face Recognition and Memory TT from OFF Face Recognition and Memory TT ($z=-1.955$, $p=.051$, $r=-.652$), ON Choice Reaction Time TT from OFF Choice Reaction Time TT ($z=-1.955$, $p=.051$, $r=.652$) and ON Stroop Test first block MRT from OFF Stroop Test first block MRT ($z=-1.955$, $p=.051$, $r=-.652$).

Table 4. Comparison of CompCog results of both stages

Patients	Subtests	ON	OFF
WMS	Choice Reaction Time TT*	103,2638 s	121,3631 s
	Face Recognition and Memory TT*	94,6501 s	87,7447 s
	Face Recognition and Memory - Late MRT	2119,067 ms	1911,333 ms
	Face Recognition and Memory – 1b MRT	2712,8810 ms	2037,6580 ms
	Stroop Test 1b MRT*	1236,8320 ms	1269,325 ms
	Stroop Test 3b MRT	2665,771 ms	1365,562 ms

HSB	Choice Reaction Time TT*	107,6928 s	137,0019 s
	Face Recognition and Memory TT*	81,9339 s	78,7689 s
	Face Recognition and Memory - Late MRT	1581,329 ms	1983,527 ms
	Face Recognition and Memory – 1b MRT	2180,144 ms	1923,97 ms
	Stroop Test 1b MRT*	1254,086 ms	1253,589 ms
	Stroop Test 3b MRT	1948,673 ms	1724,907 ms
SLGS	Choice Reaction Time TT*	95,3231 s	130,7281 s
	Face Recognition and Memory TT*	67,7881 s	76,0310 s
	Face Recognition and Memory - Late MRT	2054,938 ms	1943,213 ms
	Face Recognition and Memory – 1b MRT	1223,623 ms	1607,086 ms
	Stroop Test 1b MRT*	966,1565 ms	1445,23 ms
	Stroop Test 3b MRT	1181,825 ms	1525,924 ms
AOCS	Choice Reaction Time TT*	100,8276 s	117,2430 s
	Face Recognition and Memory TT*	73,8819 s	70,4697 s
	Face Recognition and Memory - Late MRT	2373,4380 ms	2372,44 ms
	Face Recognition and Memory – 1b MRT	1377,6960 ms	1615,9570 ms
	Stroop Test 1b MRT*	1205,17 ms	990,0635 ms
	Stroop Test 3b MRT	1237,347 ms	1277,844 ms
ESG	Choice Reaction Time TT*	99,6133 s	97,5163 s
	Face Recognition and Memory TT*	113,6087 s	109,1237 s
	Face Recognition and Memory - Late MRT	4082,4580 ms	3199,1750 ms
	Face Recognition and Memory – 1b MRT	1543,443 ms	1589,09 ms
	Stroop Test 1b MRT*	942,0075 ms	949,4655 ms
	Stroop Test 3b MRT	1388,804 ms	1365,0810 ms
VHSM	Choice Reaction Time TT*	82,9802 s	98,3556 s
	Face Recognition and Memory TT*	82,8587 s	73,5678 s
	Face Recognition and Memory - Late MRT	3420,9110 ms	1935,131 ms
	Face Recognition and Memory – 1b MRT	1630,6940 ms	1910,888 ms
	Stroop Test 1b MRT*	996,9505 ms	1389,82 ms
	Stroop Test 3b MRT	1341,13 ms	1581,593 ms
MSMO	Choice Reaction Time TT*	96,9133 s	96,9233 s
	Face Recognition and Memory TT*	70,6400 s	70,6399 s
	Face Recognition and Memory - Late MRT	1478,996 ms	1534,89 ms
	Face Recognition and Memory – 1b MRT	1534,8910 ms	1478,9960 ms
	Stroop Test 1b MRT*	1011,6040 ms	1011,60 ms
	Stroop Test 3b MRT	1348,813 ms	1348,81 ms
APM	Choice Reaction Time TT*	85,7498 s	88,1841 s
	Face Recognition and Memory TT*	104,6703 s	88,9504 s
	Face Recognition and Memory - Late MRT	2822,0950 ms	1907,6610 ms
	Face Recognition and Memory – 1b MRT	1910,1490 ms	2033,2380 ms
	Stroop Test 1b MRT*	941,3310 ms	924,9935 ms
	Stroop Test 3b MRT	1355,4500 ms	1173,1820 ms
RFJ	Choice Reaction Time TT*	85,1279 s	85,4049 s
	Face Recognition and Memory TT*	78,1840 s	66,4248 s
	Face Recognition and Memory - Late MRT	2689,3740 ms	1653,5140 ms
	Face Recognition and Memory – 1b MRT	1206,2970 ms	1510,0410 ms
	Stroop Test 1b MRT*	988,5155 ms	884,6790 ms
	Stroop Test 3b MRT	1101,8520 ms	998,8005 ms

TT: total time; MRT: median reaction time; 1b: first block; 3b: third block
**showed a tendency to discriminate*

It was observed that the median reaction time was able to distinguish the performance of subjects with stimulation on and off in incidental and delayed episodic memory, in addition to inhibitory control. The total time showed a tendency to distinguish between the two stages in episodic memory, while the average reaction time showed this same trend in processing speed and attention.

DISCUSSION

Cognitive changes in PD are explained by the fact that in addition to projections of the motor cortex, the striatum receives projections from cortical areas of association, in the sensitive cortex. Currently five circuits are well defined: the motor circuit, which originates in the supplementary motor area; the oculomotor circuit, originating in the frontal cortex in Broadmann's area; and the dorsolateral, lateral orbitofrontal and anterior cingulate circuits, all originating in the prefrontal cortex. All circuits share the same structures: frontal, striated lobe, GPi, nigra substance and thalamus. They are contiguous circuits, but they remain anatomically segregated along the neuronal loop of each circuit (Yang, 2016).

Of the above circuits, the three originating in prefrontal cortex apparently does not have a motor function. Therefore, it is not surprising that many clinical findings reveal the involvement of the basal ganglia nuclei in a wide variety of non-motor functions.

There are discussions in literature about the impairment of PD patients' performance in tasks involving implicit memory associating activation of the basal ganglia nuclei. In addition to it, there is also a deficit in tests of response inhibition, retention and manipulation of information and planning - activities that require working memory (Pavão, 2007). With the dopaminergic deficit and the degeneration of the neurons of the basal ganglia nuclei in the pathology of PD, this processing and the level of pre-activation of priming and procedural learning are impaired. Barbosa and Charchat-Fichman (2019b) brought results of several studies showing that executive functions were the most impaired function after DBS, however we cannot consider it something unique due to its characteristic of encompassing different aspects such as flexibility, monitoring and inhibitory

control - aspects that showed a difference between the ON stages and OFF. Attention appears both discriminating the two stages and having a tendency to discrimination and, obviously, causing a reduction in latency in simple reaction time and with choice, as noted, but normally isn´t much assessed (Barbosa and Charchat-Fichman, 2019b). The DBS is an instrument for controlling motor symptoms and its electrodes are placed in specific areas (subthalamic nucleus or GPi), involved in the motor circuit. Although they may get worse over the years (Pavão, 2007; Lewis et al, 2014), this may be the result of the disease evolution in a way that could occur, even more quickly, if the surgery had not happened.

More important than the functions themselves that appeared discriminating the two stages, but the time variables that were capable of that instead of the success and error variables, showing how much the influence of stimulation on the motor part, helps in the performance of cognitive tasks. CompCog subtests can be performed in order to reduce the impact that impaired physical ability can have on running a test. In addition, it is possible to record and compare the subject's performance in the highly efficient way during the course of the disease. A neuropsychological assessment prior to surgery is of great importance due to the fact that the presence of any cognitive impairment before surgery, especially in executive function and memory, should serve as an exclusion criterion and lower cognitive functioning at the baseline is predictive worse cognitive outcome after surgery.

Some of the limitations were the difficulty in evaluating these patients who had already undergone the surgery due to the fact that they had a large interval between one return and another to the neurosurgeon, when they returned. In addition, some did not want to turn off the device for fear of experiencing or increasing motor symptoms again. The future perspective is to investigate other aspects before and after surgery, such as mood and quality of life, to see if they are influenced by motor improvements and/or influence other aspects. Besides, it is important to increase the sample and replicate the analyzes.

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FINAL CONSIDERATIONS

The neuropsychological evaluation provides information about the interaction between the neurological, psychological and behavioral functioning of the patient, thus defines the clinical management and its subsequent results. The analysis of the neuropsychological and neuropsychiatric aspects is well described in the literature and they serve both in screening and in the evolution of the patients undergoing surgery (VAZQUEZ et al, 2013).

The general purpose of this thesis was to think and develop innovative perspectives for diagnosis and treatment and, in this context, it was possible to validate a computerized instrument for a neuropsychological assessment of PD patients in a sensitive and specific way and we verified, at least in this small sample, that the use of DBS does not compromise the cognitive functioning of patients who underwent this intervention.

The first part of this work focused on understanding the neuropsychological profile of patients with PD who underwent DBS implantation. The systematic review focused on observing which instruments were used to assess these subjects (BARBOSA and CHARCHAT-FICHMAN, 2019a) and whether there were changes in their cognitive profile (BARBOSA and CHARCHAT-FICHMAN, 2019b). In clinical settings, these findings have great impact because it can be established as a neuropsychological assessment protocol, or that facilitates the creation of standards and the comparison between different specifications with specificities. This can guide both health professionals and researchers to better understand how the cognitive profile of these patients occurs and identify, as soon as possible, when the onset of the compromise begins

The second part of this work focused on put into practice the use of the neuropsychological assessment protocol in PD patients from a public hospital in the state of Rio de Janeiro as well as clinically validate a computerized neuropsychological battery for this population. In addition, take advantage of this computerized neuropsychological battery and compare two moments of patients with PD who have DBS: ON and OFF stages, on and off stimulation, to see if there is any influence of surgery on the cognitive profile of this group. In clinical settings, these findings allow the use of a new instrument, with high sensitivity

and specificity to assist in the identification of the disease, in addition to offering very detailed and precise information regarding the subject's cognitive performance - which was perceived when used, bringing average data on reaction time, learning and processing speed.

In conclusion, this thesis shows the importance of studying and developing innovative methods to identify and treat PD due to its wide reach currently in the population and the need for improvement in the way it has been worked. The risk for the evolution of a cognitive impairment in different cognitive functions for a MCI and hence for dementia is great and it is necessary to neuropsychological assessment of these patients periodically in order to prevent and remedy, as soon as possible.

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