Effectiveness of cognitive rehabilitation and predictors of quality of life in Parkinson's disease and psychoeducation in family caregivers

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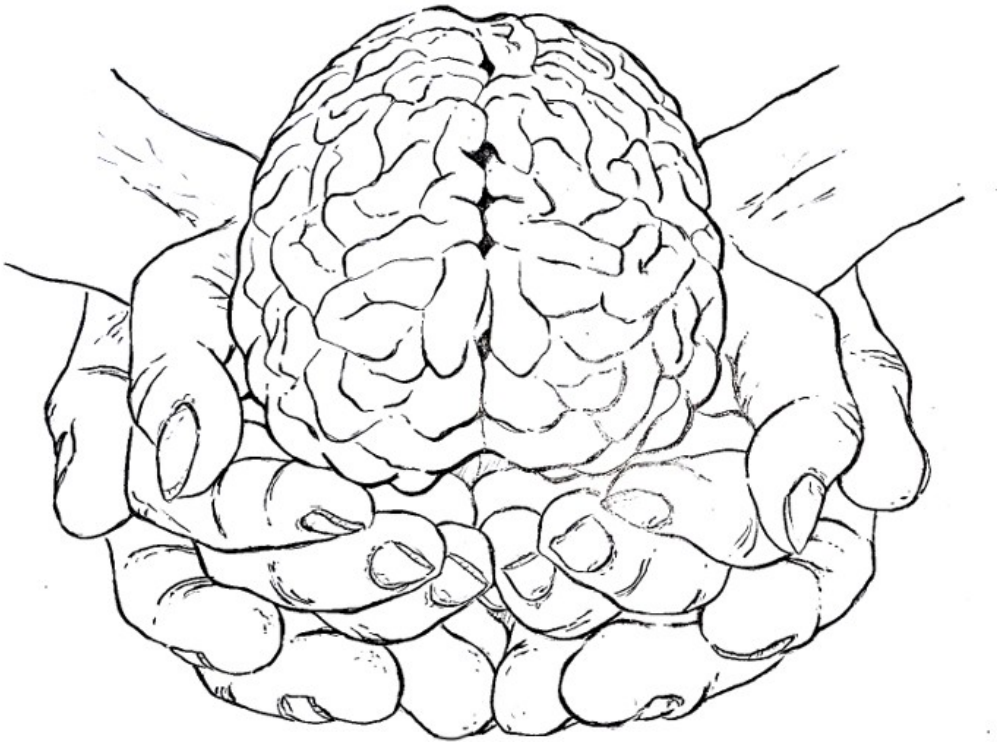

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To obtain the degree of Doctor of Psychology by the University of Deusto

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Dr. Naroa Ibarretxe Bilbao, Director of the Master in Clinical Neuropsychology, Full Professor of the Department of Psychology, Director of the present thesis; and Dr. Javier Peña Lasa, coordinator of the Doctoral program in Psychology, member of the academic commission of the Doctoral program in Psychology, Full Professor of the Department Psychology, Director of this thesis, certify that the present thesis entitled "Effectiveness of cognitive rehabilitation and predictors of quality of life in Parkinson's disease and psychoeducation in family caregivers", represents an original research work, which is presented by Itsasne Sanchez Luengos to obtain the grade of Doctor of Psychology.

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Foreword

The present thesis has been presented to obtain the degree of Doctor of Psychology by the University of Deusto and is the result of three studies conducted in the Neuropsychology of Severe Mental Condition research group, at the Department of Psychology, Faculty of Health Sciences, University of Deusto. In *study I*, a systematic review and meta-analysis of the effectiveness of cognitive rehabilitation in people with Parkinson´s disease was performed; in *study II*, the efficacy of a combined intervention of cognitive rehabilitation in people with Parkinson´s disease and psychoeducation in their family caregivers was conducted; and in *study III*, a cross-sectional study was conducted to analyze predictors of Health-Related Quality of Life controlling the overlap between Health-Related Quality of Life and clinical measures in Parkinson's disease.

Study I

Effectiveness of Cognitive Rehabilitation in Parkinson's disease: A Systematic Review and Meta-Analysis. Published in: Journal of Personalized Medicine, 11 (5): 429. https://doi.org/10.3390/jpm11050429

Study II

Combined intervention of cognitive rehabilitation in patients with Parkinson's disease and psychoeducation in their family caregivers (in preparation).

Study III

Predictors of health-related quality of life in Parkinson's disease: the impact of overlap between health-related quality of life and clinical measures. Published in: Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation, 31(11), 3241–3252. https://doi.org/10.1007/s11136-022-03187-y

Glossary of Abbreviations

ACG= Active Control Group

AD= Alzheimer´s Disease

ADL= Activities of Daily Living

ANCOVA = Analysis of Covariance

ASOPARA= Parkinson´s disease Alava Association

ASPARBI= Parkinson´s disease Biscay Association

BELA-A-K= Belastungsfragebogen Parkinson Angehörigen-kurzversion

BVMT-R= Brief Visual Memory Test Revised

CCT = Computer Cognitive Training

CDT= Clock Drawing Test

CEIm-E= Research Ethics Committee of the Basque Country

CG= Control Group

CI= confidence Interval

CIFA= Calibrated Ideational Fluency Assessment

COMTIs= Catechol-O-methyl Transferase Inhibitors

CONSORT = Consolidated Standards of Reporting Trials

COVID-19= SARS-CoV-2 virus

CR= Cognitive Rehabilitation

CRQ = Cognitive Reserve Questionnaire

CSI= Caregiver Strain Index

DSM-IV-TR= Diagnostic and Statistical Manual of Mental Disorders- IV-TR

EduPark= European Consortium

EQ-5D= EuroQoL-5D

FSS= Fatigue Severity Scale

HRQoL= Health-Related Quality of Life

H&Y= Hoehn and Yahr

GHQ-12 = General Health Questionnaire 12

HADS= Hospital Anxiety and Depression Scale

HVLT-R= Hopkins Verbal Learning Test Revised

LARS= Lille Apathy Rating Scale

LEDD= Levodopa equivalent daily dose

MAOIs=Monoamine Oxidase-B Inhibitors

MCI= Mild Cognitive Impairment

MDS= Movement Disorder Society

MF= Mentally fit

MoCA= Montreal Cognitive Assessment

M-WCST= Modified Wisconsin Card Sorting Test

NEAR= Neuropsychoeducational Approach to remediation

NV= NEUROvitalis

NHP= Nottingham Health Profile

PACS= Positive Aspects of Caregiving Scale

Pc= Percentile

PCT = Paper-pencil Cognitive Training

PD= Parkinson´s Disease

PDQ-39= Parkinson's Disease Questionnaire-39

PDQ-8= Parkinson’s Disease Questionnaire Short Form

PDQL= Parkinson’s Disease Quality of Life Questionnaire

PEDro-P= Physiotherapy Evidence Database Rating Scale

PEPP= Parkinson's Education Program

PIMS= Parkinson’s Disease Impact Scale

PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO= Prospective International Registry of Systematic Reviews

Q= Cochrane’s Q test

RCT= Randomized controlled trials

REM= Rapid Eye Movement

SCOPA-PS= Scales for Outcomes in Parkinson’s Disease– Psychosocial

SD= Standard Deviation

SDS= Self-rating Depression Scale

SF-36= Short Form-36 Health Survey

SIP= Sickness Impact Profile

SMD= Standardized Mean Difference

SPCT= Salthouse Perceptual Comparison Test

TMT-A= Trail Making Test-A

ToM= Theory of Mind

UKPDSBB= United Kingdom Parkinson's Disease Society Brain Bank

UPDRS= Unified Parkinson's Disease Rating Scale

VAS= Visual Analogous Scale

VIF= Variance Inflation Factor

WAIS-III = Wechler Adult Intelligence Scale III

WAT= Word Accentuation Test

WHO-DAS II= World Health Organization Disability Assessment Scale

ZBI= Zarit Caregiver Burden Interview

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I. Abstract

1. Abstract

1.1. Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. PD is characterized by the presence of motor and non-motor symptoms that affect the quality of life of people with PD. Neuropsychiatric symptoms and cognitive impairment are among the most common non-motor symptoms in PD. Non-pharmacological interventions, specifically, cognitive rehabilitation are developed to improve cognition, clinical, and functional impairment of people with PD. As the disease progresses, the need for caregivers becomes essential, resulting in numerous health and psychosocial problems for the careers themselves. However, there is limited research on interventions of family caregivers. Family caregivers´ participation in psychoeducation programs may increase the benefits of cognitive rehabilitation in PD and could improve the quality of life of family caregivers. In addition, an increasing number of studies investigate the impact of motor and non-motor symptoms on the Health-related quality of life (HRQoL) of people with PD. However, studies have not taken into account the possible overlap of HRQoL measures with clinical symptom measures.

This thesis is composed of three studies. The first study analyzed the efficacy of cognitive rehabilitation in PD through a systematic review and meta-analysis. The second study aimed to evaluate the efficacy of a combined intervention of cognitive rehabilitation in PD patients and psychoeducation in their family caregivers. The third study analyzed predictors of HRQoL in PD before and after removing the overlap of items between HRQoL and clinical measures.

The systematic review in *study I* revealed that attention, working memory, verbal memory, executive functions, and processing speed were the domains that most frequently showed improvements after cognitive rehabilitation. The results of the meta-

analysis indicated that global cognitive status and working memory showed moderate effect size; verbal memory, overall cognitive functions, attention, executive functions, visual memory, verbal fluency, processing speed, and depression showed small effects; and visuospatial and visuoconstructive abilities and quality of life showed no effect. In *study II*, PD patients of the combined group (cognitive rehabilitation in PD patients + psychoeducation in family caregivers) showed improvements in verbal memory, facial emotion recognition, general health, emotional well-being dimension and communication dimension of HRQoL after cognitive rehabilitation; and family caregivers who participated in psychoeducation showed improvements in general health and anxiety scores. *In study III*, anxiety, fatigue, motor symptoms, and depression were the main predictors of the HRQoL total index in PD patients. However, after controlling overlapping items between HRQoL and clinical measures, fatigue predominated over anxiety, motor symptoms, and depression. In fact, depression was no longer a predictor and neurocognition emerged as a predictor. Regarding dimensions, fatigue predicted mobility, activities of daily living (ADL), emotional well-being, and bodily discomfort dimensions; motor symptoms predicted mobility, ADL, social support, and communication dimensions; anxiety predicted social support, cognition, and bodily discomfort dimensions; and neurocognition predicted communication dimension.

In conclusion, findings suggest that cognitive rehabilitation may be beneficial in improving the cognitive functions of people with PD. Moreover, the combined application of cognitive rehabilitation in PD and psychoeducation in family caregivers can provide a comprehensive approach to PD patients and their families, promoting the benefits of cognitive rehabilitation in PD and providing family caregivers with the necessary techniques to improve their health. Finally, fatigue, anxiety, motor symptoms, and neurocognition, but not depression, were identified as the main predictors of HRQoL

in patients with PD. These results shed light on the importance of taking into account the overlap of items between HRQoL and clinical measures for an accurate interpretation of the results.

Keywords: Parkinson´s disease, family caregivers, intervention, cognitive rehabilitation, psychoeducation, HRQoL, cognition, anxiety, depression, fatigue, neurocognition, motor symptoms.

1.2. Resumen

La enfermedad de Parkinson (EP) es la segunda enfermedad neurodegenerativa más común después de la enfermedad de Alzheimer. La EP se caracteriza por la presencia de síntomas motores y no motores que afectan a la calidad de vida de las personas con EP. Los síntomas neuropsiquiátricos y el deterioro cognitivo se encuentran entre los síntomas no motores más comunes de la EP. Las intervenciones no farmacológicas, en concreto la rehabilitación cognitiva, son intervenciones desarrolladas para mejorar el deterioro cognitivo, clínico, y funcional de las personas con EP. A medida que la enfermedad avanza, la necesidad de un cuidador es imprescindible, lo que conlleva numerosos problemas de salud y psicosociales para los propios cuidadores. Sin embargo, la investigación sobre las intervenciones de los familiares cuidadores es limitada. La participación de los familiares cuidadores en programas de psicoeducación puede aumentar los beneficios de la rehabilitación cognitiva en la EP y podría mejorar la calidad de vida de los familiares cuidadores. Además, cada vez más estudios investigan el impacto de los síntomas motores y no motores en la Calidad de Vida Relacionada con la Salud (CVRS) de las personas con EP. Sin embargo, los estudios no tienen en cuenta el posible solapamiento de las medidas de CVRS con las medidas de los síntomas clínicos.

Esta tesis se compone de tres estudios. El primer estudio analizó la eficacia de la rehabilitación cognitiva en personas con EP a través de una revisión sistemática y un meta-análisis. El segundo estudio tenía como objetivo evaluar la eficacia de una intervención combinada de rehabilitación cognitiva en pacientes con EP y psicoeducación en sus familiares cuidadores. El tercer estudio analizó los predictores de la CVRS en la EP antes y después de eliminar el solapamiento de ítems entre la CVRS y las medidas clínicas.

La revisión sistemática del *estudio I* mostró que la atención, la memoria de trabajo, la memoria verbal, las funciones ejecutivas, y la velocidad de procesamiento fueron los dominios que con mayor frecuencia mostraron mejoras tras la rehabilitación cognitiva. Los resultados del meta-análisis indicaron que el estado cognitivo global y la memoria de trabajo mostraron tamaños del efecto moderados; la memoria verbal, las funciones cognitivas globales, la atención, las funciones ejecutivas, la memoria visual, la fluidez verbal, la velocidad de procesamiento, y la depresión mostraron efectos pequeños; y las habilidades visoespaciales y visoconstructivas y la calidad de vida no mostraron ningún efecto. En el *estudio II*, los pacientes con EP del grupo combinado (rehabilitación cognitiva en pacientes con EP + psicoeducación en familiares cuidadores) mostraron mejoras en la memoria verbal, el reconocimiento de emociones faciales, la salud general, la dimensión de bienestar emocional y la dimensión de comunicación de la CVRS tras la rehabilitación cognitiva; y los familiares cuidadores que participaron en la psicoeducación mostraron mejoras en las puntuaciones de salud general y ansiedad. En el *estudio III* la ansiedad, la fatiga, los síntomas motores, y la depresión fueron los principales predictores del índice total de la CVRS en los pacientes con EP. Sin embargo, tras controlar el solapamiento de ítems entre la CVRS y las medidas clínicas, la fatiga predominó sobre la ansiedad, los síntomas motores, y la depresión. De hecho, la depresión dejó de ser un predictor y la neurocognición surgió como un predictor. En cuanto a las dimensiones, la fatiga predijo las dimensiones de movilidad, actividades de la vida diaria (AVD), bienestar emocional, y malestar corporal; los síntomas motores predijeron las dimensiones de movilidad, AVD, apoyo social, y comunicación; la ansiedad predijo las dimensiones de apoyo social, cognición, y malestar corporal; y la neurocognición predijo la dimensión de comunicación.

En conclusión, los resultados sugieren que la rehabilitación cognitiva puede ser beneficiosa para mejorar las funciones cognitivas de las personas con EP. Además, la aplicación combinada de la rehabilitación cognitiva en la EP y la psicoeducación en sus familiares cuidadores puede proporcionar un enfoque integral a los pacientes con EP y sus familias, promoviendo los beneficios de la rehabilitación cognitiva en la EP y proporcionando a los familiares cuidadores las técnicas necesarias para mejorar su salud. Por último, se identificó que la fatiga, la ansiedad, los síntomas motores, y la neurocognición, pero no la depresión, eran los principales predictores de la CVRS en pacientes con EP. Estos resultados arrojan luz sobre la importancia de tener en cuenta el solapamiento de los ítems entre la CVRS y las medidas clínicas para realizar una interpretación precisa de los resultados.

Palabras clave: Enfermedad de Parkinson, familiares cuidadores, intervención, rehabilitación cognitiva, psicoeducación, CVRS, cognición, ansiedad, depresión, fatiga, neurocognición, síntomas motores.

II. Introduction

2. Introduction

2.1. Parkinson´s disease

Parkinson's disease (PD) is a neurodegenerative disease characterized by motor and non-motor symptoms (Poewe et al., 2017). This disease was first mentioned by the doctor James Parkinson in 1817 as paralysis agitans or shaking palsy in his monograph entitled "*An Essay on the Shaking Paralysis*", and was later designated with the term Parkinson's disease by Jean-Marie Charcot (Goetz, 2011).

PD is the second most frequent neurodegenerative disease and the most common movement disorder of the central nervous system (Aarsland et al., 2021; Tysnes & Storstein, 2017). It is one of the main reasons for neurological consultation in Spain (García-Ramos et al., 2016), it has a negative impact on the quality of life of approximately 120,000-150,000 people, and its prevalence is expected to increase in the future (Santos-García et al., 2021).

The incidence of PD increases with age (Hirsch et al., 2016), affecting 1% of the population over 65 years of age (Aarsland et al., 2021). PD is approximately one to four times more common in men than in women (Dorsey et al., 2018), specifically between the ages of 60 and 79 (Hirsch et al., 2016). The etiology of PD in most cases is multifactorial, due to a combination of environmental and genetic factors (Simon et al., 2020). Three to five percent of cases are affected by a genetic variant, whereas, the majority of cases in PD are idiopathic (Klein & Westenberg, 2012). The risk of developing PD can be increased due to toxic chemicals exposure and head trauma (Simon et al., 2020).

The neuropathological features of PD consist of degeneration of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies containing misfolded alpha-synuclein (Balestrino & Schapira, 2020; Tolosa et al., 2021; Tysnes &

Storstein, 2017). At the time of diagnosis, degeneration of dopaminergic neurons and extension of degeneration to other regions of the central nervous system have already been observed (Balestrino & Schapira, 2020). As the disease progresses, a deterioration in components of the autonomic, limbic, and somatomotor systems is detected, extending to the neocortex (Braak et al., 2004).

2.2. Diagnosis of Parkinson's disease

The diagnosis of PD is mainly based on clinical criteria (Jankovic, 2008). The first formal criteria for diagnosing PD was created by the United Kingdom Parkinson's disease Society Brain Bank (UKPDSBB) (Hughes et al., 1992), in which the diagnosis is made by a three-step process: 1) Diagnosis of Parkinsonian syndrome; 2) Exclusion criteria for PD; and 3) Supportive prospective positive criteria for PD. Additionally, the Movement disorder Society (MDS) Task Force, proposed a clinical diagnosis of PD for use in clinical research based on: 1) Diagnosis of Parkinsonism; 2) Exclusion criteria; 3) Supportive criteria; 4) Red flags; 5) Clinically established PD; and 6) Clinically probable PD (Postuma et al., 2015).

Once the diagnosis is made, two specific scales are usually used to evaluate the evolution of the disease: the Unified Parkinson Disease Rating Scale (UPDRS) (Martínez-Martín et al., 1994; Movement Disorder Society [MDS] Task Force on Rating Scales for Parkinson's Disease, 2003) and the Hoehn and Yahr (H&Y) scale (Hoehn & Yahr, 1967). The UPDRS evaluates the severity and progression of the disease by means of four subscales: 1) Mentation, behavior, and mood; 2) Activities of Daily Living; 3) Motor examination; and 4) Complications of therapy (Martínez-Martín et al., 1994; MDS Task Force on Rating Scales for Parkinson's Disease, 2003). The H&Y scale (Hoehn & Yahr, 1967) is used to assess the evolution of the disease. This scale evaluates motor dysfunction by means of five stages: 1) Unilateral symptoms with minimal or no

functional disability; 2) Bilateral symptoms without balance impairment; 3) Mild to moderate bilateral symptoms, some postural instability but physically independent; 4) Severe symptoms but still able to walk or stand unassisted; and 5) Confinement to bed or wheelchair, unless with assistance. Later, this scale was adapted to incorporate two other intermediate stages (Goetz et al., 2004).

2.3. Motor and non-motor symptoms of Parkinson`s disease

PD has been known as a primary motor disorder characterized by bradykinesia, resting tremor, and rigidity, as well as postural instability and gait alterations (Poewe et al., 2017; Tolosa et al., 2021). Bradykinesia, rigidity, tremor, and gait alterations are named as the classic or cardinal motor symptoms that occur in the early stages of the disease. Postural alterations, freezing of gait, balance alterations, and dysarthria and dysphagia are usually present in later stages of the disease (Tolosa et al., 2021).

Although PD has been considered a motor disorder, non-motor symptoms may develop in the prodromal phase, several years before the onset or manifestation of motor symptoms (Hanagasi et al., 2017). In the early stages of the disease, non-motor symptoms such as olfactory loss, sleep disturbances, autonomic dysfunction, pain and somatosensory disturbances, mild cognitive impairment (MCI), and neuropsychiatric features are observed (Tolosa et al., 2021). The main non-motor symptoms of PD are shown in Table 1.

As the disease progresses, early non-motor symptoms often persist and worsen at this stage, and the prevalence of the development of dementia increases with the duration of the disease (Tolosa et al., 2021).

Table 1

Non-motor symptoms of PD

Non-motor symptoms	
Olfactory dysfunction	Olfactory dysfunction (hyposmia and anosmia) is an early and sensitive marker of the preclinical phase of PD usually occurring in 90% of people with PD (Doty, 2012). Hyposmia can help to differentiate PD from other causes of Parkinsonism, and may also help to identify "premotor" PD due to early pathological involvement of the olfactory pathways (Fullard et al., 2017).
Sleep disorders	Sleep disorders are present in 30% of people with PD (Hu et al., 2015). These disorders are rapid eye movement (REM)-sleep behavior disorder, restless-legs syndrome, daytime sleepiness with sleep attacks, and insomnia (Schrempf et al., 2014).
Autonomic dysfunction	Autonomic dysfunction includes constipation, erectile dysfunction, urinary urgency or incontinence, delayed gastric emptying, orthostatic hypotension, and heat intolerance (Tolosa et al., 2021). Dysautonomia is a common and disabling symptom of PD, with a prevalence of 30-40% (Merola et al., 2018).
Chronic pain	Pain is present from the early stages of the disease with a prevalence ranging from 34% to 83%, causing suffering and disability in PD and impacting their quality of life (Rotondo et al., 2019). In some patients, the severe and intractable pain of the disease predominates over the motor symptoms (Ford, 2010).
Mild cognitive impairment (MCI)	Mild cognitive impairment (MCI) is another important non-motor feature of PD due to its prevalence. It is defined by changes in cognitive functions and alterations in neuropsychological tests, but activities of daily living (ADL) are relatively unimpaired (Dunne et al., 2021).
Neuropsychiatric symptoms	Neuropsychiatric symptoms identified by studies in PD range from 70-90% (Dlay et al., 2020), being depression, apathy, anxiety, and fatigue the most common neuropsychiatric symptoms (Schapira et al., 2017).

2.3.1. Cognitive impairment in Parkinson's disease

Interest in cognitive impairment in PD has increased because it is one of the most important non-motor manifestations of PD (Aarsland et al., 2021). Cognitive changes may occur before, at the time of diagnosis or decades later, with great variability in the rate of progression (Aarsland et al., 2021). At the time of diagnosis, 20% of people with PD have cognitive impairment (Aarsland et al., 2011), with 40% of PD patients developing MCI during the course of the disease (Baiano et al., 2020). In addition, patients with PD may have some degree of cognitive deficits which do not significantly affect their functional independence after the diagnosis (Martínez-Horta & Kulisevsky, 2019), although difficulties may be observed in more complex functional tasks (Litvan et al., 2012). With disease progression and deterioration of cognitive functioning, the risk of dementia increases, being four to six times higher than in the general population (Emre et al., 2007; Monchi et al., 2016). It is estimated that 10% of PD patients develop dementia after 3 years (Williams-Gray et al., 2007), 17% of PD patients after 5 years (Williams-Gray et al., 2009), 46% after 10 years (Williams-Gray et al., 2013), 80-83% of PD patients with cognitive impairment develop dementia after 20 years (Hely et al., 2008; Monchi et al., 2016) and in the long term only 15% of people with PD maintain intact cognition (Aarsland et al., 2010).

It is essential to perform an accurate diagnosis of cognitive impairment in PD patients (Aarsland et al., 2021). Early studies described the neuropsychological deficits of PD-MCI in terms of the tests observed in Alzheimer´s Disease (AD)-type MCI defined by Petersen and colleagues (1999): (1) memory complaint preferably corroborated by an informant; (2) objective memory impairment; (3) preserved general cognitive functions; (4) minimal influence on impairment in daily functioning; and (5) absence of dementia (Petersen et al., 1999). These criteria have been adapted over time (Petersen et al.,

2014). However, the need for unification of criteria for establishing the specific diagnosis of MCI in PD was recognized for the identification of (1) the clinical features of the initial stage of cognitive impairment in PD; (2) the most accurate indicators of PD-MCI to PD-dementia conversion; (3) the impact of PD-MCI on daily functioning and quality of life; (4) a patient population that is well-characterized and a possible clinical trial outcome measure; and (5) a helpful clinical entity that will improve communication among clinicians, patients, caregivers, and researchers, enhancing both patient care and research activities (Litvan et al., 2012). For this reason, MDS established two types of classification of MCI in PD: level I (abbreviated assessment) and level II (comprehensive assessment) (Litvan et al., 2012) (Table 2).

Table 2

Specific guidelines for PD-MCI types

Specific guidelines for PD-MCI level I and level II categories (Litvan et al., 2012)
Level I: Abbreviated Assessment
• This level provides a diagnosis of MCI with an abbreviated cognitive assessment or a global cognitive scale. • This level provides less diagnostic certainty than level II.
Level II: Comprehensive Assessment

• This level recommends an extensive testing including at least two tests per cognitive domain (attention and working memory, executive functions, language, memory, and visuospatial abilities).
• The impairment must be present in at least two tests, either within one cognitive domain or across different cognitive domains.
  o Single-domain subtype: Impairment of one cognitive domain, by the presence of two impaired tests.
  o Multiple domains: Impairment in at least one test in two or more cognitive domains.

In general, people with PD show greater impairment in all neuropsychological tests compared to healthy controls (Aarsland et al., 2009). Research has focused on early cognitive changes, with executive functions and visuospatial abilities being the most altered cognitive domains (Aarsland et al., 2021). These alterations may be accompanied by memory impairment, which increases the risk of early progression to dementia (Aarsland et al., 2021). In fact, a meta-analysis showed that visuospatial abilities, verbal memory, and frontal executive domains are impaired in PD in comparison to healthy subjects (Curtis et al., 2019). Generalized cognitive impairment is an important aspect of the profile of PD without dementia (Curtis et al., 2019). A meta-analysis of initially non-demented PD patients revealed, as the disease progresses, a significant decline in global cognitive ability, visuoconstructive abilities, and memory (Muslimovic et al., 2007). A summary of the main findings in cognitive functioning in PD will be presented below:

Attention. In prodromal PD, attention appears to be less affected than other cognitive domains (Fengler et al., 2017). Attention system has limited capacity (McKinlay, 2013) and its performance could be affected when the task requires more attentional capacity than is available (Rochester et al., 2004). PD patients with MCI and attentional processing deficits are more likely to develop dementia (J. Yang et al., 2021).

Memory. Memory performance is the most diverse and complex of the cognitive domains (Ross & Favela, 2019). Memory impairment is a featured aspect in the prodromal phase and early PD (Liepelt-Scarfone et al., 2022). Memory deficits in PD have been traditionally related to a deterioration in the retrieval process, but acquisition and learning are also impacted in the disease (Chiaravalloti et al., 2014). A meta-analysis showed impairment in tests of working memory in PD patients (Siegert et al., 2008), specifically, a small impairment was observed in the verbal span, while complex verbal tasks and simple and complex visuospatial tasks showed a moderate impairment,

suggesting a more pronounced impairment in visuospatial than verbal memory management (Siegert et al., 2008). Additionally, another meta-analysis suggested moderate deficits in verbal memory of people with PD (Curtis et al., 2019).

Visuoconstructive and visuospatial abilities. Visuospatial abilities are impaired in prodromal (Fengler et al., 2017) and early stages of PD (Aarsland et al., 2021; Curtis et al., 2019). As the disease progresses, visuoconstructive abilities are also impaired in PD patients (Muslimovic et al., 2007), being a predictor of dementia risk (Williams-Gray et al., 2009).

Executive functions. Executive functions impairment is one of the first cognitive problems identified in the prodromal phase (Fengler et al., 2017) and early stages of PD (Aarsland et al., 2021; Curtis et al., 2019; Kudlicka et al., 2011). In addition, a meta-analysis showed deficits in different subcomponents of executive functions (cognitive flexibility, inhibition, selective attention/working memory, and concept formation) in PD patients in comparison to controls (Kudlicka et al., 2011). However, as this meta-analysis suggests, there is a lack of consensus in the selection and interpretation of the measures used to assess executive function (Kudlicka et al., 2011).

Cognitive flexibility. The inhibition related to cognitive flexibility has also been found negatively impacted in PD (Siquier & Andrés, 2021). Furthermore, these results are supported by a meta-analysis examining executive functions in PD, suggesting that cognitive flexibility is impaired in PD (Kudlicka et al., 2011).

Processing speed. Processing speed is a basic characteristic that underlies other higher cognitive processes, so the impact of impaired processing speed is most prominent in multi-step complex tasks (Marco et al., 2012). In PD, several studies have shown that processing speed is impaired (Cholerton et al., 2021; Nguyen et al., 2017; Sawamoto et al., 2002). Cognitive and motor slowing occurs from the early stages of the disease, so

decreased performance on other cognitive tasks before significant deterioration may be related to reducing psychomotor speed (Cholerton et al., 2021). Another study analyzed processing speed without the motor component, showing the existence of cognitive slowing, although they also found an association with motor slowing (Sawamoto et al., 2002).

Verbal fluency. Deficits in verbal fluency are often assessed using semantic and phonemic categories (McKinlay, 2013). A meta-analysis showed that both phonemic and semantic fluency were moderately impaired in PD, but a greater impairment was observed in semantic fluency (Henry & Crawford, 2004), being also an impairment in semantic fluency a predictor of dementia (Williams-Gray et al., 2009).

Theory of mind (ToM). ToM is the ability to attribute mental states (beliefs, intentions, and desires) to itself and others (Bora et al., 2015; Freedman & Stuss, 2011), in addition to understanding and predicting their behavior, which makes it a fundamental ability to adapt to the social environment (Bora et al., 2015). ToM is a less studied variable that is affected from the early stages of PD (Poletti et al., 2011), but may become more severe as the disease progresses (Bora et al., 2015). ToM is a multidimensional construct that can be divided into affective and cognitive ToM. Affective ToM refers to the capacity to infer how a person feels, whereas cognitive ToM relates to the ability to form inferences about beliefs and motives (Shamay-Tsoory et al., 2010). One meta-analysis showed that both cognitive and affective ToM tasks were impaired in people with PD with mild to moderate levels of the disease (Bora et al., 2015).

Facial Emotion Recognition. Facial emotion recognition is a fundamental characteristic of emotional functioning and social behavior (Argaud et al., 2018). Deficits in emotion recognition are linked to impoverished social competence, interpersonal functioning, and communication, as well as lower quality of life (Ruffman et al., 2009).

Sixty-four percent of the studies included in a systematic review indicated that emotion recognition is impaired in PD, with negative emotions being the most affected (Argaud et al., 2018).

2.3.2. Clinical symptoms in Parkinson's disease

People with PD show a negative impact on quality of life (Martínez-Martín et al., 2011), due to both motor and non-motor symptoms, including neuropsychiatric aspects, such as anxiety, depression, apathy, and fatigue (Poewe et al., 2017; Schapira et al., 2017).

Depression and anxiety may appear even before the onset of the first motor symptoms or before the diagnosis of PD is made (Schrag, 2006). According to a systematic review, the prevalence range of depressive disorders in PD is variable (2.7% to 90%), with clinically significant depressive symptoms being present in 35% of PD patients (Reijnders et al., 2008). In most PD samples, the severity of depressive symptoms ranges from mild to severe (Chikatimalla et al., 2022). The overlap of symptoms between depressive disorders and PD increases the difficulty in detecting depression in PD patients, making the diagnosis of depression more difficult (Schrag, 2006).

A range of physiological, neurochemical, and sociocultural factors are attributed to anxiety in PD (Chen & Marsh, 2014). Anxiety is one of the primary symptoms of PD and in some cases, it might be a subsequent reaction to the PD diagnosis (Khatri et al., 2020). Anxiety symptoms affected approximately 25.7% of people with PD (Broen et al., 2016), but it is often undiagnosed and untreated (Pontone et al., 2019).

Apathy has been linked to progressive cognitive decline in several neurodegenerative diseases (Pagonabarraga et al., 2015). Apathy is a characteristic symptom of PD (Dujardin et al., 2007), especially in patients with cognitive complications (Dujardin et al., 2007). Apathy appears at all the stages of PD, including in prodromal and advanced stages of PD (De Waele et al., 2022). Its prevalence is around

40% in PD (den Brok et al., 2015). However, levels of apathy might vary among patients (De Waele et al., 2022).

Fatigue is another non-motor symptom that appears in the early stages of the disease and persists throughout the disease process (Chaudhuri et al., 2005). Lou and colleagues' study (2001) showed increased levels of general and physical fatigue in patients with PD (Lou et al., 2001). Its prevalence is around 50% in PD patients (Siciliano et al., 2018), being one of the three most disabling symptoms of PD (Friedman, 1993).

2.4. Health-related quality of life in Parkinson´s disease

The impact of motor and non-motor symptoms of patients with PD influence the patient's expectation of functionality and physical, social, and mental well-being, as well as the person's quality of life (Cano-de la Cuerda et al., 2010). Health-related quality of life (HRQoL) involves life satisfaction perception of the patient and self-evaluation of the experience and effects of the disease, being the physical and psychological dimensions, functional capacity, and social interactions the most significant aspects (Klepac et al., 2008; Martínez-Martín et al., 2011; WHOQOL Group, 1993). HRQoL can be considered as a resulting assessment of a disease's complete influence on a patient's life (Klepac et al., 2008).

The way to assess HRQoL differs between studies. Some of the most recommended instruments to measure this concept in PD are EuroQoL (EQ-5D), Nottingham Health Profile (NHP), Short Form-36 Health Survey (SF-36), Sickness Impact Profile (SIP), and 5 PD specific scales; Parkinson’s Disease Questionnaire-39 (PDQ-39), Parkinson’s Disease Questionnaire Short Form (PDQ-8), Parkinson’s Disease Quality of Life Questionnaire (PDQL), Parkinson’s Disease Impact Scale (PIMS) and Scales for Outcomes in Parkinson’s Disease– Psychosocial (SCOPA-PS) (Martínez-Martín et al., 2011). Nevertheless, PDQ-39 is the most commonly used instrument for

HRQoL assessment (Martínez-Martín et al., 2011). This questionnaire has been designed to assess different aspects of functioning and well-being of people affected by PD through eight different dimensions (Jenkinson et al., 1997). These dimensions are mobility, ADL, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort (Jenkinson et al., 1997; Martínez-Martín & Frades, 1998).

Additionally, loss of independence and disability are essential outcome variables in PD. Functional dependency is characterized by the need to receive assistance with basic ADL such as walking, washing, dressing, toileting, and feeding (Macleod & Counsell, 2016). In fact, a systematic review identified observational studies on dependence in PD with at least a three-year follow-up. The results showed that the risk of dependence in newly diagnosed PD patients was 10-25% at 5 years and 20-50% at 10 years (Macleod et al., 2016). However, functional dependence has not been studied enough in PD (Macleod & Counsell, 2016). In fact, in order to set treatment priorities and reduce the effects of the functional and emotional consequences of PD in patients, identification of the most important predictors of HRQoL is essential (Soh et al., 2011). Motor complications decrease significantly the HRQoL of people with PD (Chapuis et al., 2005; Schrag et al., 2000), specifically, symptoms such as instability, gait disturbances, and fluctuations are the characteristics that most influence HRQoL (Gómez-Esteban et al., 2007). However, in recent years the study of the impact of non-motor symptoms in HRQoL has gained a more important role. Depression has been reported as the main determinant of HRQoL in PD (Schrag, 2006; Schrag et al., 2000; Soh et al., 2011), showing that the higher the depressive symptoms, the worse the HRQoL (Menon et al., 2015; Schrag, 2006; Schrag et al., 2000). Although research generally focuses on depressive symptoms, anxiety is a common symptom in PD (Broen et al., 2016) and both have been reported to affect the quality of life of people with PD (Carod-Artal et al., 2008; Hanna & Cronin-Golomb,

2012; Schrag, 2006). Additionally, fatigue is also recognized as one of the most disabling symptoms of PD (Friedman et al., 2010). However, it has not been such a studied predictor as anxiety and depression. Fatigue was a significant predictor of HRQoL in four of the five studies included in one systematic review (Soh et al., 2011). In fact, a meta-analysis suggests that PD patients with fatigue had worse HRQoL compared to PD patients without fatigue (Siciliano et al., 2018). Finally, cognition has not been studied as often as the clinical and motor variables of the disease. Most of the studies that have assessed predictors of HRQoL in PD have analyzed cognition with cognitive functioning screening tests (Cubo et al., 2002; Hanna & Cronin-Golomb, 2012; Kadastik-Eerme et al., 2015; Ophey et al., 2018; Schrag et al., 2000; Simpson et al., 2014; Sławek et al., 2005). Therefore, further research is needed to analyze the impact of cognition on HRQoL using a comprehensive neuropsychological assessment.

Research has increased the focus on the study of predictors of HRQoL, but predictors of HRQoL dimensions have been less studied. Studies have shown that the main predictors of HRQoL dimensions are depression and anxiety (Jones et al., 2015; McKinlay et al., 2008; Simpson et al., 2014; Tu et al., 2017), although fatigue (Havlikova, 2008; McKinlay et al., 2008; Tu et al., 2017) and UPDRS (Havlikova, 2008; Simpson et al., 2014; Tu et al., 2017) also predict some of these dimensions. Regarding cognition, although some studies have explored its impact on HRQoL dimensions (Simpson et al., 2014; Stegemöller et al., 2014; Tu et al., 2017), only one study that evaluated verbal fluency and working memory found that both functions were predictors of mobility, ADL, cognition, and communication dimensions (Stegemöller et al., 2014). Most publications published to date have incorporated clinical variables and HRQoL measurements, but these studies have not considered the possible conceptual and empirical overlap between the measures (Hays & Fayers, 2021). In fact, most of the quality of life measures include

emotional distress as a construct (Hays & Fayers, 2021; Katschnig, 2006), with particular questions that actually reflect psychopathology (Aigner et al., 2006; Katschnig, 2006), like depressive symptoms (Aigner et al., 2006; Hays & Fayers, 2021) and anxiety. As a result, it would be logical that quality of life is linked to measurements of psychopathology (Hays & Fayers, 2021; Katschnig, 2006). Controlling for the presence of psychopathological items in quality of life measures is suggested (Katschnig, 2006) because the recognition of the overlap between these variables is necessary for interpreting correlations and avoiding false causal inferences (Hays & Fayers, 2021).

2.5. Treatments in Parkinson´s disease

Treatments for PD are mainly pharmacological. Levodopa is the most effective pharmacological therapy for PD (Connolly & Lang, 2014; Lee & Yankee, 2021). Other pharmacological treatments for the reduction of motor symptoms are dopamine agonists, monoamine oxidase-B inhibitors (MAOIs), catechol-O-methyl transferase inhibitors (COMTIs), and anticholinergics (Connolly & Lang, 2014; Salat & Tolosa, 2013). Dopamine agonists are effective to reduce the risk of motor complications (Salat & Tolosa, 2013). There is no known cure for PD, but pharmacological, surgical, and non-pharmacological interventions, such as physical, occupational, speech, and cognitive behavioral therapies, have been developed for the treatment of PD that reduce the symptoms of the disease (Lee & Yankee, 2021). In addition, new interventions are emerging to reduce the side effects of pharmacological treatments and the symptoms of PD (Lee & Yankee, 2021).

Non-pharmacological therapies are theoretically supported, targeted, and replicable interventions delivered with the patient or caregiver that are potentially capable of obtaining significant benefits (Olazarán et al., 2010). Furthermore, these interventions are increasingly recognized as valuable treatment options to address cognitive and

functional deficits in people with PD (Van de Weijer et al., 2018) and their family caregivers. Cognitive rehabilitation is proposed as a non-pharmacological therapy (Petersen et al., 2014) and personalized medicine strategy for the management of cognitive impairment (Titova & Chaudhuri, 2017a, 2017b). This intervention can be administered along with other pharmacological therapies (Calleo et al., 2012).

2.5.1. Cognitive rehabilitation in Parkinson's disease

To reduce and prevent cognitive deficits, cognitive rehabilitation interventions have been developed in PD (Díez-Cirarda et al., 2018a), based theoretically on three principles (Zangill, 1947) (Figure 1). These interventions consist in the execution of repetition of cognitive tasks to improve cognitive functions (Biundo et al., 2017).

Figure 1

Cognitive rehabilitations´ three basic principles

Restoration	Compensation	Optimization
Restoration refers to the recovery of a lost function and the reactivation of brain circuits through repetition of exercises and tasks	Compensation is based on compensating for the lost function through external aids and alternative strategies	Optimization works on the preserved cognitive systems to compensate for the loss of a function

Note: Figure created based on the three cognitive rehabilitations' principles proposed by Zangill (Zangill, 1947).

Cognitive rehabilitation studies in PD have used different cognitive rehabilitation programs such as "Rehacom" (Cerasa et al., 2014), "NeuroVitalis" (Petrelli et al., 2014), "CoRE" (Bernini et al., 2020), "Neuronation" (Ophey et al., 2020), "Neuropsychoeducational Approach to Remediation (NEAR)" (Naismith et al., 2013), "SmartBrain" (París et al., 2011), and REHACOP (Peña et al., 2014).

Format (group vs. individual), modality (paper/pencil or computer-based exercises), frequency and length of sessions, duration of the complete intervention,

standardized vs. personalized, qualifications and training of the therapists are different between the programs (Díez-Cirarda et al., 2018a). The REHACOP program is a comprehensive cognitive rehabilitation program based on the three basic principles by training cognition, social cognition, social skills, and functional skills (Ojeda et al., 2012). The efficacy of this program has been initially demonstrated in pathologies such as psychosis and schizophrenia (Peña et al., 2016; Sánchez et al., 2014). However, this program has been also validated in elderly people (Montoya-Murillo et al., 2020) and neurodegenerative diseases such as multiple sclerosis (Rilo et al., 2018) and PD (Peña et al., 2014). The REHACOP program will be explained in more detail in the methodology section 4.5.1.

There are several systematic review studies that examine the benefits of cognitive rehabilitation in PD, but few meta-analyses have analyzed the effectiveness of cognitive rehabilitation in PD (Lawrence et al., 2017; Leung et al., 2015; Orgeta et al., 2020). In 2015, Leung and colleagues (2015) conducted the first meta-analysis focused on the analysis of seven randomized controlled trials (RCTs), in which they showed improvements in working memory, executive functions, and processing speed (Leung et al., 2015). In 2017, Lawrence and colleagues (2017) examined the effectiveness of cognitive rehabilitation and repetitive transcranial magnetic stimulation (rTMS) interventions, and found improvements in attention/working memory, memory, and executive functions only after cognitive rehabilitation (Lawrence et al., 2017). In 2020, Orgeta and colleagues (2020) published the latest meta-analysis, which covered the effects of cognitive rehabilitation from seven RCTs in PD patients with MCI or dementia (excluding PD patients without MCI or dementia), and found no evidence of cognitive improvement after cognitive rehabilitation (Orgeta et al., 2020). Therefore, it is essential

to conduct an updated review of the literature to include and analyze the effect sizes that have been published to date.

In general, studies included in the meta-analyses analyzing the effects of cognitive rehabilitation differ in format, modality, duration and frequency of intervention, and therapist qualifications and training (Díez-Cirarda et al., 2018a). In addition, variables such as disease characteristics and progression could also interfere with the benefit of rehabilitation in people with PD (Vlagsma et al., 2016). However, despite these differences, meta-analyses have shown the benefits of cognitive rehabilitation on cognition in people with PD (Lawrence et al., 2017; Leung et al., 2015).

Additionally, most of the cognitive rehabilitation research in PD has been focused on the study of cognition, while depression, functionality, and quality of life have not been frequently studied. The benefits of cognitive rehabilitation on these variables have been observed through transference effects (Díez-Cirarda et al., 2018b). However, although significant changes in depressive symptoms have been observed in some studies, the results of a meta-analysis indicated that there is no evidence of an effect of cognitive rehabilitation in improving depressive symptomatology (Leung et al., 2015). These results may be due to the exclusion of patients with a diagnosis of depression in some of the studies included in the meta-analysis. Along the same lines, there is also no evidence of the impact of cognitive rehabilitation on quality of life in people with PD (Leung et al., 2015) and in people with PD with cognitive impairment or dementia (Orgeta et al., 2020). In addition, quality of life is usually assessed using the PDQ-39 questionnaire, however, the lack of evidence found in meta-analyses may be due to the fact that most studies only analyze the overall score of the questionnaire and not its different dimensions.

Other functional and clinical variables present from the onset of the disease, such as anxiety, apathy, and fatigue have been analyzed in certain studies. One study found

improvements in the functional and mood states of PD patients after a multidisciplinary intervention consisting of motor, cognitive, and language training (Lo Buono et al., 2021). However, only one study has observed benefits in functional disability after participating in a specific cognitive rehabilitation program (Peña et al., 2014). In conclusion, cognitive rehabilitation is an effective treatment for the improvement of cognitive performance. However, its implication on clinical and functional variables is unclear, so further studies are needed.

2.6. Family caregivers of people with Parkinson's disease

Unfortunately, PD does not only affect the person who suffers from the disease but also their family caregivers (Tew et al., 2013). Since the disease progresses, the need for family caregivers increases (Peters et al., 2011). Most of the studies concerning the care of patients with neurodegenerative diseases such as PD indicate that informal caregivers, usually spouses (Aarsland et al., 1999; de Vugt et al., 2006), often provide such care. In fact, older adults in better health are the ones who become the primary caregiver (Bertrand et al., 2012). Providing care may cause a disconnection with the work environment, social activities, and free time, conditioning their social relations and quality of life (Bhimani, 2014). Moreover, the care of people with PD has a major impact on the physical, emotional, and psychosocial aspects of caregivers, influencing their quality of life (Martínez-Martín et al., 2012).

The role of care is usually lower in the early stages of the disease (Greenwell et al., 2015). However, in the case of neurodegenerative diseases, the role of the caregiver is progressive over time, when disease management becomes more complex (Tessitore et al., 2018). These caregivers usually provide several years of care, continuously adapting to the demands of the disease (de Vugt et al., 2006). As the disease progresses, people with PD show greater difficulty in carrying out ADL so the presence of a caregiver is

critical, leading to an increased caregiver´s burden (Greenwell et al., 2015; Leiknes et al., 2010; Rodríguez-Violante et al., 2015).

Caregivers may suffer from distress and have a lower quality of life due to patients' and caregivers' sociodemographic, psychological, and disease aspects which have been identified in different studies (Martínez-Martín et al., 2012). A systematic review showed that the depression of PD patients, their mental state, and neuropsychiatric symptoms were the most influential predictors of caregiver burden (Greenwell et al., 2015). The burden associated with neuropsychiatric problems is variable; the presence of apathy, irritability, depression, and anxiety is also associated with caregiver distress, being a common problem even at the time of PD diagnosis, which underlies the importance of focusing on affective states in the early treatment of PD (Leiknes et al., 2010).

On the other hand, the impact of caregiving on the family may also be conditioned by the age of the family caregivers (de Vugt et al., 2006; Tew et al., 2013), as the care provided by spouses may be affected by age-related cognitive impairment (de Vugt et al., 2006). In addition to age-related impairment, exposure to chronic stressful situations negatively impacts people's cognitive abilities, showing poorer general cognitive performance and memory dysfunction (Lupien et al., 2007). This impact may be related to a decrease in competence to provide adequate care (de Vugt et al., 2006). The number of studies focusing on family caregivers of people with neurodegenerative diseases has increased. Generally, these studies are focused on caregivers of patients with dementia (Corrêa et al., 2015; de Vugt et al., 2006; Lathan et al., 2016; O'Sullivan et al., 2019). The main results of studies analyzing the care of people with dementia showed that family caregivers had poorer cognitive performance (de Vugt et al., 2006) in domains such as memory (Corrêa et al., 2015; de Vugt et al., 2006) and processing speed (de Vugt et al.,

2006; Lathan et al., 2016). Nonetheless, O'Sullivan and colleagues (2019) showed that family caregivers of people with dementia had faster processing speed than non-caregivers did (O'Sullivan et al., 2019). These results were associated with the healthy caregiver hypothesis (O'Sullivan et al., 2019). This hypothesis suggests that caregiving-related variables may preserve the physical and cognitive health of the family caregiver (Bertrand et al., 2012). This theory was developed by Bertrand and colleagues (2012) through a study of family caregivers of people with osteoporotic fractures, in which they showed that caregivers had better memory and processing speed than non-caregivers (Bertrand et al., 2012).

Therefore, in order to develop appropriate interventions, it is important to identify the risk factors that impact the well-being and the own health of the family caregivers, in order to reduce the burden of the caregivers and improve the quality of life of the patients and their families (Santos-García & de la Fuente-Fernández, 2015).

2.6.1. Interventions for family caregivers

The adaptation process of the family member in the caregiver role may be affected by motor and non-motor symptoms of PD, side effects of treatment, and economic and health care organization resources, contributing to a reduction in the caregiver's well-being (Mosley et al., 2017). Therefore, it is essential to understand their needs, specifically in the areas of increased support and respite, and to provide tailored interventions dedicated to family caregivers (Abendroth et al., 2012). However, more studies related to caregivers are needed due to the increase in PD treatments that increase the survival of these individuals (Abendroth et al., 2012). Additionally, supporting caregivers to mitigate the burden and adapt to the effect of disability on the functioning in the family may help reduce premature institutionalization of the person with PD (Abendroth et al., 2012; Mosley et al., 2017).

Interventions for family caregivers of people with dementia developed to date whose efficacy has been demonstrated have four common characteristics: a psychological and not purely educational approach, multidimensionality, flexibility, and sufficiency in the amount or dose of treatment (Zarit & Femia, 2008). Specifically, interventions focused on the psychoeducational approach apply the general information received during the intervention on a day-to-day basis (Zarit & Femia, 2008). Through psychoeducation, patients and their families improve their knowledge of the disease and treatment, learn to cooperate with caregivers, lead a healthy life and maintain or improve their quality of life (Morin & Franck, 2017). Furthermore, these improvements influence on functional determinants, such as engagement with services (active participation in defining treatment plans and ability to seek service help if needed), resilience, and self-stigma (Morin & Franck, 2017). These programs are usually conducted in a group format in order to learn from each other's feedback and to model behaviors with psychological skills. In addition, psychoeducation is usually conducted weekly for a certain number of sessions (usually 8 to 10) (Gallagher-Thompson et al., 2000). Psychoeducational interventions are the most implemented interventions for caregivers of people with dementia to acquire knowledge, develop coping skills in difficult caregiving situations, and provide social support (Vandepitte et al., 2016). Additionally, studies have shown that psychoeducational interventions are practical interventions that can have protective effects on the caregiver and its burden (Frias et al., 2020; Jensen et al., 2015). This protective effect can occur by increasing their knowledge about the disease and developing problem-solving skills that lead to an improvement in self-efficacy and a reduction in symptoms such as anxiety and depression (Frias et al., 2020).

Few studies have analyzed the effects of psychoeducational programs specifically in PD. Navarta-Sanchez and colleagues (2020) found that both psychoeducational and

educational programs improved quality of life and psychosocial adjustment in PD patients, and psychosocial adjustment and coping skills in family caregivers (Navarta-Sánchez et al., 2020). In another study, the authors analyzed a psychoeducational program in family caregivers and they saw an improvement in the knowledge of the disease and in the competence to cope in difficult caregiving situations (Reuter et al., 2012).

In order to investigate the benefits associated with a specific and standardized educational program for people with PD and their family caregivers, the European consortium (EduPark) has developed a Parkinson's education program (PEPP) (Bayés et al., 2007; Macht et al., 2007). This program is composed of eight working sessions addressing the following aspects: information about the disease, self-regulation/self-monitoring, health promotion, stress and anxiety management, depression and caregiver´s challenge, social skills/competence, social support, and a final summary/evaluation (Bayés et al., 2007; Macht et al., 2007). Specifically, three studies have analyzed the impact of the Edupark psychoeducation program in family caregivers of PD patients (A'Campo, Spliethoff-Kamminga, et al., 2010; A'Campo, Wekking, et al., 2010; Simons et al., 2006). These three studies used the same evaluation measures. Psychosocial problems were evaluated by means of the Belastungsfragebogen Parkinson Angehörigen-kurzversion questionnaire (BELA-A-K) consisting of two scales: (1) bothered by the psychosocial problem, and (2) the need for help for some form of professional support/counseling (Spliethoff-Kamminga et al., 2003). Health state was assessed by EQ-5D, quality of life by PDQ-39, mood by Mood Visual Analogous Scale (VAS), and depression by Self-rating depression scale (SDS) (A'Campo, Spliethoff-Kamminga, et al., 2010; A'Campo, Wekking, et al., 2010; Simons et al., 2006).

The first study using the Edupark psychoeducation program was conducted by Simons and colleagues (2006) in 36 family caregivers of PD patients, but these results

did not show a significant improvement in the BELA-A-K questionnaire, quality of life, health status, and specific depression scale (Simons et al., 2006). A'campo and colleagues (2010) conducted a study with PD patients and their family caregivers involving seven European countries (Estonia, Finland, Germany, Italy, The Netherlands, Spain, and The United Kingdom). The results showed improvements in psychosocial problems, specifically in psychosocial problems and need for help of BELA-A-K questionnaire (A'Campo, Spliethoff-Kamminga, et al., 2010). However, no significant improvements were found in the quality of life, health status, and specific depression scale (A'Campo, Spliethoff-Kamminga, et al., 2010). A'campo and colleagues (2010) conducted another study that analyzed the effectiveness of the Edupark psychoeducation program in PD patients and their family caregivers (A'Campo, Wekking, et al., 2010). In this study, caregivers showed significant improvements in psychosocial problems and caregivers' need for help of BELA-A-K questionnaire and a trend of improvement in quality of life, while depression scale scores did not show any significant improvement (A'Campo, Wekking, et al., 2010). Although these three studies did not show any improvement after the psychoeducation program in the depression scale, mood improved significantly in family caregivers after each psychoeducation session according to the VAS (A'Campo, Spliethoff-Kamminga, et al., 2010; A'Campo, Wekking, et al., 2010; Simons et al., 2006). Incorporating psychoeducation programs and measurements of the impact on cognitive and clinical symptoms can be beneficial for people with PD and their family caregivers. Therefore, further studies conducting combined interventions that include patients and their family caregivers are needed, to enhance the benefits of the interventions and improve the health of both.

III. Approach to the present work, general objectives, and hypotheses

3. Approach to the present work, objectives, and hypotheses

This thesis consists of three studies that analyze the effectiveness of cognitive rehabilitation in PD by a systematic review and meta-analysis (*study I*); efficacy of a combined intervention of a cognitive rehabilitation in people with PD and psychoeducation in their family caregivers (*study II*); and predictors of the HRQoL of people with PD controlling the overlap between HRQoL and clinical measures (*study III*).

3.1. Study I

"Effectiveness of Cognitive Rehabilitation in Parkinson's Disease: A Systematic Review and Meta-Analysis"

Background

Cognitive impairment is a common non-motor symptom in people with PD, which has a direct and negative impact on their quality of life. In order to reduce cognitive impairment and progression to dementia, cognitive rehabilitation programs have been developed.

Objectives

- The main objective of this study was to conduct a systematic review and meta-analysis of the efficacy of cognitive rehabilitation and to analyze whether cognitive rehabilitation improves cognition, functionality, depressive symptoms, and quality of life in PD patients.
- The second objective was to observe the influence of age and years of education, variables related to intervention, baseline global cognitive scores, and PD patient-related features on the effectiveness of cognitive rehabilitation in PD.

Hypotheses

- Cognitive rehabilitation would be effective in order to improve cognition, functionality, depressive symptoms, and quality of life in people with PD.

- Age and years of education, variables related to intervention, baseline global cognitive scores, and PD patient-related features would influence on the effectiveness of cognitive rehabilitation in PD.

3.2. Study II

“Combined intervention of cognitive rehabilitation in patients with Parkinson's disease and psychoeducation in their family caregivers”

Background

Cognitive rehabilitation programs have been used to improve cognition in PD. However, there are a few studies analyzing the impact of psychoeducation on family caregivers. Family participation in psychoeducation programs may enhance the benefits of cognitive rehabilitation in PD patients and improve the quality of life of family caregivers.

Objectives

- The first goal of this study was to evaluate in PD patients the efficacy of a combined intervention of cognitive rehabilitation in PD patients and simultaneous psychoeducation in their family caregivers to improve cognition, mood, functionality, and quality of life.
- The second goal of this study was to analyze in family caregivers the efficacy of the psychoeducation program to improve cognition, mood, functionality, quality of life, and caregiver burden.

Hypotheses

- PD patients who participated in the cognitive rehabilitation program would improve cognition, mood states, functionality, and quality of life. This improvement will be higher in the combined intervention group highlighting the

importance of the involvement of family caregivers in the management of cognitive deficits associated with PD.

- Family caregivers who participated in the psychoeducation program would also show significant improvement in cognitive functioning, mood states, functionality, quality of life, and caregiver burden.

3.3. Study III

"Predictors of Health-Related Quality of Life in Parkinson´s disease: The impact of overlap between Health-Related Quality of Life and clinical measures"

Background

PD is characterized by both motor and non-motor symptoms that negatively affect PD patients' HRQoL. Increasing numbers of studies are analyzing predictors of HRQoL in people with PD. However, the majority of these studies have not taken into account the possible overlap between clinical variables and quality of life measures. Additionally, few studies have investigated predictors of HRQoL dimensions in PD.

Objectives

- The main aim of this study was to investigate simultaneously the predictive value of scores of anxiety, depression, apathy and fatigue, cognition, and motor symptoms that impact on the HRQoL and its dimensions in PD patients.
- The second goal of this study was to observe the predictive value of scores of anxiety, depression, apathy and fatigue, cognition, and motor symptoms after identifying and controlling the overlap between HRQoL items and clinical measures.

Hypotheses

- Anxiety, depression, apathy, fatigue, cognition, and motor symptoms would predict HRQoL and its dimensions.

- The predictive value of anxiety, depression, apathy, fatigue, cognition, and motor symptoms would be different after controlling for the overlapping items between HRQoL and clinical measures.

IV. Methods

4. Methods

Study I

4.1. Study I search strategy

The literature search was conducted in December 2020 and April 2021; and was registered in the Prospective International Registry of Systematic Reviews (PROSPERO) (CRD42021243716). This systematic review and meta-analysis was conducted according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) (Page et al., 2021).

The PubMed database was used to identify studies investigating the efficacy of cognitive rehabilitation in PD. The following search terms were used for the identification and selection of studies: (1) Parkinson's disease and Parkinson disease; (2) cognitive rehabilitation/training/remediation/stimulation; (3) attention; (4) working memory; (5) memory; (6) executive functions; and (7) rehabilitation/training/remediation/stimulation. The terms were combined in order to conduct a more comprehensive search: (1) + (2); (1) + (3) + (7); (1) + (4) + (7); (1) + (5) + (7); and (1) + (6) + (7). The search was filtered by title/abstract. Additionally, the references of the meta-analyses of cognitive rehabilitation in PD published to date were reviewed (Lawrence et al., 2017; Leung et al., 2015; Orgeta et al., 2020). The detailed description of the search strategy used and the number of results obtained can be seen in the supplementary material in Table S1. The eligibility criteria for the systematic review and meta-analysis were based on the following inclusion/exclusion criteria (Table 3).

Table 3

Inclusion and exclusion criteria of papers for the study I

Inclusion criteria	Exclusion criteria
• Patients with a diagnosis of idiopathic PD • PD patients receiving structured cognitive rehabilitation • Analysis of the effects on cognition and (if included in the studies) on functionality, depression, and quality of life • Study design (parallel controlled trials) • Studies that compared structured cognitive intervention with a control group receiving no specific cognitive intervention or unstructured cognitive intervention • Studies assessing outcomes immediately after the intervention period	• Review papers • Single case studies • Conference abstract or presentation • PD patients diagnosed with dementia • Brain stimulation studies • Only neuroimaging data • Lack of available data for effect size estimation • Lack of PD control group • Article language, as those written in any language other than English were excluded

4.2. Quality assessment and risk of bias in the included studies

The Cochrane Manual for Systematic Reviews of Interventions for RCTs (RoB 2 tool) (Sterne et al., 2019) and non-randomized trials (ROBINS-I tool) (Sterne et al., 2016) were used to assess different aspects of study design, conduct, and reporting to obtain information on study characteristics relevant to risk of bias (Higgins et al., 2021). Physiotherapy Evidence Database (PEDro-P) Rating Scale (Maher et al., 2003) was used to evaluate the methodological quality of the RCTs. Two independent researchers

assessed the quality and risk of bias of the studies, obtaining an inter-rater reliability of 83.56%. The risk of bias was classified as low, unclear, or high (Table S2).

4.3. Data extraction

Specific information was extracted for the systematic review from the studies selected, which included: (1) first author and year of publication; (2) sample size of the study; (3) characteristics of the sample; (4) characteristics of the disease; (5) type of intervention; (6) format of the intervention; (7) duration of the intervention; (8) cognitive domains trained; and (9) variables in which improvements have been obtained after cognitive rehabilitation. Effect sizes of the meta-analysis were calculated using means and standard deviations (SD), and/or *F*-scores. Effect sizes were calculated for overall cognitive functions, global cognitive status, and eight specific cognitive subdomains: attention, working memory, verbal memory, visual memory, verbal fluency, executive functions, visuospatial and visuoconstructive abilities, and processing speed. Effect sizes for overall cognitive functions were calculated from the mean of global cognitive status and cognitive subdomains obtained in this meta-analysis, selecting only the studies that reported at least two cognitive domains. Moreover, the effect sizes of depressive symptoms and quality of life were also calculated. The neuropsychological tests included in the domains of the meta-analysis were classified according to the assessment measure of the test itself (Table S3). For the moderator or meta-regression analyses, the following were selected: specific scores of the age and years of education, variables related to intervention time, the modality of delivering the cognitive training (pencil and paper or computer), baseline global cognitive scores, and PD patient-related features (disease duration, the UPDRS, and the H&Y).

4.4. Statistical analysis

To analyze the impact of cognitive rehabilitation programs in PD, the effect sizes of 12 articles were estimated. The standardized mean difference (SMD) was calculated using Cohen's *d* formula (Cohen, 1988). SMD values were calculated with a 95% confidence interval (CI) from the means and SD, and *F*-scores provided by the studies. Subsequently, they were corrected using the Hedges' *g* small sample size bias adjustment formula (Cumming, 2012). Change scores to estimate effect sizes for those studies that had the necessary data were calculated based on the conservative approach used in Orgeta and colleagues' (2020) meta-analysis, assuming that the correlation between measures at pre and post-test time points is zero (Orgeta et al., 2020).

To perform all meta-analysis estimations a random-effects model was used. Any effect size was not detected or eliminated as an outlier. The interpretation of the effect sizes were: small ≥0.20, moderate ≥0.50, or large ≥0.80. Cochrane's *Q* test (*Q*) and I^2 indexes estimated the heterogeneity across the studies. I^2 index can indicate low (25%), medium (50%), or high (75%) heterogeneity (Huedo-Medina et al., 2006).

The influence of different predictors' variables on the effect sizes of overall cognitive functions was examined with multiple meta-regression analyses with the rma function and the dmetar package available in RStudio (Harrer et al., 2019). A mixed-effects model (Cheung & Vijayakumar, 2016) was used to conduct moderator analyses.

Publication bias, defined as the tendency to submit or accept articles for publication only from positive results (Dickersin, 1990) may influence the validity of analyses performed in meta-analyses (Rothstein et al., 2006). Therefore, funnel plots and the Egger regression test (Egger et al., 1997) were used to assess the publication bias of the studies. Finally, to assess whether the results would be different if only RCTs were included, sensitivity analyses were performed.

Practical Meta-Analysis Effect Size Calculator, Review Manager (RevMan, Version 5.4, Cochrane, London, UK), and the meta and metafor packages in RStudio (Version 1.3.1093, RStudio, PBC, Boston, MA) were used to perform effect size calculations and analyses.

Study II and III

4.1. Study II and III sample

One hundred and fifteen PD patients and 75 family caregivers from the Department of Neurology at the Hospital of Galdakao, the Cruces University Hospital, the PD Biscay Association (ASPARBI), and the PD Alava Association (ASOPARA) participated in the study.

4.1.1. Parkinson's disease patients sample

PD patients were included in the study according to the following criteria: (1) diagnosis of PD based on the diagnostic criteria of the UKPDSBB (Hughes et al., 1992); (2) age ≥45; and (3) either male or female. The exclusion criteria were as follows: (1) diagnosis of dementia as defined by Diagnostic and Statistical Manual of Mental Disorders- IV-TR (DSM-IV-TR) and the MDS specific clinical criteria for PD dementia (American Psychiatric Association, 2000; Emre et al., 2007); and (2) diagnosis of other major neurological or psychiatric disorders. All patients received their pharmacological treatment and all evaluations were done in the on medication state.

4.1.2. Family caregivers sample

The inclusion criteria for family caregivers were: (1) being an informal caregiver of a PD patient; and (2) male or female. Family caregivers were also excluded from the study if: (1) had the diagnosis of other major neurological or psychiatric disorders.

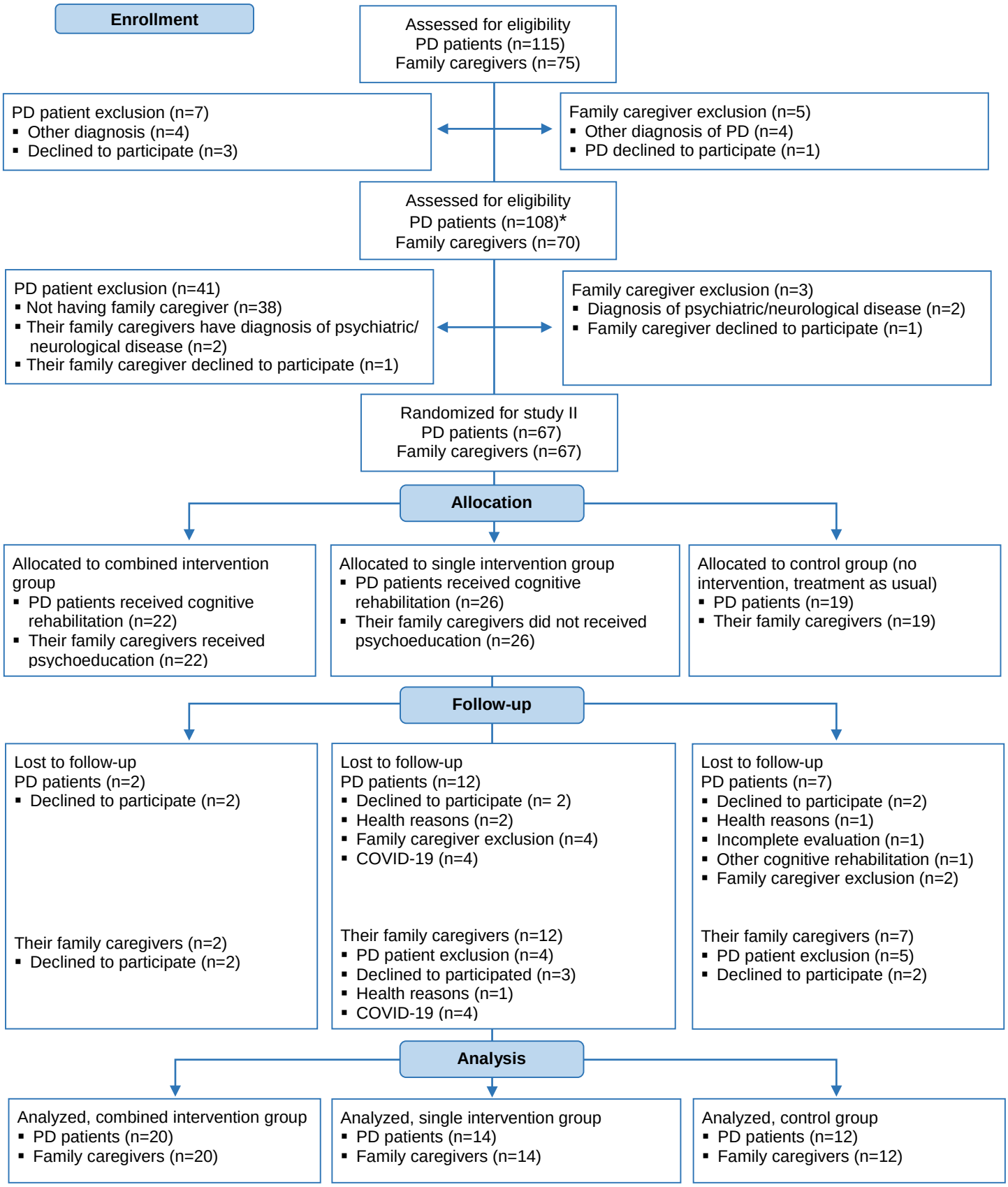
4.1.3. Specific inclusion and exclusion criteria for study II and III

For the participation in the cognitive rehabilitation groups of *study II*, and in order to be able to assess the efficacy of the combined intervention additional inclusion and exclusion criteria were included: (1) the person with PD was required to have a family caregiver; and (2) participants could not be receiving other cognitive rehabilitation or psychoeducation programs. The recruitment process of the participants is detailed in figure 2. Sixty-seven PD patients were randomly allocated to the intervention groups along with their family caregivers: Combined intervention group (cognitive rehabilitation in PD patients + psychoeducation in family caregivers), single intervention group (cognitive rehabilitation in PD patients), and control group (treatment as usual). Due to the health crisis caused by the SARS-CoV-2 virus (COVID-19), some participants did not complete the intervention and post-intervention neuropsychological assessment. The study was conducted in a matched method (the patient along with their family caregiver). If a PD patient was excluded by inclusion/exclusion criteria, declined to participate in the study, or did not complete the post-test evaluation, simultaneously his/her family caregiver was excluded from the analyses and vice versa. The analyses were performed in 46 PD patients [combined (n=20), single (n=14), and control group (n=12)] and 46 family caregivers [combined (n=20), single (n=14), and control group (n=12)] who completed the post-intervention neuropsychological assessment, which reflects an attrition rate of 31.34 % (Figure 2).

For *study III*, from the initial sample of 115 PD patients, four patients were excluded due to other diagnoses (atypical Parkinsonism disorders and Alzheimer's disease) and three participants dropped out of the study. A cross-sectional study was carried out with 108 PD participants (Figure 2).

Figure 2

CONSORT 2010 Flow diagram



Note: *These PD patients were included in the study III.

4.2. Procedure

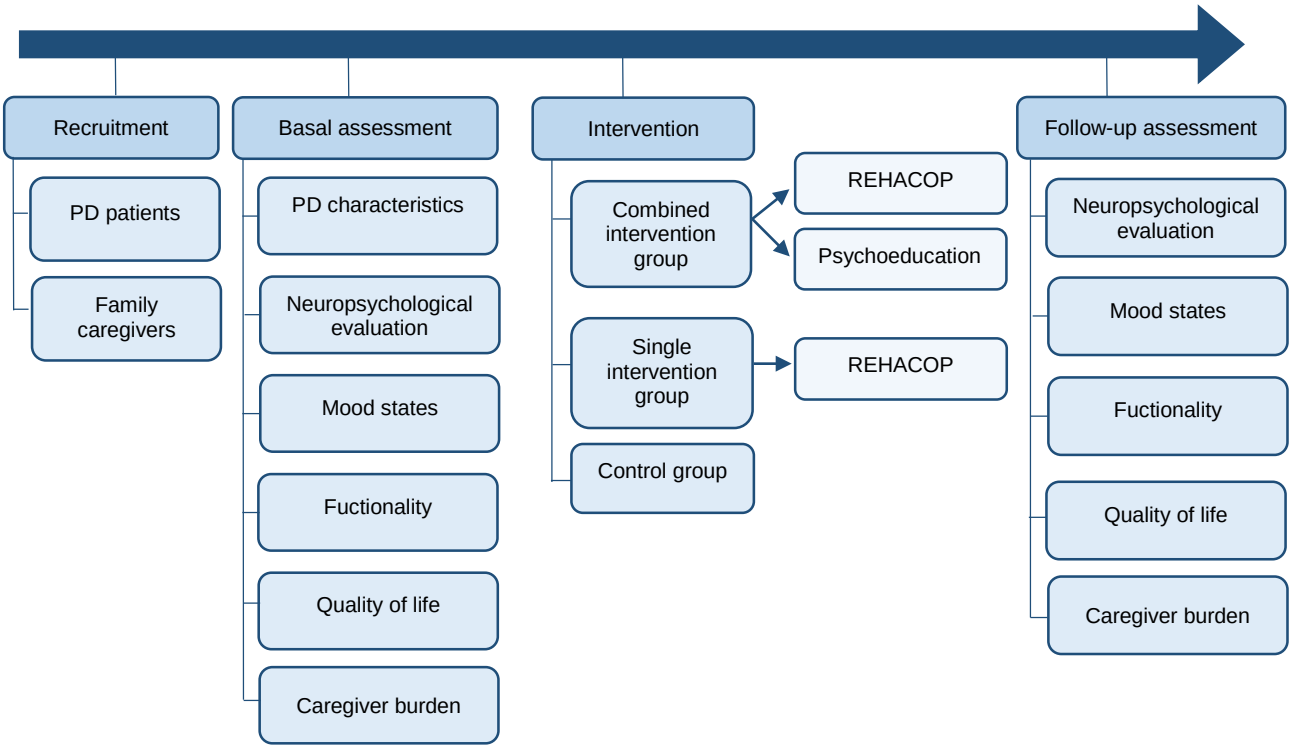
The recruitment of the participants was conducted via: 1) the neurologists from the Hospital of Galdakao and the Cruces University Hospital involved in the study, who recruited outpatients regularly attending appointments at the hospital; and 2) ASPARBI and ASOPARA Parkinson's Associations, where informative talks were organized and patients who were members of the association were recruited. Contact information of interested participants was collected to establish evaluation dates. The neurologists performed a clinical evaluation in which they collected sociodemographic data, administered UPDRS part III (Martínez-Martín et al., 1994), and the H&Y stages (Hoehn & Yahr, 1967) to confirm the diagnosis of PD by evaluating the motor symptoms of PD. A baseline and follow-up assessment were performed by specialized neuropsychologists, including neuropsychological domains, mood, functionality, quality of life, and caregiver burden.

For *study II*, the intervention with REHACOP in PD patients consisted of a group format treatment with three weekly sessions of 60 minutes during three months carried out by psychologists. Psychoeducation sessions in family caregivers were carried out in a group format, in parallel with the cognitive rehabilitation sessions for PD patients, for three months, and with a frequency of once a week. The participants of the control group received treatment as usual. Finally, post-treatment evaluation was completed in the first week after the end of the intervention. The design of the study is summarized in Figure 3.

For *study III*, a cross-sectional study with the whole PD sample at baseline was performed.

Figure 3

Project design



4.3. Ethics statement

The Ethics Committee of the University of Deusto (ETK-20/15-16) and the Research Ethics Committee of the Basque Country (CEIm-E) (PI2018147) approved this research project conducted by the Neuropsychology of Severe Medical Condition team of the University of Deusto. All participants signed an informed consent document after being informed of the objective of the study, its risks and benefits, their rights, and the confidentiality and management of data during the study.

4.4. Parkinson´s disease related features, neuropsychological and non-motor symptoms assessment

Estimations of the stage and evolution of the disease were assessed by specialized neurologists. In addition, years of disease evolution were recorded. All participants underwent an extensive neuropsychological battery in which global cognitive status, premorbid intelligence, cognitive reserve, attention and working memory, verbal

memory, visual memory, verbal fluency, executive functions, cognitive flexibility, processing speed, visuoconstructive abilities, ToM, and facial emotion recognition were assessed (Table 4). In addition, other non-motor symptoms such as general health, functional disability, fatigue, anxiety, depression, apathy, quality of life, and variables related to caregiver burden were assessed. A trained neuropsychologist administered all tests on two times, at baseline (T0) and in the first week after the end of the intervention (T1).

Table 4

PD related features, neuropsychological, other non-motor symptoms and caregiver's specific assessment

Area	Test
PD related features assessment	
Motor symptoms	Unified Parkinson's Disease Rating Scale (UPDRS) part III
PD stages	Hoehn and Yahr Staging Scale (H&Y)
Medication	Levodopa Equivalent Daily Dose (LEDD)
Neuropsychological assessment	
Global cognition	Montreal Cognitive Assessment (MoCA)
Premorbid intelligence	Word Accentuation Test (WAT)
Cognitive reserve	Cognitive Reserve Questionnaire (CRQ)
Attention and working memory	Digits forward and backward Test (WAIS-III)
Verbal memory	Hopkins Verbal Learning Test Revised (HVLT-R)
Visual memory	Brief Visuospatial Memory Test Revised (BVMT-R)
Verbal fluency	Calibrated Ideational Fluency Assessment (CIFA) (semantic fluency)
	Montreal Cognitive Assessment (MoCA) fluency subtest of language category (phonemic fluency)

Executive functions	UD interference test (Words-Colors and interference)
Cognitive flexibility	Modified Wisconsin Card Sorting Test (M-WSCT)- categories and perseverative errors
Processing speed	Salthouse Perceptual Comparison Test (SPCT)
	Trail Making test- A (TMT-A)
Visuoconstructive abilities	Clock Drawing Test (CDT) (draw+copy)
Theory of Mind	Happe's Strange Stories
Facial emotions recognition	Facial Emotions Recognition Test of the Mini-SEA Test
Other non-motor symptoms	
General health	General Health Questionnaire scale (GHQ-12)
Functional disability	World Health Organization Disability Assessment Scale (WHO-DAS II)
Fatigue	Fatigue Severity Scale (FSS)
Anxiety and depression	Hospital Anxiety and Depression Scale (HADS)
Apathy	Lille Apathy Rating Scale (LARS)
Quality of life	Parkinson's Disease Questionnaire-39 (PDQ-39)
Caregivers specific assessment	
Quality of life	EuroQoL-5D (EQ-5D)
Caregiver burden	Zarit Caregiver Burden Interview (ZBI)
	Caregiver Strain Index (CSI)
	Positive Aspects of Caregiving Scale (PACS)

4.4.1. Parkinson´s disease related features assessment

PD-related features. Estimation of disease stage and progression of PD motor symptoms was assessed using the UPDRS part III (Martínez-Martín et al., 1994) and the H&Y staging scale (Hoehn & Yahr, 1967). The dose and frequency of medications of people with PD were collected to calculate the Levodopa Equivalent Daily Dose (LEDD) (Tomlinson et al., 2010).

4.4.2. Neuropsychological and clinical assessment in Parkinson´s disease and caregivers

Global cognitive status. The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) was used to evaluate global cognitive status. This test is composed of nine categories (visuospatial, executive functions, naming, memory, attention, language, abstraction, delayed recall, and orientation) whose total score ranges from 0 to 30 (Nasreddine et al., 2005). Internal consistency measured by Cronbach's alpha was α= .76 in MCI population (Lozano et al., 2009).

Premorbid intelligence. The Spanish version of the National Adult reading test, the Word accentuation Test (WAT) (Gomar et al., 2011) was applied to estimate premorbid intelligence through the pronunciation of 30 words whose accents have been removed. Internal consistency was high α= .91 (Del Ser et al., 1997).

Cognitive reserve. Cognitive reserve was assessed through the Cognitive Reserve Questionnaire (CRQ) (Rami et al., 2011). This questionnaire is composed of 8 subscales measuring various aspects of the subject's intellectual activity (schooling, schooling of parents, training courses, employment, musical training, language skills, reading activity, and intellectual games) (Rami et al., 2011). The validity of this test was calculated based on the relationship with external variables, showing significant correlations with the

scores obtained in WAT, Mini-mental state examination (MMSE), digit span, verbal fluency, and Trail Making test A (TMT-A) (Rami et al., 2011).

Attention and working memory. Attention and working memory domains were evaluated by the digits forward and backward subtests of the Weschler Adult Intelligence Scale III (WAIS-III) (Weschler, 2001). The forward digit test consists of repeating a series of digits in the same order in which they are presented, while the backward digit test consists of repeating a series of digits in the inverse order in which are presented (Weschler, 2001). Reliability score for digit span was .90 (Silva, 2008).

Verbal and visual memory. These domains were measured through the Hopkins Verbal Learning Test-Revised (HVLT-R) (Brandt & Benedict, 2001), and the Brief Visual Memory Test-Revised (BVMT-R) (Benedict, 1997). HVLT-R assesses verbal learning using three learning trials with a list of 12 nouns divided into three semantic categories with four words in each category and long-term recall capacity by means of the word free recall test after a period of 20 minutes (Brandt & Benedict, 2001). Reliability coefficient was .74 for the total score of three learning trials and .66 for the long-term recall score (Benedict et al., 1998; Brandt & Benedict, 2001). BVMT-R measures visual learning using six geometric forms in a 2x3 matrix over three trials, and long-term recall capacity after 20 minutes using free recall (Benedict, 1997). Reliability coefficients for the three learning trials, total recall and long-term recall range from .96 to .97 (Benedict, 1997).

Verbal fluency. Calibrated Ideational Fluency Assessment, CIFA (Schretlen & Vannorsdall, 2010), and MoCA fluency subtest of language category (Nasreddine et al., 2005) were administered to assess semantic and phonemic verbal fluency. CIFA measures semantic verbal fluency by means of the animal categories test, in which the participant has to produce the largest number of animals in one minute. Internal consistency for

category fluency of the test was α=.73 (Schretlen & Vannorsdall, 2010). The MoCA fluency subtest assesses phonemic verbal fluency by the P-word test, in which the participant has to produce the largest number of words beginning with the letter "P" in one minute (Nasreddine et al., 2005).

Executive functions. The executive functions domain was assessed by the UD interference test (Sáez-Atxukarro et al., 2021). This test is composed of 3 tasks: 1) Words: a list of colors is presented in black ink that the participant has to read (pink, blue and black); 2) Colors: a list of circles of printed colors is presented that the participant has to read (pink, blue and black); and 3) Color-words: names of colors are presented printed in an ink of a color that does not correspond to that of the written word (Sáez-Atxukarro et al., 2021). All three tasks must be read aloud as fast as possible in 30 seconds and without finger guidance. Lower scores on the interference index mean higher cognitive interference (Sáez-Atxukarro et al., 2021). This test showed good internal consistency (α = .88) (Sáez-Atxukarro et al., 2021).

Cognitive flexibility. The Modified Wisconsin Card Sorting Test (M-WCST) (Ojeda et al., 2010) was used to evaluate the mental flexibility of the participant's performance in sorting 48 cards according to certain rules. The test performance depends on the number of correctly completed categories, perseverative errors, and total errors (Ojeda et al., 2010). The reliability of this test showed adequate stability in the test-retest correlations (number of correct categories = .54; number of perseverative errors = .57) (Ojeda et al., 2010).

Processing speed. Processing speed was assessed by the Salthouse Perceptual Comparison Test (SPCT) (Salthouse & Babcock, 1991) and Trail Making Test-A (TMT-A) (Reitan, 1958). In the SPCT, the participant must compare two pairs of letters (3 or 6) and mark them as dissimilar ("D") or equal ("I") as quickly as possible during a period of

30 seconds (Salthouse & Babcock, 1991). The TMT-A consists of ordering twenty-five numbers from lowest to highest in the shortest possible time (period 90 seconds) (Reitan, 1958).

Visuoconstructive abilities. The clock-drawing test (CDT) (Cacho et al., 1999) was selected to measure visual-motor coordination, constructive and planning ability, and motor execution. In this test, the participant draws a clock (on command and copy) showing the time 11:10 (Cacho et al., 1999). Cacho and colleagues (1999) developed this test based on the Sunderland criteria (Sunderland et al., 1989) and with the norms of the scale revised by Rouleau and colleagues (Rouleau et al., 1992). The interrater reliability was high varying from .92 to .97 in AD, Huntington´s disease, and healthy population (Rouleau et al., 1992).

Theory of Mind (ToM). ToM was measured using the Spanish version of the Happé Test 'Strange Stories Task' (Pousa, 1999). This test is composed of eight stories classified as double bluffs, mistakes, persuasion, and white lies. In this test, the participant must read and answer a question in each story, which required making an inference about the character's thoughts and intentions. Four stories were used and a total score was obtained from the four stories ranging from 0 to 8 (Pousa, 1999).

Facial Emotions Recognition. Facial emotion recognition was measured by the Facial Emotions Recognition Test of the Mini-SEA Test (Bertoux et al., 2012) which consists of thirty-five faces with seven different emotions presented five times (fear, sadness, disgust, surprise, anger, happiness, and neutral).

General health. The Spanish version of the General Health Questionnaire scale (GHQ-12) (Rocha et al., 2011) was administered to assess general health and is a scale of 12 items that measure the risk of developing psychiatric disorders. Internal consistency was α=.86 for general population and α=.90 for elderly population (Rocha et al., 2011).

Functional disability. World Health Organization Disability Assessment Scale (WHO-DAS II) (Vázquez-Barquero et al., 2006) was administered to assess disability and functional impairment due to health conditions during the last 30 days. The participant has to answer a series of questions whose scores range from 1 to 5 (Vázquez-Barquero et al., 2006). Internal consistency was high α = .98 (Vázquez-Barquero et al., 2006).

Fatigue. Physical and mental fatigue was measured by the Fatigue Severity Scale (FSS) (Krupp et al., 1988). This scale is a self-administered scale composed of nine items. Internal consistency was high α=.88 (Krupp et al., 1988).

Anxiety and depression. Anxiety and depressive scores were assessed through the two subscales of anxiety and depression of the Spanish version of the Hospital Anxiety and Depression Scale (HADS) (Quintana et al., 2003). This questionnaire has been designed to know the emotional state of the participant. It is composed of two 7-item Likert subscales to evaluate anxiety and depression. The score of each of the subscales ranges from 0 to 21 (Quintana et al., 2003; Zigmond & Snaith, 1983). Internal consistency was α=.86 for both subscales (Quintana et al., 2003).

Apathy. The Spanish version of the Lille Apathy Rating Scale (LARS) (García-Ramos et al., 2014) was administered to evaluate apathy scores. This scale is composed of 33 items with a total score of a possible range of -36 to 36 points. The scale can be divided into 9 subscales (daily productivity, interest, initiative taking, novelty seeking/motivation, emotional responses, preoccupation, social life, and self-awareness). Lower scores indicate a higher degree of apathy (García-Ramos et al., 2014; Sockeel et al., 2006). Internal consistency (α=.81) and test-retest reliability (.97) were high (García-Ramos et al., 2014).

Quality of life. The HRQoL of people with PD was evaluated with the Spanish version of the PDQ-39 (Martínez-Martín & Frades, 1998). This questionnaire is divided into eight dimensions: mobility (10 items, 0-40), ADL (6 items, 0-24), emotional well-being (6 items, 0-24), stigma (4 items, 0-16), social support (3 items, 0-12), cognition (4 items, 0-16), communication (3 items, 0-12) and bodily discomfort (3 items, 0-12) and a PDQ-39 summary index (Jenkinson et al., 1997; Martínez-Martín & Frades, 1998). The scores for each dimension were calculated by the sum of the raw scores of each item divided by the maximum possible score of each dimension and multiplied by 100 (Peto et al., 1995). The PDQ-39 summary index (HRQoL total index) was calculated by the sum of the scores of the 8 dimensions and divided by the number of dimensions (Peto et al., 1995). These scores range from 0 (no problem) to 100 (maximum level of problems) and higher scores indicate a lower HRQoL (Jenkinson et al., 1997; Martínez-Martín & Frades, 1998). The internal consistency of eight dimensions ranged between α=.63 and α=.64 (Martínez-Martín & Frades, 1998).

4.4.3. Caregivers' specific assessment

Quality of life. The quality of life of family caregivers was assessed by EuroQoL-5D (EQ-5D) (Herdman et al., 2001). EQ-5D is designed to describe and assess the quality of life through dimensional severity levels (Herdman et al., 2001). It is also composed of a visual analog scale (VAS) for a more general evaluation (Herdman et al., 2001). The scores were transformed into utility values ranging from 0 to 1 (from the worst to the perfect state of health) (Herdman et al., 2001). Internal consistency of this test was α= .64 for caregivers of institutionalized elderly people with dementia (Díaz-Redondo et al., 2012).

Caregiver burden. Caregiver burden was assessed using the Spanish version of the Zarit Caregiver Burden Interview and Caregiver Strain Index (Gojenola et al., 2008).

Zarit Caregiver Burden Interview is a questionnaire that assesses subjective caregiver burden (Gojenola et al., 2008). It is a Likert scale questionnaire composed of 22 items with five points (0-4) (Gojenola et al., 2008). The score ranges from 0 to 88, showing that the higher the score, the higher the perceived caregiver burden (Gojenola et al., 2008). Internal consistency of the items of the scale ranged between α=.69 and α=.90 (Montorio et al., 1998). The Caregiver Strain Index is an instrument designed to measure the perceived burden of caregivers (López & Moral, 2005). It is composed of 13 dichotomous questions (True-False). Scoring ranges from 0 to 13 and each true answer scores 1 (Gojenola et al., 2008). Internal consistency was α=.81 (López & Moral, 2005).

Positive Aspects of caregiving. The Spanish version of the Positive Aspects of Caregiving Scale (PACS) (Las Hayas et al., 2014) was used to evaluate positive aspects of caregiving. The PACS is a Likert scale (0-4) of nine items reflecting various positive aspects that may occur during care. Internal consistency was α=.82 (Las Hayas et al., 2014).

4.5. Intervention programs

4.5.1. REHACOP cognitive rehabilitation program

The REHACOP program has been developed at the University of Deusto and is a comprehensive cognitive rehabilitation program based on restoring, compensating, and optimizing cognitive functions, through top-down and bottom-up strategies (Ojeda et al., 2012). This program is comprised of more than 300 paper-and-pencil tasks, organized in a hierarchical way to provide a bottom-up and orderly approach to therapists, in order to allow patients to gradually acquire skills from the most basic cognitive processes to the most demanding ones (Ojeda et al., 2012). The domains trained during the sessions were: attention (4 weeks), memory and learning (3 weeks), language (3 weeks), executive functions (2 weeks), social cognition (1 week), and processing speed (Table 5).

Table 5

Cognitive rehabilitation timetable: REHACOP program

Module	Week	Functions
Attention and concentration*	1-4	Sustained attention Selective attention Alternating attention Divided attention
Memory and learning*	5-7	Environmental factors Reading and memory strategies Techniques to improve memory Mnemonic rules Short-term memory Working memory Visual memory Verbal memory
Language*	8-10	Syntax Grammar Vocabulary Verbal comprehension Verbal fluency Abstract language
Executive functions*	11-12	Planning and attainment objectives Social and verbal reasoning Behavioral self-regulation Planning, categorization, and conceptualization
Social cognition	13	Theory of mind Social reasoning Moral dilemmas

Note: *Processing speed was trained cross-sectional in the first four modules through timed activities.

Thirty-nine sessions were carried out in a group format, with a duration of 60 minutes, with a frequency of three times a week for three months. Due to the difficulties of PD patients associated with age and the symptoms of the disease itself, some tasks were adapted: increase of font size, oral tasks, and reduction of the number of items (Gómez-Gastiasoro et al., 2019).

Cognitive rehabilitation sessions were conducted by psychologists at ASPARBI, Basauri Health Center, and ASOPARA. All psychologists received the same REHACOP training and used identical materials and instructions.

4.5.2. Psychoeducation program

The psychoeducation program for family caregivers was based on PEPP, a standardized psychosocial intervention developed by the EduPark. Through this program, the family caregiver receives information and skills to improve their quality of life and PD patients' quality of life (Bayés et al., 2007; Macht et al., 2007). PEPP is composed of eight work sessions with the family caregiver that address the following aspects: information about the disease, self-regulation/self-monitoring, health care/promotion, stress management, management of depressive moods and anxiety/caregiver challenge, social skills/competence, social support, and a final summary/assessment (Table 6).

Four additional sessions have been incorporated for this study: *ad hoc* suggestions from the family caregivers themselves from the Parkinson's association, introduction to the REHACOP program, home support or boosting at home (reinforcement sessions with family members at home), and leisure activities. Among the suggestions from family caregivers, interest in nutritional aspects and dietary guidelines were the most demanded topics. In the introductory session to the REHACOP program, a joint session was held for the family caregiver to acquire an active role in the cognitive rehabilitation process in order to help PD patients appropriately in the cognitive training activities at home. For boosting, therapists set up a number of activities from the REHACOP program that people with PD had to perform at home and established face-to-face and/or telephone meetings to conduct a weekly follow-up with family caregivers to support, reinforce, and help solving any doubts that have arisen regarding the cognitive rehabilitation exercises at

home. Finally, in the leisure time session, disconnection, caring for the caregiver, and pleasurable activities for the caregiver were performed (Table 6).

Table 6

Psychoeducation timetable

Module	Week	Functions
Introduction/ Program Information*	1	Program Introduction PD information
Self-monitoring*	2	Why is it important How to do it
Health care*	3	Promoting health Pleasant activities
Stress management*	4	Stress management strategies Relaxation exercises
Caregiver challenge*	5	Positive and negative aspects of caregiving Preventing health problems
Social skills/competence*	6	Communication Coping with social situations
Social support*	7	Strategies for requesting and giving support
Family suggestions	8	*Ad hoc* questionnaires Work on the demands revealed
Approach to cognitive rehabilitation	9	Approach to the REHACOP program Joint rehabilitation session involving patients and caregivers
Boosting at home	10	Strategies for helping to carry out cognitive activities at home
Leisure time	11	Leisure activities
Summary and final assessment*	12	Summary of the sessions Final reflection

Note: *Sessions based on the psychoeducation manual for PD patients and their caregivers: manual Edupark (Bayés et al., 2007).

Twelve psychoeducation sessions were carried out in a group format, for three months with a duration of 90 minutes and a frequency of once a week. Sessions were carried out by psychologists at ASPARBI and Basauri Health Center.

4.6. Statistical analyses

4.6.1. Study II

The Kolmogorov-Smirnov test was performed to test the normality of data. All cognitive measures were converted into *z* scores, and TMT-A scores were recoded so that lower scores indicated worse performance. Composite scores were created for attention and working memory (total scores of the forward and backward digits of WAIS-III), verbal memory (learning and long-term recall of HVLT-R), visual memory (learning and long-term recall of BVMT-R), executive functions (Words-Colors and interference of UD interference test), semantic and phonemic fluency (total score of animals category of CIFA and words starting with P of verbal fluency subtest of MoCA), cognitive flexibility (categories and perseverative errors of M-WSCT) and processing speed (SPCT and TMT-A). All the composites reached satisfactory internal consistency (higher than $\alpha = .70$).

In order to analyze the results of family caregivers who participated in psychoeducation (n= 20) compared to those who did not participate (n=26), a variable comprised of the single intervention group (n=14) + the control group (n=12) was created in the database. For the examination of the demographic data at the basal level, Kruskal-Wallis analyses were carried out among the three PD groups and Man Whitney *U* analyses between the two groups of family caregivers for quantitative variables, while for the categorical variables the Chi-square test was used. Change scores (post-treatment - baseline) were calculated for each of the variables (neuropsychological domains, mood, functionality, quality of life, and caregiver burden). Differences in change scores between PD combined, single, and control groups were assessed by analysis of covariance

(ANCOVA), including change score as the dependent variable and pre-test performance as a covariate. Change scores were compared between family caregivers who participated in psychoeducation (combined group) and no psychoeducation group (single intervention group + control group) using ANCOVA analysis. The effect sizes were obtained by the Eta partial square (η^2), which were interpreted as small (.01), medium (.06), and large (.14) (Cohen, 1988). The Bootstrapping sample technique (Efron & Tibshirani, 1994) was used to obtain adjusted mean differences in change scores, generating random subsamples from the observed sample. By using the Bonferroni correction, all the analyses were corrected by covariables and the bootstrap estimation by a 1000 resamples bias. Statistical analyses of these variables will be carried out using the statistical data package IBM SPSS version 27.

4.6.2. Study III

The normality of data was calculated with the Kolmogorov-Smirnov test. The Expectation-Maximization (EM) algorithm was used to impute missing values. The percentage of missing values was 0.047%.

All raw cognitive scores were converted to *z*-scores and the TMT-A test was recoded to indicate that higher scores higher performance. An overall neurocognition composite score with the main cognitive domains was created: attention and working memory (forward and backward digits of WAIS-III), verbal memory (learning and long-term of the HVLT-R), visual memory (learning and long-term recall of the BVMT-R), executive functions (Words-Colors and interference of UD interference test), semantic and phonemic fluency (animals category of CIFA and words starting with P of verbal fluency subtest of MoCA), visuoconstructive abilities (order and copy of CDT), cognitive flexibility (categories and perseverative errors of M-WSCT) and processing speed (SPCT

and TMT-A). The neurocognition composite score showed a satisfactory internal consistency (α=.87).

The items of the PDQ-39 questionnaire that could overlap with the clinical variables included in the study (fatigue, depression, anxiety, and apathy) were assessed. An overlap between HADS and the emotional well-being dimension items (*"17. Felt depressed"*, *"18. Felt isolated and lonely"*, *"19. Felt weepy or tearful"*, *"20. Felt angry or bitter"*, *"21. Felt anxious"*, and *"22. Felt worried about the future"*) was found, so a new HRQoL total index without the overlapping items of the emotional well-being dimension was created.

Spearman´s rho correlation test was performed to determine the relationship of HRQoL total index (before and after overlapping items) and its eight dimensions with demographic characteristics (age and sex), cognitive reserve, and LEDD. These variables were used to adjust the regression models in step 1 as covariates only in the cases that significantly correlated with the HRQoL total index (before and after overlapping items) and the different HRQoL dimensions. As the H&Y scale and years of disease duration in PD patients were seen as global measures of PD severity, these aspects were not included in the model (Kuhlman et al., 2019). Secondly, Spearman´s rho correlation test was used to evaluate the association of HRQoL total index (before and after overlapping items) and its eight dimensions, with the potential determining variables (scores of anxiety, depression, apathy and fatigue, neurocognition composite, and motor symptoms). The association between anxiety and depression scores and the emotional well-being dimension was not considered due to overlap of items between the emotional well-being dimension and the HADS scale.

Stepwise Multiple Regression analyses were performed to determine which variables predict HRQoL total index (before and after overlapping items) and its

dimensions. In the regression analyses, those variables that correlated significantly with HRQoL total index (before and after overlapping items) and its dimensions were included. Regression analyses were adjusted in step 1 (enter method) by covariates showing significant correlations. In step 2 (forward method) scores of anxiety, depression, apathy and fatigue, neurocognition composite, and motor symptoms were included in the models. Statistical analyses were performed with the IBM SPSS v27 statistical software.

V. Results

5. Results

5.1. Study I

5.1.1. Study selection

The search results showed 1472 studies from the PubMed database, of which 452 were excluded as duplicate publications and 994 were eliminated after initial screening based on title and abstract. From the 26 studies evaluated for eligibility, 15 were excluded due to the inclusion and exclusion criteria. Additionally, three studies were selected by citation searching, of which two were excluded. Finally, 12 articles were included in the systematic review and the meta-analysis (Figure 4).

5.1.2. Study characteristics

Twelve studies between 2004 and 2020 were included in the systematic review and meta-analysis. The number of participants in the studies ranged from 15 to 75, with a total of 512 participants. Eleven studies showed no differences in demographic variables at baseline, while a single study reported significant differences in sex, age, and years of disease progression, so the subsequent analyses were adjusted. The H&Y score ranged from one to three in most studies. The duration of the interventions was a maximum of 90 minutes, for a period ranging from three weeks to six months, with a frequency of two to five times per week. Regarding intervention methods, four studies conducted cognitive rehabilitation activities with pencil-paper; five studies with computer-based format and three studies used both methods (pencil-paper and computer-based activities) in their sessions. Six studies conducted the intervention in a group format, one individually and one in both formats; the remaining studies did not specify the format. The research focused on cognitive outcomes and reported improvements despite the diversity in the number of cognitive domains showing improvement (from a single domain to six). A summary of cognitive rehabilitation studies for PD is provided in table 7.

Figure 4

PRISMA summary of identified studies included in the review

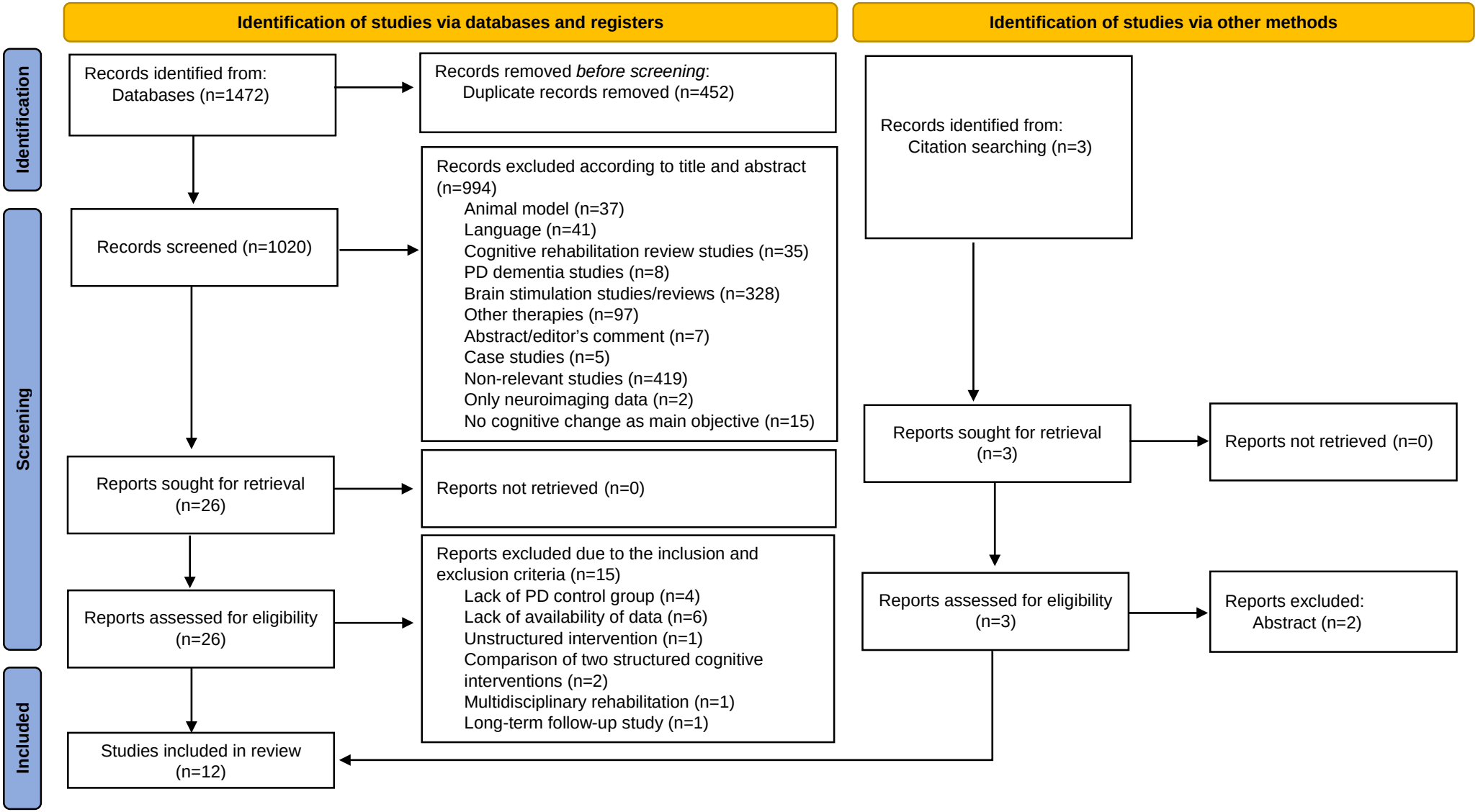


Table 7

Summary of cognitive rehabilitation studies for PD

Authors	Sample	Sample Characteristics	H&Y Stages	Intervention	Format	Duration	Domains Trained	Outcomes
(Sammer et al., 2006)	26 PD 12 PD-CR 14 PD-ACG	*Age:* 70.8 PD-CR 68.5 PD-ACG *Education:* -	2–3	CR: Executive Function Training ACG: Standard Treatment (Paper)	Group	10 sessions 30 min/session	-Working memory -Executive functions	*Improvements in PD-CR:* -Executive functions
(París et al., 2011)	28 PD 12 PD-CR 16 PD-CG	*Age:* 64.7 PD-CR 65.4 PD-CG *Education:* 9.8 PD-CR 9.5 PD-CG	1–3	"SmartBrain Tool" (Paper + Computer)	Group + home	12 sessions 3 times/week 4 weeks 45 min/session	-Attention -Memory -Psychomotor speed -Executive functions -Visuospatial abilities -Language -Calculation abilities	*Improvements in PD-CR:* -Attention -Processing speed -Visual memory -Visuospatial and visuoconstructive abilities -Semantic fluency -Executive functions

(Edwards et al., 2013)	74 PD 32 PD-CR 42 PD-CG	*Age:* 69.4 PD-CR 68.2 PD-CG *Education:* 14.8 PD-CR 15.4 PD-CG	1–3	"Insight Software" (Computer)	Home	36 sessions 3 times/week 3 months 60 min/session	-Processing speed	*Improvements in PD-CR:* -Processing speed
(Naismith et al., 2013)	50 PD 35 PD-CR 15 PD-CG	*Age:* 68.5 PD-CR 64.9 PD-CG *Education:* 14.9 PD-CR 14.0 PD-CG	1–3	CR: NEAR + Psychoeducation (Computer)	Group	14 sessions 7 weeks 2 times/week 60 min of CR 60 min psycho-education	-Memory -Psychomotor speed -Mental flexibility -Verbal fluency	*Improvements in PD-CR:* -Verbal memory
(Cerasa et al., 2014)	15 PD 8 PD-CR 7 PD-CG	*Age:* 61.1 PD-CR 58.3 PD-CG *Education:* 8 PD-CR 8 PD-CG	1–3	CR: "Rehacom" CG: Simple visuomotor coordination tapping task (Computer)	Group (CR) + Individual (CG)	6 weeks 2 times/week 60 min/session	-Attention -Information processing task	*Improvements in PD-CR:* -Attention/ Processing speed -Working memory *Increased functional brain activity:* -Left dorsolateral prefrontal cortex -Superior left parietal cortex

(Costa et al., 2014)	17 PD-MCI 9 PD-CR 8 PD-CG	*Age:* 66.1 PD-CR 70.9 PD-CG *Education:* 11.2 PD-CR 10.6 PD-CG	1–3	CR: Cognitive change training CG: Breathing training (Paper)	-	4 weeks 3 times/week 45 min/session	-Shifting abilities (Verbal fluency and Trail Making Test)	*Improvements in PD-CR:* - Verbal fluency task -Trail Making Test -Prospective memory procedures
(Peña et al., 2014)	42 PD 20 PD-CR 22 PD-ACG	*Age:* 67.7 PD-CR 68.1 PD-ACG *Education:* 10.5 PD-CR 10.2 PD-ACG	1–3	CR: “REHACOP” ACG: Occupational activities (Paper)	Group	39 sessions 13 weeks 2 times/week 60 min/session	-Attention -Memory -Language -Executive functions -Social cognition -Processing speed	*Improvements in PD-CR:* -Processing speed -Visual memory -Social cognition -Functional disability
(Petrelli et al., 2014)	65 PD 22 PD-NV 22 PD-MF 21 PD-CG	*Age:* 69.2 PD-NV 68.8 PD-MF 69.1 PD-CG *Education:* 13.1 PD-NV 13.6 PD-MF 12.8 PD-CG	1–3	NV :“NEUROvitalis” (Computer) MF: “Mentally fit” (Paper)	Group + Individual	12 sessions 6 weeks 2 times/week 90 min/session	*NV* -Attention -Verbal memory -Visual memory -Executive functions *MF* -Attention -Memory -Creativity	*Improvements in PD-NV versus PD-CG:* -Working memory -Verbal memory *Improvements in PD-MF versus PD-CG:* -Depressive symptoms *Improvements in PD-NV versus PD-MF:* -Working memory

(Angelucci et al., 2015)	15 PD-MCI 7 PD-CR 8 PD-CG	*Age:* 67.6 PD-CR 71.9 PD-CG *Education:* 11.7 PD-CR 10.6 PD-CG	-	CR: Cognitive change training CG: Simple cognitive tests (Paper)	-	12 sessions 4 weeks 3 times/week 45 min/session	-Executive functions	*Improvements in PD-CR:* -Executive functions
(Fellman et al., 2020)	52 PD 26 PD-CR 26 PD-ACG	*Age:* 64.8 PD-CR 65.5 PD-ACG *Education:* 5.3 PD-CR 5.5 PD-ACG	-	CR: Working memory ACG: Online quiz task “Älypää” (Computer)	Home	3 weeks 3 times/week 30 min/session	-Working memory	*Improvements in PD-CR:* -Working memory -Depressive symptoms
(Bernini et al., 2020)	53 PD 18 PD-CCT 12 PD-PCT 18 PD-CG	*Age:* 74.6 PD-CCT 69.8 PD-PCT 69.3 PD-CG *Education:* 9.5 PD-CCT 8.0 PD-PCT 7.6 PD-CG	≤3	CCT: “CoRe” (Computer) PCT: “CoRe” (Paper) CG: Unstructured activities	Group	3 weeks 4 times/week 45 min/session	-Logical executive functions -Attention/processing speed -Working memory -Episodic long-term memory	*Improvements in PD-CCT versus PD-PCT:* -Global cognition *Improvements in PD-CCT versus CG:* -Global cognition -Attention/ processing speed

(Ophey et al., 2020)	75 PD 37 PD-CR 38 PD-CG	*Age:* 64.0 PD-CR 63.8 PD-CG *Education:* 15.0 PD-CR 15.5 PD-CG	2–3	CR: "NeuroNation" (Computer)	Individual + home	5 weeks 5 times/week 30 min/session	-Working memory	*Improvements in PD-CR:* -No improvements *Assessment after 3 months:* -Verbal working memory -Visuoconstructive abilities

Note: PD = Parkinson's disease; CR = Cognitive rehabilitation; ACG = Active control group; NEAR= Neuropsychological Educational Approach to Remediation; NV= NEUROvitalis; MF= Mentally fit; CCT = Computer cognitive training; PCT = Paper-pencil cognitive training; CG = Control group; H&Y = Hoehn and Yahr scale; MCI= Mild cognitive impairment

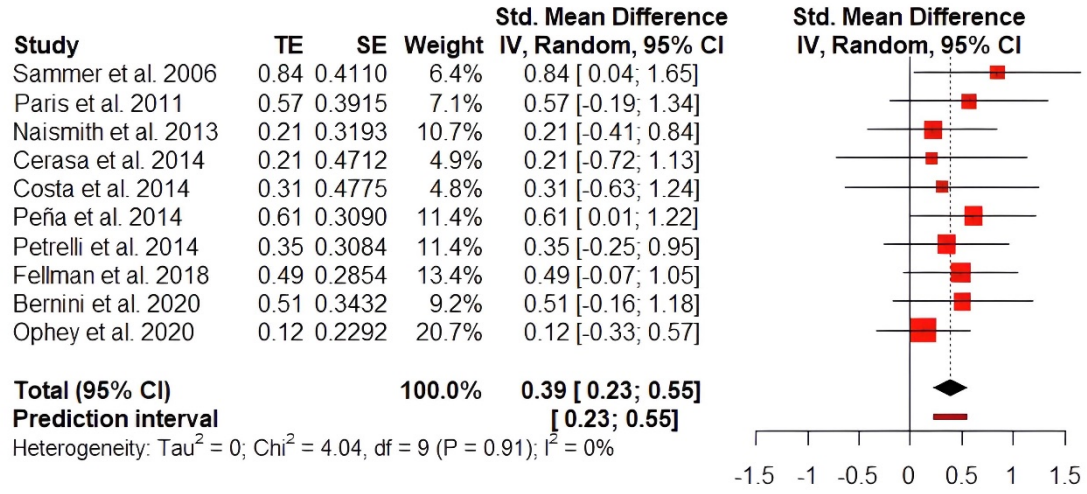
5.1.3. Effectiveness of cognitive rehabilitation

5.1.3.1. Overall cognitive functions

Overall cognitive functions´ effect size was calculated based on the mean of global cognitive status and cognitive subdomains from 10 studies reporting at least two cognitive variables. The effect sizes of a random-effects model of overall cognitive functions in cognitive rehabilitation accuracy were small and statistically significant (g = 0.39, p = .01) with a 95% CI (0.23 to 0.55). Heterogeneity was low across the studies (Q = 4.04, p = .91; I^2 = 0%) (Figure 5).

Figure 5

Effectiveness of cognitive rehabilitation in overall cognitive functions

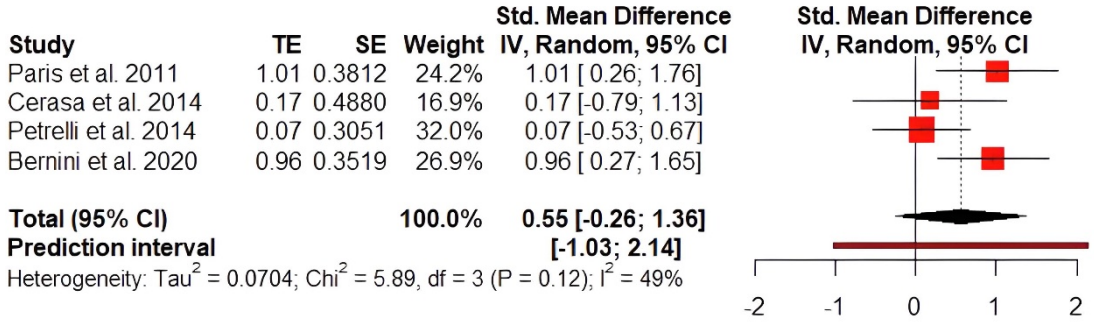


5.1.3.2. Global cognitive status

Global cognitive status assessed by global cognitive screening tests were analyzed in four studies. The effect sizes of a random-effects model of global cognitive status in cognitive rehabilitation accuracy were moderate and not significant (g = 0.55, p = .12) with a 95% CI (-0.26 to 1.36). Heterogeneity was moderate across the studies (Q = 5.89, p = .12; I^2 = 49%) (Figure 6).

Figure 6

Effectiveness of cognitive rehabilitation in global cognitive status

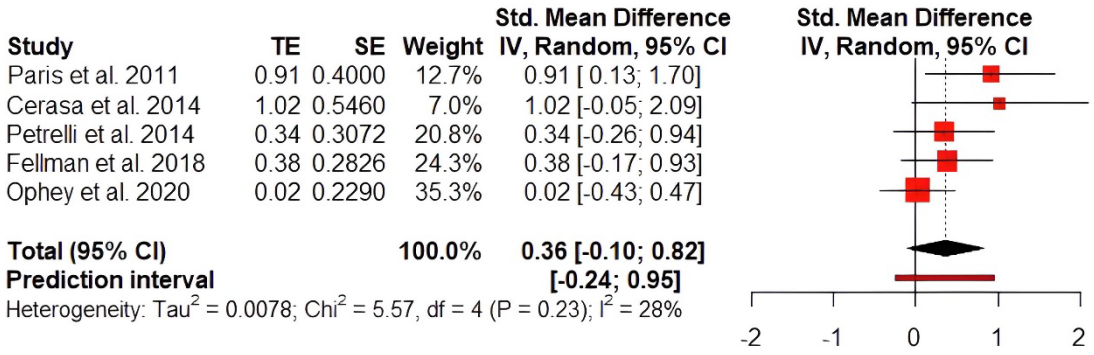


5.1.3.3. Attention

Attention changes after cognitive rehabilitation were analyzed in five studies. The effect sizes of a random-effects model of attention in cognitive rehabilitation accuracy were small and not significant (g = 0.36, p = .09) with a 95% CI (-0.10 to 0.82). Heterogeneity was low across the studies (Q = 5.57, p = .23; I^2 = 28%) (Figure 7).

Figure 7

Effectiveness of cognitive rehabilitation in attention



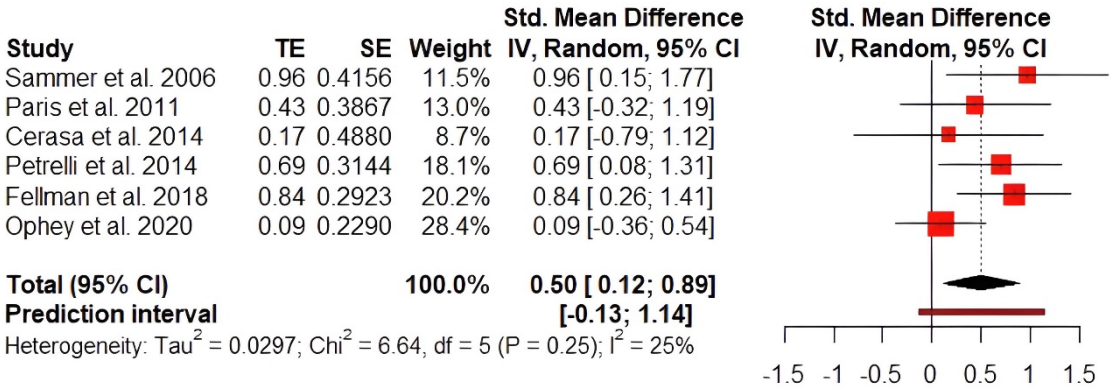
5.1.3.4. Working memory

Working memory changes after cognitive rehabilitation were evaluated in six studies. The effect sizes of a random-effects model of working memory in cognitive rehabilitation accuracy were moderate and statistically significant (g = 0.50, p = .02) with

a 95% CI (0.12 to 0.89). Heterogeneity was low across the studies (Q = 6.64, p = .25; I^2 = 25%) (Figure 8).

Figure 8

Effectiveness of cognitive rehabilitation in working memory

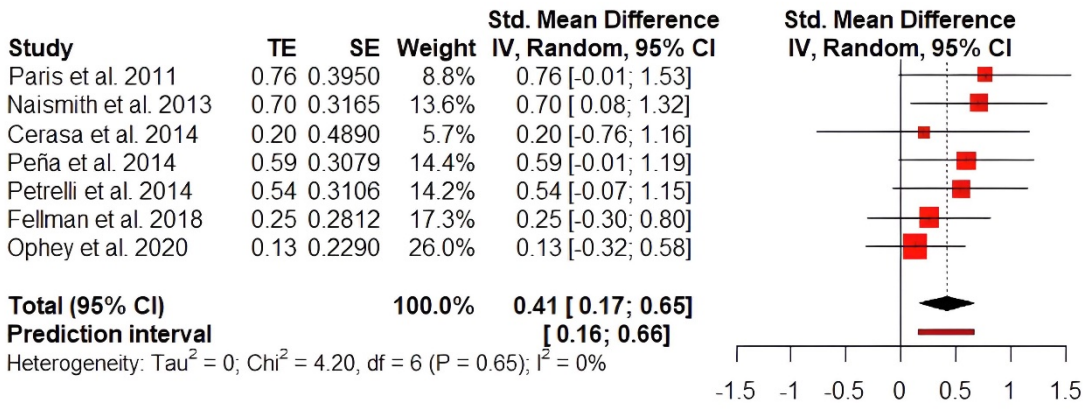


5.1.3.5. Verbal memory

Verbal memory was assessed in seven studies after cognitive rehabilitation. The effect sizes of a random-effects model of verbal memory in cognitive rehabilitation accuracy were small and statistically significant (g = 0.41, p = .00) with a 95% CI (0.17 to 0.65). Heterogeneity was low across the studies (Q = 4.20, p = .65; I^2 = 0%) (Figure 9).

Figure 9

Effectiveness of cognitive rehabilitation in verbal memory

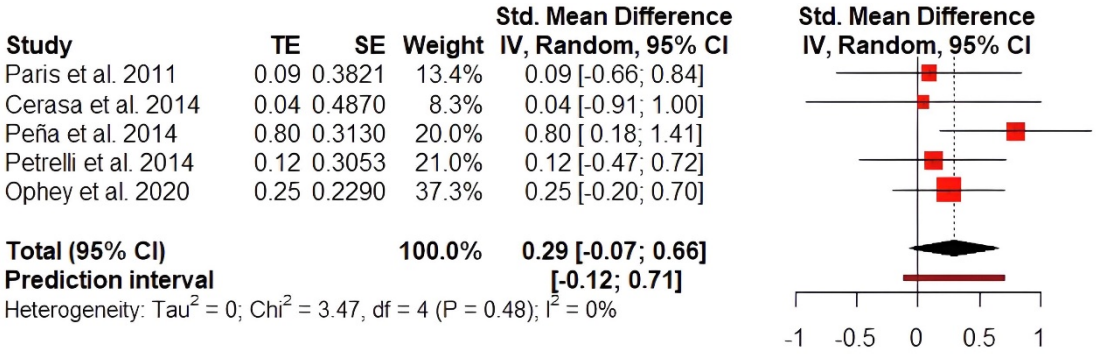


5.1.3.6. Visual memory

Visual memory was measured in five studies. The effect sizes of a random-effects model of visual memory in cognitive rehabilitation accuracy were small and not significant (g = 0.29, p = .08) with a 95% CI (-0.07 to 0.66). Heterogeneity was low across the studies (Q = 3.47, p = .48; I^2 = 0%) (Figure 10).

Figure 10

Effectiveness of cognitive rehabilitation in visual memory

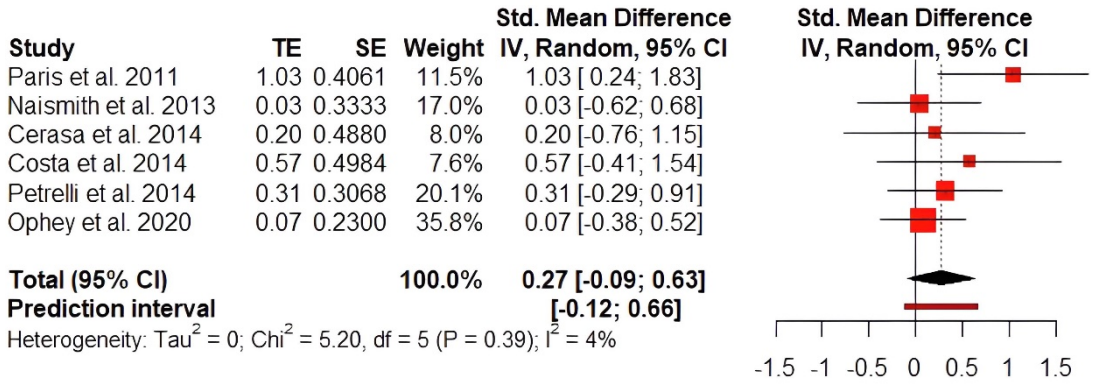


5.1.3.7. Verbal fluency

After cognitive rehabilitation, six studies measured verbal fluency. The effect sizes of a random-effects model of verbal fluency in cognitive rehabilitation accuracy were small and not significant (g = 0.27, p = .11) with a 95% CI (-0.09 to 0.63). Heterogeneity was low across the studies (Q = 5.20, p = .39; I^2 = 4%) (Figure 11).

Figure 11

Effectiveness of cognitive rehabilitation in verbal fluency

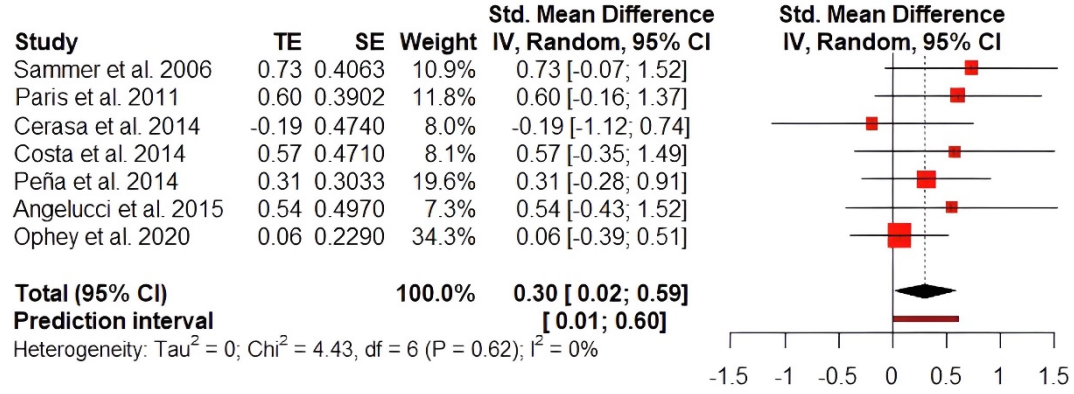


5.1.3.8. Executive functions

Executive function measures were assessed by seven studies. The effect sizes of a random-effects model of executive functions in cognitive rehabilitation accuracy were small and statistically significant (g = 0.30, p = .04) with a 95% CI (0.02 to 0.59). Heterogeneity was low across the studies (Q = 4.43, p = .62; I^2 = 0%) (Figure 12).

Figure 12

Effectiveness of cognitive rehabilitation in executive functions

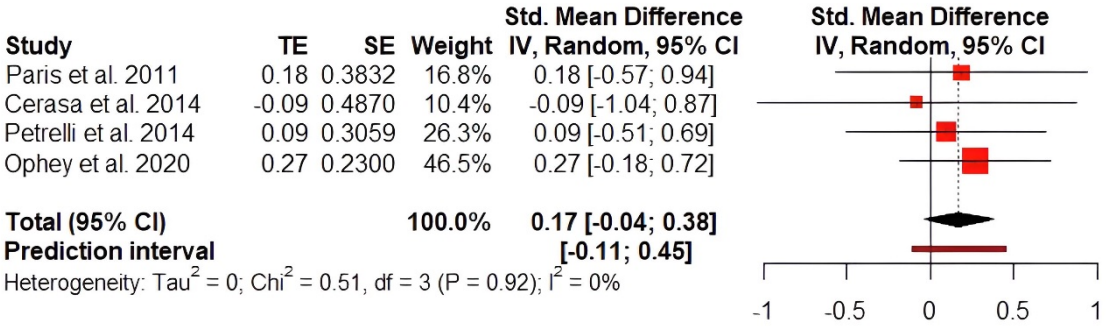


5.1.3.9. Visuospatial and visuoconstructive abilities

Visuospatial and visuoconstructive abilities changes after cognitive rehabilitation were reported by four studies. The effect sizes of visuospatial and visuoconstructive abilities in cognitive rehabilitation accuracy showed no effect (g = 0.17, p = .11) with a 95% CI (-0.04 to 0.38). Heterogeneity was low across the studies (Q = 0.51, p = .92; I^2 = 0%) (Figure 13).

Figure 13

Effectiveness of cognitive rehabilitation in visuospatial and visuoconstructive abilities

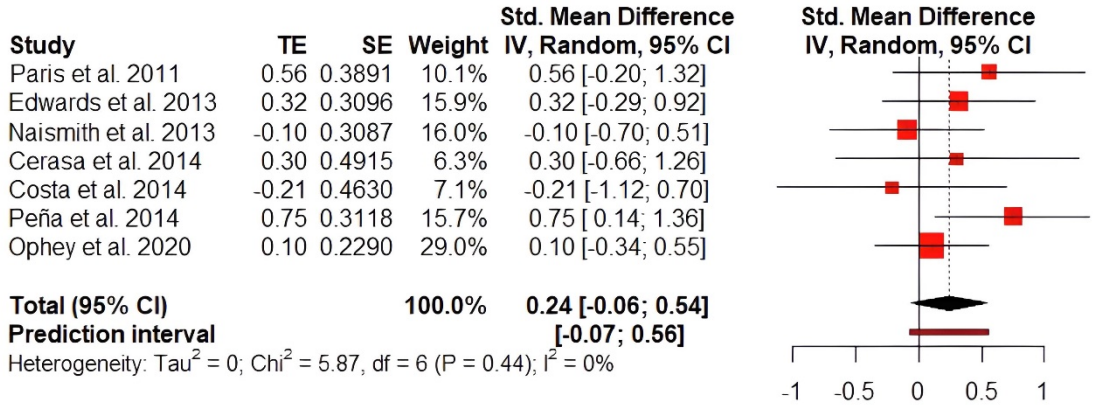


5.1.3.10. Processing speed

Processing speed was reported by seven studies. The effect sizes of a random-effects model of processing speed in cognitive rehabilitation accuracy were small and not significant (g = 0.24, p = .09) with a 95% CI (-0.06 to 0.54). Heterogeneity was low across the studies (Q = 5.87, p = .44; I^2 = 0%) (Figure 14).

Figure 14

Effectiveness of cognitive rehabilitation in processing speed



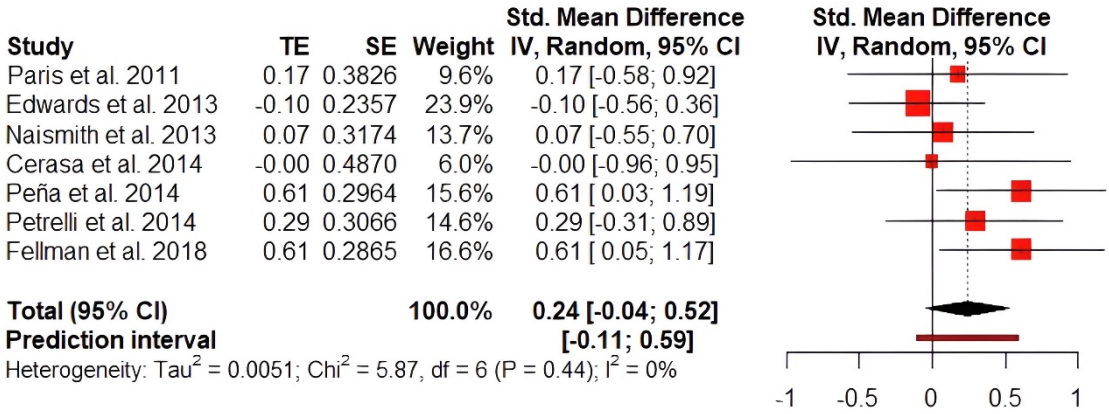
5.1.3.11. Others: functionality, depressive symptoms and quality of life

Only two studies reported changes after cognitive rehabilitation in functionality, so a meta-analysis could not be performed. Depressive symptoms were assessed in seven studies. The effect sizes of a random-effects model of depressive symptoms in cognitive

rehabilitation accuracy were small and not significant (g = 0.24, p = .08) with a 95% CI (-0.04 to 0.52). Heterogeneity was low across the studies (Q = 5.87, p = .44; I^2= 0%) (Figure 15).

Figure 15

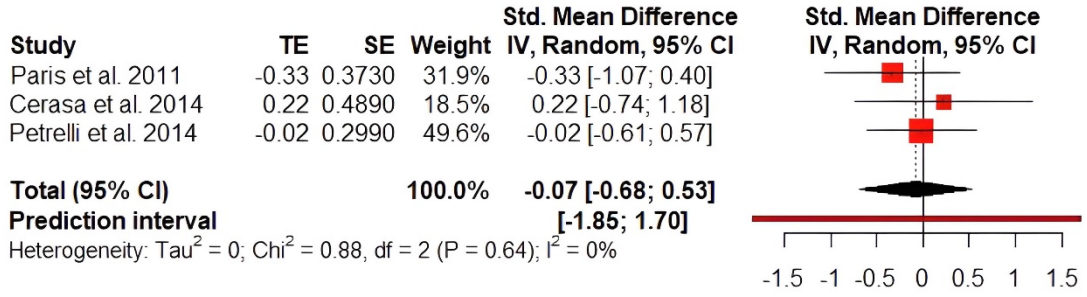
Effectiveness of cognitive rehabilitation in depressive symptoms



Quality of life outcome was only reported in three studies. The effect sizes of quality of life in cognitive rehabilitation accuracy showed no effect (g = -0.07, p = .64) with a broad 95% CI (-0.68 to 0.53). Heterogeneity was low across the studies (Q = 0.88, p = .64; I^2 = 0%) (Figure 16).

Figure 16

Effectiveness of cognitive rehabilitation in quality of life



5.1.4. Moderator analyses

In order to explore possible parameters that could explain the differences between the effect sizes obtained, moderator analyses were performed. The mixed-effects model meta-regression analyses were conducted with the estimated overall cognitive function effect sizes and the following predictor variables: age and years of education, intervention time variables (number, frequency, and duration of sessions), cognitive training modality (pencil-paper or computer), baseline global cognitive scores, and PD patient-related features [disease duration, H&Y scale (Hoehn & Yahr, 1967) and UPDRS III (Martínez-Martín et al., 1994)] (Table 8).

No significant effects were found among the main effects of the predictor variables (models 1 to 10). Interaction between predictor variables (models 11 to 16) was tested through a meta-regression analysis. There were no significant interactions in models 11, 12, 13, 14, and 16. However, a statistically significant and negative association was observed in the interaction between the number of sessions conducted and frequency of weekly sessions (model 15) with the overall cognitive function effect sizes ($F(3, 5) = 4.4$; $\beta = -0.02$; $p = .04$). These results suggested that the number of sessions in a cognitive rehabilitation program could influence the effect sizes obtained when the weekly frequency of these sessions is also taken into account. Nonetheless, this interaction did not explain the possible heterogeneity between the different effect sizes ($R^2 = 0\%$).

Table 8

Results of overall cognitive function meta-regression analyses

Model Number	Predictor Variables	k	df	$F_{moderator}$	$Q_{residual}$	R^2	β	*p*
1	Age of participants	10	8	3.96	2.70	0%	0.04	.08
2	Years of education	9	7	4.45	4.45	0%	-0.03	.07
3	H&Y	8	6	2.03	2.79	0%	0.66	.20
4	Duration of PD (years)	9	7	1.10	2.36	0%	0.01	.32
5	Baseline global cognitive scores	10	8	0.30	3.90	0%	0.00	.60
6	Total number of conducted sessions	10	8	0.02	4.03	0%	-0.00	.89
7	Training session duration (min)	10	8	0.02	4.03	0%	0.01	.87
8	Frequency of weekly sessions	9	7	1.72	2.19	0%	-0.08	.23
9	UPDRS-III	8	6	0.03	2.40	0%	0.01	.87
10	Tools for cognitive training (pencil & paper or computer)	10	7	1.71	2.71	0%	-0.12	.24
11	Age × Years of education	9	5	2.71	1.04	0%	0.01	.15
12	Duration of PD × H&Y	8	4	1.70	1.64	0%	-0.06	.30
13	H&Y × UPDRS-III	6	2	0.43	1.05	0%	-1.54	.75
14	Total number of sessions conducted × Training session duration (min)	10	6	4.04	1.33	0%	0.00	.07
15	Total number of sessions conducted × Frequency of weekly sessions	9	5	4.41	0.75	0%	-0.02	.04*
16	Training session duration (min) × Frequency of weekly sessions	9	5	2.21	1.17	0%	0.01	.20

Note: k = number of studies; $F_{moderator}$ = test of moderators; $Q_{residual}$ = test for residual heterogeneity; R^2 = amount of heterogeneity accounted for; β = estimate; * $p \leq .05$; PD = Parkinson's disease; H&Y = Hoehn and Yahr scale; UPDRS-III = Unified Parkinson's Disease Rating Scale-part III.

5.1.5. Publication bias

In order to analyze the presence of publication bias, funnel plots and the Eggers regression test were performed. No evidence of asymmetry was observed in the funnel plots of the overall cognitive functions, global cognitive status, cognitive subdomains, depressive symptoms, and quality of life (Figure S1). Egger's regression test was not significant for most of the variables ($p > .15$), except for a significant result that was found in the attention domain ($p = .01$). However, Egger's test does not provide sufficient information for global cognitive status, cognitive subdomains, depressive symptoms, and quality of life, as there are fewer than 10 studies in each of the domains (Sterne et al., 2011). In addition, the results indicate low levels of publication bias, but it is necessary to consider the levels of publication bias in isolation.

5.1.6. Sensitivity analyses

Sensitivity analyses were performed to examine whether the results obtained above would change if only the randomized studies were analyzed. Consequently, analyses were performed only in the cognitive subdomains of verbal memory, verbal fluency, executive function, and processing speed. Small changes were observed in the effect sizes in verbal memory (from $g = 0.41$, $p = .00$; to $g = 0.37$, $p = .01$), verbal fluency (from $g = 0.27$, $p = .11$; to $g = 0.32$, $p = .11$), and executive function (from $g = 0.30$, $p = .04$; to $g = 0.30$, $p = .03$) domains. Despite this, the effect size and significance of the previous domains were not significantly changed after the exclusion of the non-randomized study. However, a small change was observed in the processing speed cognitive domain, which, although still having a small effect size (from $g = 0.24$ to $g = 0.31$), becomes marginally significant (from $p = .09$ to $p = .06$) (Figure S2).

5.2. Study II

5.2.1. Parkinson´s disease patients

No significant differences in demographic characteristics were found between PD groups (Table 9). Significant differences at baseline were found in verbal memory between the combined intervention group compared to the single intervention group (p = .043) and the control group (p = .035); and processing speed between the combined intervention group and the control group (p = .010), while in the remaining variables significant differences were not observed (Table 10).

Table 9

Demographic characteristics, global cognitive status, premorbid intelligence, cognitive reserve, and PD-related features in the baseline assessment of PD

	Combined intervention (n=20)		**Single intervention (n=14)**		**Control group (n=12)**			
	M	SD	M	SD	M	SD	χ^2	*p*
Sex (male)	15	75%	12	85.7%	10	83.3%	0.69	.709
Age	71.35	9.25	68.71	8.13	67.50	5.20	3.95	.139
MoCA (MCI)	14	70%	8	57.1%	8	66.7%	0.62	.735
WAT	23.25	6.81	23.43	4.74	24.17	4.73	0.27	.875
Cognitive Reserve	12.20	3.64	13.21	4.26	12.25	3.33	0.49	.784
UPDRS III	25.65	9.67	28.14	12.18	20.83	10.21	3.17	.205
H&Y	2.15	0.59	2.36	0.66	1.96	0.75	2.36	.307
LEDD	593.25	499.59	577.57	269.19	674.92	467.72	0.62	.733
Years of disease duration	5.65	3.60	7.26	7.41	5.69	4.79	0.03	.986

Note: M=Mean; SD=Standard deviation; MoCA= Montreal Cognitive Assessment; MCI= Mild Cognitive Impairment; Pc= Percentile; WAT= Word Accentuation Test; UPDRS III= Unified Parkinson's Disease Rating Scale (UPDRS) part III; H&Y= Hoehn and Yahr Staging Scale; LEDD= Levodopa Equivalent Daily Dose.

Table 10

Cognitive and clinical characteristic of PD at baseline and post-treatment

		Combined intervention (n=20)		Single intervention (n=14)		Control group (n=12)		Baseline comparison	
		M	SD	M	SD	M	SD	χ^2	*p*
Cognition									
Attention/working memory	Pre	-0.11	0.93	0.20	0.92	-0.06	0.87	0.89	.639
	Post	-0.08	0.92	0.02	0.91	0.12	0.90		
Processing speed	Pre	-0.33	0.83	-0.05	0.88	0.55	0.85	6.65	.036
	Post	-0.24	0.91	0.09	0.75	0.30	1.00		
Visual memory	Pre	-0.38	0.79	0.31	1.06	0.28	1.02	4.72	.094
	Post	-0.18	0.90	0.19	0.95	0.08	1.13		
Verbal memory	Pre	-0.38	0.87	0.36	1.02	0.22	0.73	6.13	.047
	Post	0.00	0.91	0.13	1.08	-0.16	0.87		
Executive functions	Pre	-0.25	1.00	0.08	0.83	0.32	1.04	2.65	.266
	Post	-0.06	0.72	0.08	1.38	0.01	0.87		
Verbal fluency	Pre	-0.01	1.12	-0.11	0.52	0.15	0.91	0.32	.851
	Post	0.13	0.95	-0.12	0.82	-0.07	0.88		
Cognitive flexibility	Pre	-0.29	1.02	0.19	0.86	0.26	0.75	3.23	.199
	Post	-0.12	1.04	-0.04	0.96	0.23	0.76		
Theory of Mind	Pre	4.55	2.11	6.00	0.88	5.83	1.40	4.61	.100
	Post	5.30	1.98	6.07	1.54	5.42	1.73		
Facial emotion recognition	Pre	23.40	3.62	25.29	4.76	23.92	4.98	1.07	.584
	Post	25.15	3.17	24.21	5.12	23.25	4.94		
Mood states									
GHQ-12	Pre	16.50	6.79	15.21	4.79	13.50	5.42	3.06	.217
	Post	9.20	6.16	11.29	5.88	13.42	3.45		
HADS-A	Pre	5.75	3.73	5.14	4.37	7.17	3.97	1.71	.425
	Post	5.30	3.44	5.64	3.13	5.92	2.78		

HADS-D	Pre	5.55	3.68	3.36	2.53	6.67	5.05	4.62	.099
	Post	3.60	2.64	4.36	2.65	5.33	3.55		
LARS	Pre	-22.70	6.05	-22.43	5.92	-23.83	6.35	0.33	.850
	Post	-25.35	4.28	-24.00	6.04	-26.33	6.01		
Functionality									
Whodas-II	Pre	22.40	7.78	21.71	6.72	23.08	7.06	0.27	.875
	Post	19.10	6.61	19.21	4.21	22.08	7.40		
FSS	Pre	29.25	15.31	29.71	16.24	33.00	13.55	0.87	.648
	Post	31.55	14.74	33.00	10.84	33.58	16.13		
Quality of life									
PDQ-39	Pre	20.70	9.58	20.07	11.76	21.55	10.39	0.17	.918
	Post	20.48	10.03	20.09	8.17	24.74	11.26		
Mobility dimension	Pre	26.13	19.71	29.46	26.24	19.58	14.88	0.90	.639
	Post	26.00	20.02	22.50	19.95	25.00	15.56		
ADL dimension	Pre	23.13	19.75	22.46	15.64	27.08	24.78	0.10	.953
	Post	22.29	21.97	22.91	13.05	27.08	16.04		
Emotional well-being dimension	Pre	25.00	19.49	23.21	20.52	28.47	23.15	0.36	.834
	Post	23.96	16.05	20.83	14.71	37.50	20.49		
Stigma dimension	Pre	8.13	8.63	18.31	22.26	10.94	16.88	0.96	.618
	Post	8.44	11.70	9.38	12.68	11.97	11.76		
Social Support dimension	Pre	6.67	13.13	3.57	7.81	10.42	24.39	0.37	.832
	Post	1.67	4.36	3.57	6.30	7.64	12.54		
Cognition dimension	Pre	26.56	16.33	19.64	13.62	30.73	14.22	3.10	.212
	Post	33.13	20.08	26.79	11.61	31.77	17.37		
Communication dimension	Pre	12.08	14.68	13.69	15.19	14.58	8.79	1.18	.554
	Post	10.42	12.65	22.02	18.66	20.14	14.46		
Bodily Discomfort dimension	Pre	37.92	28.29	30.36	27.46	30.56	21.12	0.90	.637
	Post	37.92	22.04	32.74	21.80	36.81	20.55		

Note: M=Mean; SD= Standard deviation; GHQ-12=General Health Questionnaire; HADS-A= Hospital Anxiety and Depression Scale- Anxiety scores; HADS-D= Hospital Anxiety and Depression Scale- Depression scores; LARS= Lille Apathy Rating Scale; FSS= Fatigue Severity Scale; PDQ-39=Parkinson's Disease Questionnaire-39.

5.2.2. Family caregivers

No significant differences were observed in demographic characteristics at baseline between the family caregivers who participated in psychoeducation program (Psychoeducation group) and the family caregivers who did not participate (No psychoeducation group) (Table 11). Significant differences at baseline between the psychoeducation group and no psychoeducation group were found in verbal memory, visual memory, and processing speed, with the psychoeducation group showing higher scores in these three domains (Table 12).

Table 11

Demographic characteristics, global cognitive status, premorbid intelligence, and cognitive reserve in the baseline assessment of family caregivers

	Psychoeducation (n=20)		**No psychoeducation (n=26)**			
	M	SD	M	SD	χ^2/u	*p*
Sex (male)	2	10%	8	30.8%	2.87	.090
Age	66.05	13.82	61.85	9.60	182.00	.084
MoCA (MCI)	9	45%	14	53.8%	0.35	.552
WAT	21.65	5.59	23.04	5.47	229.50	.497
Cognitive Reserve	11.75	3.80	12.35	3.86	237.50	.616

Note: M=Mean; SD=Standard deviation; MoCA= Montreal Cognitive Assessment; MCI= Mild Cognitive Impairment; Pc= Percentile; WAT= Word Accentuation Test.

Table 12

Cognitive and clinical characteristic of family caregivers at baseline and post-treatment

		Psychoeducation (n=20)		**No psychoeducation (n=26)**		**Baseline comparison**	
		M	SD	M	SD	*U*	*p*
Cognition							
Attention/working memory	Pre	-0.29	0.79	0.22	0.98	178.00	.069
	Post	-0.22	0.65	0.17	1.08		
Processing speed	Pre	-0.29	0.95	0.23	0.81	165.00	.035
	Post	-0.26	0.86	0.20	0.87		
Visual memory	Pre	-0.54	0.87	0.42	0.86	105.50	.001
	Post	-0.34	1.00	0.26	0.86		
Verbal memory	Pre	-0.35	0.90	0.27	0.88	156.00	.021
	Post	-0.08	0.74	0.06	1.02		
Executive functions	Pre	-0.25	0.90	0.19	0.90	190.00	.121
	Post	-0.22	0.90	0.17	1.00		
Verbal fluency	Pre	-0.31	0.88	0.24	0.81	174.00	.057
	Post	-0.23	0.84	0.18	0.87		
Cognitive flexibility	Pre	-0.31	0.99	0.24	0.81	179.50	.074
	Post	-0.00	1.00	0.00	0.95		
Theory of Mind	Pre	5.90	1.77	5.69	1.64	234.00	.553
	Post	5.95	1.70	6.54	1.30		
Facial emotion recognition	Pre	26.00	3.51	26.12	4.79	252.50	.859
	Post	27.15	3.08	27.00	4.21		
Mood states							
GHQ-12	Pre	13.30	2.94	13.31	2.77	254.00	.891
	Post	9.10	4.81	12.65	4.20		

HADS-A	Pre	6.50	4.07	5.35	3.36	220.00	.374
	Post	5.05	3.58	6.38	3.16		
HADS-D	Pre	2.80	2.98	2.96	2.39	231.00	.515
	Post	1.85	2.74	3.12	2.47		
LARS	Pre	-27.60	5.08	-26.81	4.81	232.50	.540
	Post	-29.95	3.71	-26.27	11.54		
Functionality							
Whodas-II	Pre	14.45	3.36	14.58	3.95	258.50	.973
	Post	13.55	2.89	14.81	3.37		
FSS	Pre	19.35	14.31	24.42	13.81	181.00	.077
	Post	15.80	7.47	22.35	13.05		
Quality of life							
EuroQol- 5D	Pre	0.86	0.15	0.87	0.14	244.00	.704
	Post	0.92	0.12	0.89	0.15		
Caregiver burden							
ZBI	Pre	15.10	10.09	13.35	10.46	232.00	.534
	Post	12.50	10.55	15.12	14.21		
CSI	Pre	2.65	4.53	2.35	3.11	228.00	.464
	Post	1.90	2.22	2.12	2.81		
PACS	Pre	21.95	11.98	20.46	11.27	235.00	.579
	Post	21.35	10.22	21.12	8.52		

Note: M=Mean; SD= Standard deviation; GHQ-12=General Health Questionnaire; HADS-A= Hospital Anxiety and Depression Scale- Anxiety scores; HADS-D= Hospital Anxiety and Depression Scale- Depression scores; LARS= Lille Apathy Rating Scale; FSS= Fatigue Severity Scale; ZBI= Zarit Burden Interview; CSI= Caregiver Strain Index; PACS= Positive Aspects of caregiving.

5.2.3. Cognitive performance, mood states, functionality and quality of life changes after intervention

5.2.3.1. Parkinson´s disease patients

ANCOVA analyses showed statistically significant improvements in verbal memory (F = 4.88; p = .012) and emotional well-being dimension (F = 3.82; p = .030) with large effect sizes (η_p^2 = .189 and η_p^2 = .154) between combined, single and control group (Table 13). Specifically, verbal memory improvements were found between the combined intervention group compared to the single intervention group (p = .027) and the control group (p = .002), where people from the combined intervention group showed better scores (Table 14). Emotional well-being improvements were observed between the combined intervention group and the control group (p = .023), and the single intervention group compared to the control group (p = .011) (Table 14). No significant differences were observed in facial emotions recognition, general health, and communication dimension between the combined, single, and control groups. However, post-hoc analyses revealed that the combined intervention group showed significant improvements in facial emotions recognition (p = .029) and general health (p = .018) compared to the control group; and communication dimension between the combined intervention group and the single intervention group (p = .044) (Table 14).

5.2.3.2. Family caregivers

ANCOVA analyses revealed that psychoeducation group showed significant improvements in general health (F = 7.21; p = .014) and anxiety scores (F = 4.45; p = .029) in comparison to those who did not participate in psychoeducation. Effect sizes were large for general health (η_p^2 = .144) and medium for anxiety (η_p^2 = .094) (Table 15).

Table 13

Cognitive and clinical characteristic of PD after intervention

	Combined intervention (n=20)		**Single intervention (n=14)**		**Control group (n=12)**				**Effect size**
	Mean change score (95% CI)	SE	Mean change score (95% CI)	SE	Mean change score (95% CI)	SE	*F*	*p*	η_p^2
Cognition									
Attention/working memory	-0.01 (-0.37 to 0.39)	0.19	-0.12 (-0.44 to 0.20)	0.17	0.16 (-0.14 to 0.44)	0.14	0.51	.603	.024
Processing speed	0.04 (-0.17 to 0.24)	0.11	0.14 (-0.20 to 0.45)	0.17	-0.17 (-0.46 to 0.17)	0.16	1.11	.339	.050
Visual memory	0.11 (-0.24 to 0.44)	0.18	-0.04 (-0.34 to 0.22)	0.14	-0.13 (-0.47 to 0.32)	0.21	0.41	.665	.019
Verbal memory	0.33 (0.02 to 0.58)	0.14	-0.17 (-0.48 to 0.15)	0.16	-0.35 (-0.63 to -0.09)	0.14	4.88	.012	.189
Executive functions	0.05 (-0.26 to 0.35)	0.15	0.04 (-0.55 to 0.86)	0.38	-0.14 (-0.46 to 0.23)	0.17	0.18	.835	.009
Verbal fluency	0.14 (-0.11 to 0.38)	0.13	-0.04 (-0.35 to 0.25)	0.15	-0.19 (-0.42 to 0.03)	0.12	1.52	.230	.068
Cognitive flexibility	0.03 (-0.38 to 0.45)	0.21	-0.13 (-0.55 to 0.30)	0.21	0.10 (-0.23 to 0.52)	0.19	0.27	.765	.013
Theory of Mind	0.30 (-0.58 to 1.12)	0.43	0.47 (-0.33 to 1.38)	0.43	-0.12 (-1.21 to 0.84)	0.53	0.41	.663	.019
Facial emotion recognition	1.54 (0.07 to 3.10)	0.77	-0.72 (-2.61 to 0.97)	0.92	-0.72 (-2.19 to 0.59)	0.69	2.97	.062	.124
Mood states									
GHQ-12	-6.80 (-10.35 to -3.13)	1.88	-4.04 (-7.46 to -1.22)	1.61	-1.95 (-5.05 to 0.37)	1.34	2.75	.076	.116
HADS-A	-0.57 (-2.16 to 1.02)	0.83	-0.01 (-1.45 to 1.60)	0.78	-0.45 (-2.32 to 1.14)	0.85	0.16	.856	.007
HADS-D	-1.69 (-3.46 to -0.02)	0.85	-0.24 (-1.65 to 0.91)	0.66	-0.32 (.-1.87 to 1.74)	0.93	1.59	.217	.070

LARS	-2.54 (-4.69 to -0.52)	1.06	-1.32 (-3.81 to 1.20)	1.27	-2.98 (-5.59 to 0.12)	1.46	0.49	.614	.023
Functionality									
Whodas-II	-3.28 (-5.98 to -1.09)	1.27	-2.93 (-6.92 to .91)	1.92	-0.53 (-4.21 to 3.35)	1.92	0.92	.406	.042
FSS	1.79 (-4.07 to 8.03)	3.03	2.99 (-2.13 to 8.34)	2.71	1.78 (-4.41 to 9.27)	3.48	0.05	.949	.002
Quality of life									
PDQ-39	-0.24 (-3.15 to 2.63)	1.48	-0.25 (-5.41 to 5.48)	2.71	3.53 (-0.46 to 8.04)	2.14	1.04	.363	.062
Mobility dimension	0.07 (-4.38 to 4.52)	2.22	-5.81 (-14.41 to 1.50)	4.15	3.74 (-4.55 to 11.64)	4.15	1.78	.182	.078
ADL dimension	-1.17 (-8.6 to 6.50)	3.88	-0.09 (-6.48 to 6.60)	3.30	1.36 (-5.55 to 8.02)	3.49	0.12	.889	.006
Emotional well-being dimension	-1.23 (-8.95 to 5.75)	3.72	-3.52 (-12.15 to 5.66)	4.45	10.67 (3.77 to 18.01)	3.62	3.82	.030	.154
Stigma dimension	-2.61 (8.39 to 2.64)	2.81	-4.10 (-11.95 to 3.82)	3.94	0.27 (-6.42 to 7.84)	3.65	0.47	.631	.022
Social Support dimension	-5.03 (-9.55 to -1.36)	2.10	-2.38 (-7.45 to 2.17)	2.34	0.05 (-6.04 to 6.72)	3.16	2.07	.139	.090
Cognition dimension	6.82 (0.93 to 11.86)	2.79	5.66 (-1.22 to 12.66)	3.38	2.34 (-5.52 to 10.21)	4.16	0.43	.653	.020
Communication dimension	-2.29 (-8.76 to 4.15)	3.24	8.59 (0.03 to 16.60)	4.15	6.29 (-1.10 to 16.16)	4.39	2.82	.071	.118
Bodily Discomfort dimension	2.47 (-7.56 to 13.18)	5.36	0.43 (-10.12 to 10.88)	5.43	4.12 (-3.99 to 13.15)	4.48	0.15	.865	.007

Note: M=Mean; SE= Standard error; CI= Confidence Interval; η_p^2= partial eta squared; GHQ-12=General Health Questionnaire; HADS-A= Hospital Anxiety and Depression Scale- Anxiety scores; HADS-D= Hospital Anxiety and Depression Scale- Depression scores; LARS= Lille Apathy Rating Scale; FSS= Fatigue Severity Scale; PDQ-39= Parkinson's Disease Questionnaire-39; ADL= Activities of daily living.
Change scores post-treatment score-pre-treatment score. Means for change scores are adjusted for the effect of the baseline score. CI and SE for change scores were derived from the bootstrap analysis.

Table 14

Post-hoc p values of cognitive and clinical characteristic of PD after intervention: Combined intervention vs. single intervention, combined intervention vs. control group, and single intervention vs. control group

	Combined intervention vs. single intervention	**Combined intervention vs. control group**	**Single intervention vs. control group**
	p	*p*	*p*
Cognition			
Attention/working memory	.669	.497	.231
Processing speed	.640	.293	.198
Visual memory	.506	.398	.754
Verbal memory	.027	.002	.404
Executive functions	.969	.393	.667
Verbal fluency	.396	.070	.427
Cognitive flexibility	.592	.790	.414
Theory of Mind	.764	.552	.378
Facial emotion recognition	.069	.029	.991
Mood states			
GHQ-12	.214	.018	.280
HADS-A	.593	.905	.682
HADS-D	.116	.228	.936
LARS	.431	.792	.363

Functionality			
Whodas-II	.870	.243	.331
FSS	.754	.998	.784
Quality of life			
PDQ-39	.975	.195	.261
Mobility dimension	.194	.433	.092
ADL dimension	.821	.623	.743
Emotional well-being dimension	.650	.023	.011
Stigma dimension	.709	.488	.329
Social Support dimension	.169	.134	.460
Cognition dimension	.788	.395	.527
Communication dimension	.044	.114	.700
Bodily Discomfort dimension	.771	.738	.520

Note: GHQ-12=General Health Questionnaire; HADS-A= Hospital Anxiety and Depression Scale- Anxiety scores; HADS-D= Hospital Anxiety and Depression Scale- Depression scores; LARS= Lille Apathy Rating Scale; FSS= Fatigue Severity Scale; PDQ-39= Parkinson's Disease Questionnaire-39; ADL= Activities of daily living.
Significance levels were determined using *F* tests based on the bootstrap SE estimate for that comparison, rather than using a pooled SE estimate.

Table 15

Cognitive and clinical characteristic of family caregivers after intervention

	Psychoeducation (n=20)		**No psychoeducation (n=26)**				**Effect size**
	Mean change score (95% CI)	SE	Mean change score (95% CI)	SE	*F*	*p*	η_p^2
Cognition							
Attention/working memory	0.04 (-0.18 to 0.25)	0.11	-0.03 (-0.22 to 0.15)	0.10	0.18	.666	.004
Processing speed	0.00 (-0.15 to 0.17)	0.08	-0.00 (-0.17 to 0.14)	0.08	0.00	.953	.000
Visual memory	0.02 (-0.52 to 0.42)	0.24	-0.02 (-0.28 to 0.31)	0.15	0.03	.907	.001
Verbal memory	0.14 (-0.23 to 0.47)	0.17	-0.10 (-0.39 to 0.27)	0.16	1.05	.333	.024
Executive functions	-0.04 (-0.34 to 0.24)	0.15	0.03 (-0.25 to 0.32)	0.15	0.09	.749	.002
Verbal fluency	0.00 (-0.23 to 0.23)	0.12	-0.00 (-0.23 to 0.25)	0.13	0.00	.979	.000
Cognitive flexibility	0.12 (-0.31 to 0.55)	0.21	-0.09 (-0.50 to 0.27)	0.20	0.56	.449	.013
Theory of Mind	0.14 (-0.60 to 0.84)	0.38	0.78 (0.17 to 1.44)	0.33	2.25	.141	.050
Facial emotion recognition	1.13 (-0.14 to 2.42)	0.64	0.90 (-0.13 to 1.93)	0.52	0.09	.776	.002

Mood states							
GHQ-12	-4.20 (-6.45 to -2.23)	1.07	-.65 (-2.50 to 1.09)	0.91	7.21	.014	.144
HADS-A	-1.10 (-2.45 to 0.37)	0.72	.77 (-0.43 to 1.99)	0.64	4.45	.029	.094
HADS-D	0.00 (-2.22 to 0.29)	0.61	.19 (-0.71 to 1.14)	0.46	3.01	.118	.065
LARS	-2.52 (-4.39 to -0.72)	0.93	.67 (-2.59 to 4.97)	1.99	1.55	.275	.035
Functionality							
Whodas-II	-0.93 (-1.88 to -0.05)	0.47	.25 (-.85 to 1.31)	0.55	2.86	.077	.062
FSS	-5.38 (-8.87 to -1.87)	1.80	-.67 (-6.21 to 4.62)	2.67	2.49	.083	.055
Quality of life							
EuroQol-5D	0.06 (-0.00 to 0.12)	0.03	.02 (-0.40 to 0.09)	0.03	0.67	.402	.015
Caregiver burden							
ZBI	-2.34 (-6.62 to 1.86)	2.15	1.57 (-2.48 to 5.56)	2.04	1.60	.205	.036
CSI	-0.64 (-2.06 to 0.94)	0.75	-.32 (-1.32 to 0.38)	0.44	0.23	.673	.005
PACS	-0.05 (-4.59 to 4.39)	2.31	.27 (-3.15 to 3.46)	1.67	0.02	.900	.000

Note: M=Mean; CI= Confidence Interval; SE= Standard error; η_p^2= partial eta squared; GHQ-12=General Health Questionnaire; HADS-A= Hospital Anxiety and Depression Scale- Anxiety; HADS-D= Hospital Anxiety and Depression Scale- Depression; LARS= Lille Apathy Rating Scale; FSS= Fatigue Severity Scale; ZBI= Zarit Burden Interview; CSI= Caregiver Strain Index; PACS= Positive Aspects of caregiving.

Change scores= post-treatment score-pre-treatment score. Means for change scores are adjusted for the effect of the baseline score. CI and SE for change scores were derived from the bootstrap analysis. Significance levels were determined using *F* tests based on the bootstrap SE estimate for that comparison, rather than using a pooled SE estimate.

5.3. Study III

Demographic, cognitive reserve, PD-related features, HRQoL, anxiety, depression, apathy, fatigue, and neurocognition composite scores of the sample are provided in Table 16.

Table 16

Demographic characteristics, cognitive reserve, PD-related features, HRQoL, anxiety, depression, apathy, fatigue, and neurocognition composite score of the study sample (n= 108)

	M/n	SD/%	95% CI
Age (years)	70.15	7.94	68.63 to 71.66
Sex (male)	75	69.4%	
Years of education	10.81	4.45	9.97 to 11.66
Cognitive reserve	11.15	3.97	10.39 to 11.91
Hoehn & Yahr			
Stage 1.0	20	18.5%	
Stage 1.5	14	13%	
Stage 2.0	41	38%	
Stage 2.5	6	5.6%	
Stage 3.0	25	23.1%	
Stage 4.0	2	1.9%	
Years of disease duration	6.35	4.94	5.41 to 7.29
LEDD	600.73	412.63	522.02 to 679.44
UDPRS III	20.61	11.80	18.36 to 22.86
HRQoL total index (PDQ-39 summary index)[a]	20.75	10.88	18.68 to 22.83
Mobility[a]	23.24	20.56	19.32 to 27.16
ADL[a]	21.26	18.51	17.73 to 24.79
Emotional well-being[a]	28.55	23.18	24.13 to 32.97
Stigma[a]	9.66	14.93	6.81 to 12.51
Social Support[a]	8.02	14.98	5.17 to 10.88

Cognition[a]	25.75	16.98	22.51 to 28.99
Communication[a]	13.66	15.85	10.63 to 16.68
Bodily Discomfort[a]	35.88	25.84	30.95 to 40.80
HADS-A	6.16	4.46	5.31 to 7.01
Scores >8	40	37%	
HADS-D	4.84	3.65	4.15 to 5.54
Scores >8	24	22.2%	
LARS	-23.38	6.55	-24.63 to -22.13
Scores >-14	9	8.3%	
FSS	30.57	15.72	27.58 to 33.57
Scores >36	43	39.8%	
Neurocognition composite score[b]	-0.00	0.67	-0.13 to 0.13

Note: M= Mean; SD= Standard Deviation; CI= Confidence Interval; H&Y= Hoehn and Yahr stage Scale; LEDD= Levodopa Equivalent Daily Dose; UPDRS III= The Unified Parkinson's Disease Rating Scale- motor part; HRQoL= Health-Related Quality of Life; ADL= Activities of Daily Living; HADS-A= Hospital Anxiety and Depression Scale- Anxiety scores; HADS-D= Hospital Anxiety and Depression Scale- Depression scores; LARS= Lille Apathy Rating Scale; FSS= Fatigue Severity Scale; [a]Scores from 0 to 100; [b]Average in z-scores.

5.3.1. Correlation analyses of HRQoL and its dimensions

HRQoL total index (before and after overlapping items), mobility, and emotional well-being dimensions were associated with cognitive reserve; HRQoL total index after overlapping items, mobility and communication dimensions with LEDD variable; mobility dimension with age and HRQoL total index, emotional well-being, and bodily discomfort dimensions with sex. The correlation coefficients showed weak associations. Consequently, cognitive reserve, LEDD, age, and sex variables were included as covariates in the models whose correlation was significant (Table 17).

Regarding the potential determining variables, in general, weak to moderate significant correlations were found between HRQoL total index (before and after overlapping items), several dimensions of HRQoL, and motor symptoms, anxiety, depression, fatigue, and neurocognition scores (Table 18 and figure S3).

Table 17

Spearman's rho correlation analyses between HRQoL and demographic characteristics, cognitive reserve and LEDD of the study sample

Criterion variable	HRQoL total index	HRQoL without overlap	Mobility	ADL	Emotional well-being	Stigma	Social Support	Cognition	Communication	Bodily Discomfort
Age	.14	.12	.25*	.05	.09	-.09	-.04	.15	.11	.03
Sex	.21*	.15	.14	.00	.27*	.10	.06	.12	-.10	.24*
Cognitive Reserve	-.29*	-.26*	-.29*	-.16	-.22*	-.02	-.11	-.08	-.15	-.13
LEDD	.15	.19*	.22*	.05	.03	.08	.07	-.03	.28*	.13

Note: HRQoL= Health-Related Quality of Life; ADL= Activities of Daily Living; LEDD= Levodopa Equivalent Daily Dose. $^{*}p \leq .05$.

Table 18

Spearman's rho correlation analyses between HRQoL and potential determining variables: motor symptoms, anxiety, depression, apathy, fatigue and cognition of the study sample

Criterion variable	HRQoL total index	HRQoL without overlap	Mobility	ADL	Emotional well-being	Stigma	Social Support	Cognition	Communication	Bodily Discomfort
Motor symptoms										
UPDRS-III	.23*	.25*	.28*	.30*	.06	.09	-.25*	.17	.29*	.19*
Anxiety, depression and fatigue scores										
HADS-A	.52*	42*	.31*	.03	.70*	.06	.22*	.33*	.18	.48*
HADS-D	.50*	.43*	.42*	.19*	.49*	.09	.27*	.24*	.08	.33*
LARS	.18	.17	.13	.16	.12	.02	.01	.18	.10	.02
FSS	.43*	.44*	.44*	.22*	.26*	.10	.02	.13	.25*	.38*
Cognition										
Neuro-cognition[a]	-.26*	-.24*	-.31*	-.15	-.20*	-.11	-.01	-.19*	-.19*	-.10

Note: HRQoL= Health-Related Quality of Life; ADL= Activities of Daily Living; UPDRS III= The Unified Parkinson's Disease Rating Scale- motor part; HADS-A= Hospital Anxiety and Depression Scale- Anxiety scores; HADS-D= Hospital Anxiety and Depression Scale- Depression scores; LARS= Lille Apathy Rating Scale; FSS= Fatigue Severity Scale. [a]Average in z-scores; $^{*}p \leq .05$.

5.3.2. Predictors of HRQoL and its dimensions

Variance inflation factor (VIF) values ≥ 10 and tolerance values ≤ 0.10 would indicate collinearity problems. Tolerance values (>0.10) and VIF values (≤10) of all predictor variables were appropriate, so multicollinearity data was not observed among measures.

Stepwise Multiple Regression analyses showed that predictive model of HRQoL was significant (F (6,101) = 17.77; $p < .001$), showing that scores of anxiety (β = .32; p = .001), fatigue (β = .24; p = .003), UPDRS-III (β = .17; p = .021), and depression (β = .18; p = .050) predicted HRQoL total index. When emotional well-being dimension overlapping items were removed, fatigue (β = .33; $p < .001$), anxiety (β = .25; p = .005), UPDRS-III (β = .20; p = .015), and neurocognition (β = -.20; p= .038) were predictors of HRQoL total index, and depression was no longer significant (Table 19).

Concerning HRQoL dimensions' regressions, the model of mobility dimension was predicted by fatigue scores (β = .41; $p < .001$) and UPDRS-III (β = .21; p = .013). ADL dimension was predicted by UPDRS-III (β = .27; p = .004) and fatigue scores (β = .23; p = .015). Emotional well-being dimension was predicted by fatigue scores (β = .28; p = .002). Social support dimension was predicted by anxiety scores (β = .39; $p < .001$) and UPDRS-III (β = -.30; p = .001). Cognition dimension was predicted by anxiety scores (β = .33; p = .001). Communication dimension was predicted by neurocognition (β = -.23; p = .013) and UPDRS-III scores (β = .19; p = .040). Bodily discomfort dimension was predicted by anxiety (β = .41; $p < .001$) and fatigue scores (β = .22; p = .012). Stigma dimension did not show significant correlations, so their regression analyses were not performed. The results of the stepwise multiple regression analyses are provided in table 19.

Table 19

Stepwise multiple regression analyses of HRQoL total index before and after removing emotional well-being dimension, HRQoL dimensions, anxiety, depression and fatigue scores, neurocognition composite score, and motor symptoms of the study sample

Criterion variable	*F*	R^2	R^2 change	β	*t*	*p*	Predictors
HRQoL total index before and after removing emotional well-being dimension							
Model 1[a]	17.77	51.3%					
HRQoL total index			26.9%	.32	3.46	.001	HADS-A
			7.2%	.24	3.09	.003	FSS
			2.8%	.17	2.35	.021	UPDRS-III
			1.9%	.18	1.99	.050	HADS-D
Model 2[b]	12.42	42.5%					
HRQoL total index without emotional well-being dimension			16.5%	.33	3.84	.000	FSS
			6.1%	.25	2.86	.005	HADS-A
			3.9%	.20	2.46	.015	UPDRS III
			2.5%	-.20	-2.10	.038	Neurocognition
HRQoL dimensions							
Model 3[c]	11.83	36.7%					
Mobility			19.7%	.41	5.09	.000	FSS
			4.0%	.21	2.54	.013	UPDRS III
Model 4	9.37	15.1%					
ADL			10.2%	.27	2.95	.004	UPDRS III
			5.0%	.23	2.48	.015	FSS

Model 5[d]	9.71	21.9%					
Emotional well-being			7.9%	.28	3.24	.002	FSS
Model 6	13.80	20.8%					
Social Support			12.2%	.39	4.44	.000	HADS-A
			8.6%	-.30	-3.38	.001	UPDRS III
Model 7	12.51	10.6%					
Cognition			10.6%	.33	3.54	.001	HADS-A
Model 8[e]	7.26	17.3%					
Communication			5.3%	-.23	-2.54	.013	Neurocognition
			3.4%	.19	2.08	.040	UPDRS III
Model 9[f]	17.76	33.9%					
Bodily discomfort			23%	.41	4.74	.000	HADS-A
			4.1%	.22	2.55	.012	FSS

Note: HRQoL= Health-Related Quality of Life; ADL= Activities of Daily Living; UPDRS III= The Unified Parkinson's Disease Rating Scale- motor part; HADS-A= Hospital Anxiety and Depression Scale- Anxiety scores; HADS-D= Hospital Anxiety and Depression Scale- Depression scores; FSS= Fatigue Severity Scale.

[a]Adjusted by cognitive reserve and sex [Significant in model 1 in cognitive reserve (β=-.16; *p*=.047)]; [b]Adjusted by cognitive reserve and Levodopa Equivalent Daily Dose (LEDD); [c]Adjusted by cognitive reserve, age and LEDD [Significant in model 3 in cognitive reserve (β=-.26; *p*=.003)]; [d]Adjusted by cognitive reserve [Significant in model 5 (β=.-21; *p*=.024)] and sex [Significant in model 5 (β=.24; *p*=.013)]; [e]Adjusted by LEDD [Significant in model 8 (β=.26; *p*=.006)]; [f]Adjusted by sex [Significant in model 9 (β=.18; *p*=.032)].

VI. Discussion

6. Discussion

The present thesis provides a systematic review and a meta-analysis of the literature regarding the effectiveness of cognitive rehabilitation in PD patients (*study I*). Moreover, this thesis shows the results after applying a combined intervention of cognitive rehabilitation in PD patients and psychoeducation in their family caregivers (*study II*). Finally, this thesis provides accurate predictors of HRQoL controlling the overlapping items of HRQoL and clinical measures (*study III*).

Efficacy of cognitive rehabilitation in Parkinson´s disease

The main objective of *study I* was to perform a systematic review and a meta-analysis of the literature on the effectiveness of cognitive rehabilitation in people with PD in cognition, functionality, depressive symptoms, and quality of life. The results obtained in the systematic review showed that attention, working memory, verbal memory, executive functions, and processing speed were the cognitive domains that most frequently improved after cognitive rehabilitation in PD. These results demonstrated that cognitive rehabilitation improved cognition in people with PD, despite the variability of intervention strategies (intervention method, duration, and frequency) (Alzahrani & Venneri, 2018). The meta-analysis' major findings revealed moderate improvements in global cognitive status and working memory. Verbal memory, overall cognitive functions, attention, executive functions, visual memory, verbal fluency, and processing speed showed small effects. Visuospatial and visuoconstructive abilities showed no effects.

The moderate effect size obtained on global cognitive status highlights the importance of including global screening tests as outcome measures in cognitive rehabilitation studies and not only reporting them at baseline to assess differences between groups. In this meta-analysis, overall cognitive functions showed a small effect

size. These results may be owing to the article's data analysis criteria, which was based on the average of global cognitive status and cognitive subdomains from research that reported at least two cognitive measures.

Memory is frequently trained in cognitive rehabilitation programs but usually through a general approach instead of through specific memory subdomains. In several studies included in our research, working memory was trained independently and the results of the meta-analysis showed a moderate effect in this domain. In fact, despite working memory being a subdomain of memory, Leung and colleagues (2015) also assessed working memory independently showing a moderate effect size after cognitive rehabilitation. Verbal memory measures were reported in seven studies and visual memory measures in five studies. However, not all studies reported improvements after cognitive rehabilitation programs. Similar to Orgeta and colleagues (2020) we analyzed separately verbal and visual memory, whereas other meta-analyses analyzed a general memory domain including both (Lawrence et al., 2017; Leung et al., 2015). Our results showed a small effect size in verbal and visual memory. In general memory domain, other meta-analyses also obtained a small effect after cognitive rehabilitation (Lawrence et al., 2017; Leung et al., 2015). Results showed a small effect size in the verbal fluency domain. Most of the studies included in the meta-analysis analyzed phonemic and semantic verbal fluency, however, only one study included in our research reported improvements in this domain, specifically in semantic fluency (París et al., 2011). Executive functions and processing speed were two of the most trained domains. Similar to other meta-analyses, our results showed small effects in executive functions (Orgeta et al., 2020). However, the other two meta-analyses conducted in PD patients, obtained moderate effect sizes in executive functions and processing speed (Lawrence et al., 2017; Leung et al., 2015). Executive functions and processing speed were two of the cognitive domains with the

most variability across the evaluation measures used, which may explain the meta-analysis' findings. In addition, after the publication of the meta-analysis presented in this thesis, a new meta-analysis that analyzed the efficacy of cognitive rehabilitation in PD patients with MCI was published, showing improvements in overall cognitive functioning, executive functions, and short- and long-term memory (Giustiniani et al., 2022).

The results of the meta-analysis showed a small effect size on depressive symptoms after cognitive rehabilitation programs. Most of the trials included in the meta-analysis that evaluated depressive symptoms showed that individuals with PD scored similarly to those obtained at the beginning of the cognitive intervention. Additionally, quality of life results showed no effect, but only was measured in three studies; and functionality was only reported in two included studies, so the meta-analysis of functionality data could not be performed. The lack of studies analyzing mood, quality of life, and functionality after cognitive rehabilitation programs suggests the need for further studies that analyze improvements in these measures after cognitive rehabilitation programs.

Importance of personalized medicine

The second goal of *study I* was to analyze if age and years of education, variables related to intervention, baseline global cognitive scores, and PD patient-related features influence on the effectiveness of cognitive rehabilitation in PD. Results showed that there was no percentage of variance accounted for in the effect sizes for any of these variables. However, it is necessary that studies continue providing the most detailed information to further control these aspects. In fact, personalized medicine in PD, takes into account age, personality, lifestyle, genetic factors, pharmacoeconomics, pharmacogenetics, and

comorbidity for the development of individualized treatment for each person with PD (Titova & Chaudhuri, 2017a, 2017b).

Regarding cognitive rehabilitation, our results showed that age and years of education did not influence on the efficacy of the cognitive interventions included in the meta-analysis. These results may be due to the fact that PD patients included in the studies of the meta-analysis showed a similar mean age, which limited the age analysis. However, it should be noted that only 10 studies were included in the moderator analyses, so further research is needed. The majority of cognitive rehabilitation studies include PD patients at the early stages of the disease (H&Y stages ≤3). Indeed, starting cognitive rehabilitation as early as possible is crucial to manage cognitive deficits in PD patients. In fact, participation in these programs before the onset of dementia has the potential to improve or maintain cognitive results over time (Biundo et al., 2017). Previous meta-analyses (Lawrence et al., 2017; Leung et al., 2015), as well as our meta-analysis, investigate the effects of cognitive rehabilitation in non-demented PD patients, showing improvements in several cognitive domains. Few studies investigated the efficacy of cognitive rehabilitation in later stages of the disease, such as PD-demented patients. A meta-analysis of PD-demented patients found no evidence of cognitive improvement after cognitive rehabilitation (Orgeta et al., 2020). As a result, it is essential to start cognitive intervention prior to the onset of cognitive impairment. However, it would be interesting to continue exploring the effects of cognitive rehabilitation in PD-MCI and dementia, to analyze further if it is feasible to preserve or reduce the progression of cognitive impairment despite the presence of dementia.

Other two important factors in the cognitive rehabilitation process are the active lifestyle and personality (Titova & Chaudhuri, 2017a, 2017b). Cognitive rehabilitation program participation needs the availability of time to attend the sessions and perform

cognitive activities at set times. Increased attendance and involvement in cognitive rehabilitation sessions, as well as positive results, can be enhanced by a proactive, active lifestyle and a positive attitude. An association between self-reported lifestyle and cognitive changes related to cognitive and physical rehabilitation was investigated in a study of older people at risk of dementia (Küster et al., 2016). Older adults at risk of dementia with a more active lifestyle had better cognitive performance during the research period than older adults at risk of dementia with a less active lifestyle (Küster et al., 2016). Furthermore, each person's personality may impact in their disposition to participate in the cognitive rehabilitation program. One study of individuals with MCI, showed that the personality trait of openness to experience increases the probability of success in the learning of a cognitive rehabilitation tool (Khayoun et al., 2021). Being comfortable with their treatment (group or individual) may also influence their disposition to participate in the programs. In fact, a study conducted with people with multiple sclerosis showed that conscientious people are more adherent to treatment, being more likely to be punctual and organized (Bruce et al., 2010). In addition, they also showed that patients with greater openness were more likely to report adherence problems at baseline (Bruce et al., 2010). A common question is whether intervention groups should be homogeneous or heterogeneous. Because all members experience similar circumstances, homogeneous groups can facilitate the integration of each participant more easily. However, it is occasionally essential to evaluate how heterogeneous groups may promote companionship and inspire individuals to help each other.

Genetics is another key factor to consider in personalized medicine. PD is a heterogeneous illness in which a genetic mutation affects 3–5% of patients (Klein & Westenberg, 2012), contributing to clinical variability and susceptibility to cognitive impairment and dementia (Fagan & Pihlstrøm, 2017). However, the researches included

in our meta-analysis were focused only on idiopathic PD. More studies analyzing the effects of cognitive rehabilitation in genetic PD are needed, particularly in individuals with a mutation linked to a higher risk of cognitive impairment.

Combined intervention of cognitive rehabilitation in Parkinson´s disease and psychoeducation in family caregivers

The first objective of *study II* was to examine the efficacy of a combined intervention of cognitive rehabilitation in PD patients and psychoeducation in their family caregivers to improve cognition, mood, functionality, and quality of life. The results showed that PD patients of the combined intervention group (cognitive rehabilitation with REHACOP in PD patients + psychoeducation in family caregivers), obtained significant improvements and large effect sizes in verbal memory and emotional well-being dimension of HRQoL; and medium effect sizes in facial emotions recognition, general health, and communication dimension of HRQoL. PD patients of the combined intervention group showed improved verbal memory compared to PD patients of the single intervention and control group. In the same line, other studies in PD also found improvements in verbal memory after performing interventions with different cognitive rehabilitation programs (Petrelli et al., 2014; Sinforiani et al., 2004). Moreover, verbal memory improvement is consistent with a study conducted with the REHACOP program in multiple sclerosis in which an improvement in verbal memory was also found (Rilo et al., 2018). The majority of studies of cognitive interventions have focused on cognitive improvements, while improvements in mood, functionality, and quality of life have received less attention. Emotional well-being dimension of HRQoL, also showed an improvement after cognitive rehabilitation in the combined intervention group and the single intervention group in comparison to the control group. Another study also found that people with PD improve emotional well-being dimension after performing a

multidisciplinary intensive rehabilitation treatment (Meng et al., 2022). Therefore, participation in cognitive rehabilitation groups could improve the sense of emotional well-being of people with PD. In addition, the improvement in functional status, motor symptoms, and cognition may be associated with an increase in mood and subjective sense of well-being (Lo Buono et al., 2021). Future studies should continue exploring the influence of motor and non-motor symptoms on the quality of life of people with PD.

Post-hoc analyses revealed that the combined intervention group also showed significant improvements compared to the control group in facial emotion recognition and general health. Results obtained in facial emotions recognition may be because REHACOP is a comprehensive cognitive rehabilitation program in which social cognition was also trained. Studies related to patients with schizophrenia and AD showed that facial emotion recognition performance was improved after rehabilitation programs (García-Casal et al., 2017; Gaudelus et al., 2016). Additionally, in our study, PD patients of combined intervention showed an improvement in their general health after cognitive rehabilitation compared to the control group. The knowledge about how to help people with PD acquired by caregivers after psychoeducation program may promote the improvement of the general health of PD patients. Regarding HRQoL, PD patients from the combined intervention group showed an improvement in communication dimension after cognitive rehabilitation compared to the single intervention group. Communication dimension items are related to speech difficulty, inability to communicate with others, and the feeling of being ignored. Therefore, the participation of the family caregiver in the psychoeducation program could promote improvements in the communication of patients with PD. In fact, these results highlight the importance not only of the family caregivers´ participation in the psychoeducation program, but also their involvement in cognitive rehabilitation tasks, enhancing the communication of people with PD.

No significant improvements were observed in the rest of the cognitive domains. However, improvements in processing speed, visual memory, and ToM with the REHACOP program have been reported in PD (Peña et al., 2014). The lack of statistically significant improvements in these cognitive domains in the present study may be due to the low sample size. Regarding clinical variables, no differences were found in depression, anxiety, apathy, fatigue, and functional disability between groups. Other studies conducted with the REHACOP program showed improvements in apathy scores in elderly adults (Montoya-Murillo et al., 2020) and in functional disability in people with PD (Peña et al., 2014). Our findings could be explained by the fact that most of the PD patients who participated in this study did not have high scores of depression, anxiety, apathy, fatigue, or functional disability. However, the implementation of complementary interventions such as pharmacological treatment (Lou, 2015), physical (Lou, 2015), and psychological therapies (S. Yang et al., 2012), could reduce fatigue, anxiety, and depressive symptoms; and help PD patients become more active in their care and improve their quality of life (S. Yang et al., 2012).

The improvements obtained in this combined intervention, in the case of the patients, cannot be attributed to the duration of the intervention since both rehabilitation groups performed the same intervention program. The improvements obtained after cognitive rehabilitation may be due to the involvement of family caregivers as necessary collaborators in the care of the person with PD.

Psychoeducation program in caregivers of Parkinson´s disease patients

The second objective of *study II* was to evaluate the efficacy of a psychoeducation program in family caregivers of PD patients to improve cognition, mood, functionality, quality of life, and caregiver burden. Results showed improvements in general health and anxiety scores in family caregivers who participated in the psychoeducation program,

producing medium and large effect sizes, respectively. Secker and colleagues (2005) showed an improvement in the general health of family caregivers of people with PD but after a cognitive-behavioral therapy intervention (Secker & Brown, 2005). The items related to the general health scale, are concentration, the loss of sleep by the worries, decision making, items related to the oppression, tension, happiness and sadness, and loss of confidence, among others (Rocha et al., 2011). Likewise, participation in a psychoeducation program provides an improvement in general health through the learning of self-regulation, health promotion, stress management, anxiety and depression, competence, and social support (Bayés et al., 2007; Macht et al., 2007). When family caregivers learn how to care people with PD and how to care themselves, it may turn into an overall improvement in their daily life. Additionally, the results of our study showed a significant improvement in anxiety scores in the psychoeducation group. These results may be because caregivers who engage in leisure activities and learn how to manage stress, anxiety, and depression which in turn may produce an improvement in their mood. No significant improvements were found in depression, apathy, quality of life, functional disability, and fatigue scores in family caregivers after participating in the psychoeducation program. Regarding depression and quality of life, these results were consistent with studies that implemented the Edupark psychoeducation program in family caregivers of people with PD, which also found no significant improvements (A'Campo, Spliethoff-Kamminga, et al., 2010; A'Campo, Wekking, et al., 2010; Simons et al., 2006). However, these studies additionally assessed mood using VAS, showing that the caregivers' mood improved significantly after each session of the Edupark psychoeducation program (A'Campo, Spliethoff-Kamminga, et al., 2010; A'Campo, Wekking, et al., 2010; Simons et al., 2006). In *study II*, no improvements were observed in caregiver burden, caregiver strain index, and positive aspects of caregiving after the

intervention. However, Rossón and colleagues (2013) found improvements in the caregiver burden after an intervention program of educational and self-help sessions for caregivers and integrative activities for patients and caregivers (Rossón et al., 2013). Our results may be due to the fact that family caregivers did not present high caregiver burden or caregiver strain at baseline and due to the fact that PD patients of this study, did not have a long disease duration and were mildly to moderately affect. In fact, studies suggest that PD severity is the main predictor of caregiver burden (Martínez-Martín et al., 2007), with caregiver burden being significantly higher in caregivers caring for people in late-stage of PD (Kalampokini et al., 2022) or PD-dementia (Leroi et al., 2012). On the other hand, some positive effects of the psychoeducation program may appear later, when participants experience real-life situations that were worked on during the program sessions (Simons et al., 2006). Psychoeducation can offer benefits on the knowledge of the disease and better performance of the care, reducing the impact of the mood states in the daily life of the family caregivers.

Predictors of HRQoL in Parkinson´s disease patients before and after controlling overlapping items between HRQoL and clinical measures

Concerning the influence of motor and non-motor symptoms on HRQoL of people with PD, the main goal of *study III* was to analyze the predictor value of motor symptoms, anxiety, depression, apathy, fatigue, and neurocognition on HRQoL and its dimensions in PD. Furthermore, after taking into account the overlapping items between HRQoL and clinical measurements, the predictive value of motor and non-motor symptoms was reanalyzed.

HRQoL total index was predicted by anxiety, fatigue, motor symptoms, and depression scores. Anxiety was the main predictor, whereas the variance of depression scores was lower than in other studies. The lack of the inclusion of anxiety and depression

variables in the same regression model (Hanna & Cronin-Golomb, 2012) may explain why depression was the primary predictor of HRQoL in the majority of the studies (Soh et al., 2011). These results should be interpreted with caution due to the possible overlap between the quality of life measures and depressive symptomatology (Aigner et al., 2006). For this reason, we conducted an additional analysis to avoid the possible overlap between HRQoL and clinical measures, removing the items of the emotional well-being dimension from the HRQoL total index. When the overlap between measures was considered, interestingly, fatigue predominated as a predictor of HRQoL over anxiety and motor symptoms; depression disappeared and neurocognition emerged as a predictor of HRQoL. The majority of the studies have not taken into account the overlap between clinical and HRQoL measures in their analyses, so depression has been considered the most important predictor of HRQoL. In order to perform accurate interpretations, future research should consider this idea of overlap between clinical and HRQoL assessments. After controlling the overlapping, fatigue was the main predictor of HRQoL total index. In fact, it is one of the most disabling symptoms of PD (Friedman et al., 2010), present in 50% of patients (Siciliano et al., 2018). In contrast to anxiety and depression, fatigue has been a less studied predictor. In four of the five studies included in a systematic review, fatigue was found as an important predictor of HRQoL in patients with PD (Soh et al., 2011), demonstrating that it emerges in the early stages of PD and persists throughout the course of the disease, negatively influencing their HRQoL (Siciliano et al., 2018). In addition, when the overlap was controlled, neurocognition was found as a predictor of HRQoL total index in our study. Most of the researches used cognitive functioning screening assessments to examine cognition (Cubo et al., 2002; Hanna & Cronin-Golomb, 2012; Kadastik-Eerme et al., 2015; Ophey et al., 2018; Schrag et al., 2000; Simpson et al., 2014; Sławek et al., 2005). Participants in our study completed a comprehensive

neuropsychological battery that included a wide range of cognitive tests, demonstrating that a neurocognition composite score predicted HRQoL. Only four studies (Klepac et al., 2008; Ophey et al., 2018; Schrag et al., 2000; Stegemöller et al., 2014) have found cognition as a predictor of HRQoL total index; two by cognitive functioning screening tests (Ophey et al., 2018; Schrag et al., 2000), while the other two using specific cognitive measures, showing that working memory and verbal fluency (Stegemöller et al., 2014), visual attention/memory, visuospatial, and executive functioning (Klepac et al., 2008) were predictors of HRQoL. This is the first study that analyzed predictors of HRQoL in PD patients controlling the possible overlap between HRQoL and clinical measures. It should also be noted that the methods used in this study, as well as the obtained results, might be generalized to other illnesses.

Predictors of HRQoL dimensions in Parkinson´s disease patients

Regarding the specific HRQoL dimensions, fatigue scores and motor symptoms, predicted mobility and ADL dimensions. Other researches have also demonstrated that physical fatigue and reduced activity are related to mobility dimension (Elbers et al., 2014; Havlikova et al., 2008) and reduced activity and motor symptoms to ADL dimension (Havlikova et al., 2008; Simpson et al., 2014; Tu et al., 2017). Additionally, fatigue was a predictor of emotional well-being dimension. Fatigue, longer disease duration, and UPDRS total score (Havlikova et al., 2008), working memory, and verbal fluency (Stegemöller et al., 2014) were also found as predictors of this dimension in other studies. Fatigue and anxiety scores predicted the bodily discomfort dimension. Depression scores were included in the regression model in our study but only anxiety and fatigue scores were the predictors of this dimension. Other studies showed that fatigue, UPDRS total scores, and female sex (Havlikova et al., 2008), motor fluctuations (Simpson et al., 2014), anxiety (Jones et al., 2015; McKinlay et al., 2008; Simpson et al.,

2014), depression and hallucinations (McKinlay et al., 2008) were the main predictors of bodily discomfort dimension. In line with other studies (McKinlay et al., 2008; Simpson et al., 2014) anxiety scores and UPDRS-III predicted social support dimension. Anxiety scores, predicted cognition dimension. PDQ-39 items of the cognition dimension assess concentration problems, the sensation of having a bad memory and hallucinations or nightmares, which generate feelings of anxiety or nervousness in PD patients. However, we expected to find neurocognition as a predictor of this dimension, but it did not happen. This may be due to the fact that the sensations of concentration problems and memory impairment approach a similar interpretation of cognition; while hallucinations or nightmares are more related to anxiety. In fact, one study showed that mood states have a greater association with cognition dimension than neurocognitive domains (Jones et al., 2014). In addition, neurocognition and motor symptoms were predictors of communication dimension. In PD, communication impairment can vary from no problems to inaudible and unintelligible speech (Smith & Caplan, 2018). Indeed, acoustic speech impairments, the use of action verbs, and pauses have been related to motor impairment, whereas linguistic abnormalities have been related to cognitive impairment (Smith & Caplan, 2018).

There were no significant associations between motor symptoms, anxiety, depression, apathy, fatigue, and neurocognition scores and the stigma dimension, hence it could not be included in the model. This could be because of the low scores on the stigma dimension in our sample. In fact, other studies showed that anxiety (Jones et al., 2015; Simpson et al., 2014), decreased activity and motivation (Havlikova et al., 2008), and sadness (Tu et al., 2017) predicted the stigma dimension. Additionally, understanding stigma requires a broader consideration from a more social context, and not only focusing on motor and non-motor symptoms (Tu et al., 2017). Regarding potential determining

variables, findings did not show significant correlations between apathy and HRQoL or its dimensions, despite previous research associated apathy to worse HRQoL (Kuhlman et al., 2019; McKinlay et al., 2008) and increased self-reported cognitive and communicative impairments (McKinlay et al., 2008).

Early detection and treatment of motor and non-motor symptoms may help people with PD to improve their HRQoL. Considering that PD is both physically and mentally debilitating disease, health care providers should adopt a holistic approach to PD rehabilitation (Kwok et al., 2019). Treatment objectives vary among individuals, highlighting the need for personalized intervention (Bloem et al., 2021). As a result, a variety of non-pharmacological therapies, such as mindfulness yoga (Kwok et al., 2019), psychological interventions (S. Yang et al., 2012), spiritual resilience (Kwok, Choi, et al., 2020), physical therapy (Lou, 2015), speech therapies (Schulz & Grant, 2000), and cognitive training (*study I*) should be taken into account. These therapies could be included in the clinical manage of PD patients.

Limitations and future lines

There are several limitations in the three studies. In *study I*, few studies met the inclusion criteria for meta-analysis, so the precision of the publication bias was limited. The lack of data, or the use of different methods in the statistical analyses of the studies included in the systematic review, limited the possibility of including these studies in the meta-analysis. The variety of trained cognitive functions allows studies to be compared across cognitive domains, however not all cognitive domains were trained in all trials, so the comparison would be limited. Several of the studies measured the cognitive domains in different ways, so only studies that reported the specific cognitive domains independently were included. Regarding *study II*, not all PD patients had a family caregiver available to participate in the study and the study was conducted in a matched

method (the patient along with their family caregiver). Thus, if PD patients decline to participate in the study or were excluded, simultaneously their family caregivers were excluded and vice versa, which increased attrition rate and sample loss. More studies with larger sample sizes are needed. *Study III* was based on cross-sectional data. The PDQ-39 scale is a specific HRQoL measure and therefore does not allow the results to be contrasted with other pathologies. This study was conducted in a Spanish population. There are studies using the PDQ-8 revealing that geographic location has an impact on non-motor symptoms that impair HRQoL (van Wamelen et al., 2021). Specifically, in European patients mood and sleep were the main predictors of HRQoL (van Wamelen et al., 2021) and in Chinese population anxiety, depression, motor symptoms, and marital status were the main predictors of HRQoL (Kwok, Auyeung, et al., 2020). However, in Indian and Japanese patients non-motor symptoms were not significant predictors of HRQoL (van Wamelen et al., 2021).

In conclusion, cognitive rehabilitation may be beneficial in improving cognitive functions in PD patients. However, there are not many studies that assess mood, functionality, and quality of life after cognitive rehabilitation. Further studies analyzing the efficacy of cognitive rehabilitation in PD patients' on mood, functionality, and quality of life are needed. In addition, individual aspects such as age, lifestyle, personality, and genetic factors, which may apply to personalized medicine, should also be examined for more precise and personalized interventions. On the other hand, cognitive impairment, functional disability, and disease progression are significant determinants that affect both patients and their family caregivers' quality of life, leading to psychological and health issues that are related to providing care. Thus, combined interventions for people with PD and their family caregivers can offer a comprehensive approach of the disease, enhancing the benefits to PD patients of cognitive rehabilitation, and providing family caregivers

with strategies for improving their quality of life and a greater understanding of the disease. Nonetheless, there is a need for further studies with larger samples. Finally, it is essential to recognize and manage motor and non-motor symptoms in the early stages of the disease to improve the HRQoL of people with PD. Further longitudinal studies and studies of patients with PD in more advanced stages are needed to determine whether the intervention of predictors of HRQoL influences long-term HRQoL.

VII. Conclusions

7. Conclusions

7.1. Conclusions

The main conclusions of this thesis can be summarized as follows:

Study I

- Cognitive rehabilitation is effective for the improvement of cognitive functions in PD patients. The systematic review showed that attention, working memory, verbal memory, executive functions, and processing speed were the most frequently improved domains after cognitive rehabilitation in PD. Meta-analysis results showed improvements with a moderate effect size in global cognitive status and working memory; and a small effect size in verbal memory, overall cognitive functions, attention, executive functions, visual memory, verbal fluency, processing speed, and depression.
- Age, years of education, intervention-related variables, baseline global cognitive scores, and PD patient-related characteristics did not significantly influence on the efficacy of the cognitive interventions included in this meta-analysis.

Study II

- PD patients who participated in the cognitive rehabilitation program and whose family caregivers are involved in psychoeducation showed improvements in verbal memory, facial emotion recognition, general health, and emotional well-being and communication dimensions of HRQoL after cognitive rehabilitation.
- Family caregivers who participated in psychoeducation program showed improvements in general health and anxiety scores. This study highlights the importance of combining intervention programs for people with PD and their family caregivers to provide a comprehensive approach, enhance the benefits of

cognitive rehabilitation in PD patients, and provide family caregivers with strategies for improving their quality of life.

Study III

- Anxiety, fatigue, motor symptoms, and depression were predictors of the HRQoL total index in PD patients before controlling the overlapping items between HRQoL and clinical measures. Additionally, fatigue, anxiety, motor symptoms, and neurocognition scores were also predictors of HRQoL dimensions in PD patients. These findings suggest the need for including a wide range of potential predictors of HRQoL in order to shed light on the specific impact of motor and non-motor predictors on both general HRQoL and its dimensions.
- After controlling the overlapping items between HRQoL and clinical measures, fatigue, anxiety, and motor symptoms were the accurate predictors of the HRQoL total index, depression disappeared and neurocognition emerged as an additional predictor of HRQoL. This study highlights the importance of identifying and controlling overlapping items between HRQoL and clinical measures for an accurate interpretation of results.

7.2. Conclusiones

Las principales conclusiones de esta tesis pueden resumirse de la siguiente manera:

Estudio I

- La rehabilitación cognitiva es eficaz para la mejora de las funciones cognitivas en los pacientes con EP. La revisión sistemática mostró que la atención, la memoria de trabajo, la memoria verbal, las funciones ejecutivas, y la velocidad de procesamiento fueron los dominios que mejoraron con mayor frecuencia después de la rehabilitación cognitiva en la EP. Los resultados del meta-análisis mostraron mejoras con un tamaño del efecto moderado en el estado cognitivo global y la memoria de trabajo; y un tamaño del efecto pequeño en la memoria verbal, las funciones cognitivas globales, la atención, las funciones ejecutivas, la memoria visual, la fluidez verbal, la velocidad de procesamiento, y la depresión.
- La edad, los años de educación, las variables relacionadas con la intervención, las puntuaciones basales del estado cognitivo global, y las características relacionadas con los pacientes con EP no influyeron significativamente en la eficacia de las intervenciones cognitivas incluidas en este meta-análisis.

Estudio II

- Los pacientes con EP que participaron en el programa de rehabilitación cognitiva y cuyos familiares cuidadores participaron en la psicoeducación mostraron mejoras en la memoria verbal, el reconocimiento de emociones faciales, la salud general, y las dimensiones del bienestar emocional y comunicación de la CVRS después de la rehabilitación cognitiva.

- Los familiares cuidadores que participaron en el programa de psicoeducación mostraron mejoras en las puntuaciones de salud general y ansiedad. Este estudio resalta la importancia de combinar programas de intervención para las personas con EP y sus familiares cuidadores, para proporcionar un enfoque integral, potenciar los beneficios de la rehabilitación cognitiva en los pacientes con EP, y proporcionar a los familiares cuidadores estrategias para la mejora de su calidad de vida.

Estudio III

- La ansiedad, la fatiga, los síntomas motores, y la depresión fueron predictores del índice total de CVRS en los pacientes con EP antes de controlar el solapamiento de ítems entre la CVRS y las medidas clínicas. Además, las puntuaciones de la fatiga, la ansiedad, los síntomas motores, y la neurocognición también fueron predictores de las dimensiones de la CVRS en los pacientes con EP. Estos resultados sugieren la necesidad de incluir una amplia gama de predictores potenciales de la CVRS para arrojar luz sobre el impacto específico de los predictores motores y no motores en la CVRS general y sus dimensiones.
- Tras controlar el solapamiento de ítems entre la CVRS y las medidas clínicas, la fatiga, la ansiedad, y los síntomas motores fueron los predictores precisos del índice total de CVRS, la depresión desapareció y la neurocognición surgió como un predictor adicional de la CVRS. Este estudio resalta la importancia de identificar y controlar los ítems que se solapan entre la CVRS y las medidas clínicas para una interpretación más precisa de los resultados.

VIII. References

8. References

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IX. Supplementary material

9. Supplementary material

Table S1

Search strategy

CONCEPT 1		**CONCEPT 2**		-	Number of obtained results (n= 1472)
(“Parkinson’s disease” OR “Parkinson disease”)	**AND**	("Cognitive rehabilitation" OR "Cognitive remediation" OR "Cognitive training" OR "Cognitive stimulation")		-	144
CONCEPT 1		**CONCEPT 2**		**CONCEPT 3**	-
(“Parkinson's disease” OR “Parkinson disease”)	**AND**	(Attention*)	**AND**	(Rehabilitation OR Remediation OR Training OR Stimulation)	527
(“Parkinson's disease” OR “Parkinson disease”)	**AND**	(“Working memory”)	**AND**	(Rehabilitation OR Remediation OR Training OR Stimulation)	106
(“Parkinson's disease” OR “Parkinson disease”)	**AND**	(Memory)	**AND**	(Rehabilitation OR Remediation OR Training OR Stimulation)	451
(“Parkinson's disease” OR “Parkinson disease”)	**AND**	(“Executive function*”)	**AND**	(Rehabilitation OR Remediation OR Training OR Stimulation)	244

Note: The search strategy was filtered by title and abstract; * Truncation (search of multiple variants of attention and executive functions).

Table S2

Methodological quality and risk of bias

ROB-2. Randomized studies							
Study	**PEDro Score**	**Bias arising from the randomization process**	**Bias due to deviation from intended interventions**	**Bias due to the missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall Risk of Bias**
Sammer et al., 2006	6	Unclear	Unclear	Low	High	Low	High
París et al., 2011	7	Unclear	Low	Unclear	Low	Low	Unclear
Edwards et al., 2013	8	Low	Low	Low	High	Low	High
Cerasa et al., 2014	8	Unclear	Low	Low	Low	Low	Unclear
Costa et al., 2014	8	Unclear	Low	Low	Low	Low	Unclear
Peña et al., 2014	8	Low	Low	Low	Low	Low	Low
Petrelli et al., 2014	8	Low	Low	Unclear	Low	Low	Unclear
Angelucci et al., 2015	7	Unclear	Low	Low	Low	Low	Unclear
Fellman et al., 2018	8	Low	Low	Low	Unclear	Low	Unclear
Bernini et al., 2020	8	Low	Low	Low	Low	Low	Low
Ophey et al., 2020	9	Low	Low	Low	Low	Low	Low

Table S2

Methodological quality and risk of bias (continued)

ROBINS-I. Non-randomized studies								
Study	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall Risk of Bias**
Naismith et al., 2013	Low	Low	Low	Low	Low	Low	Low	Low

Table S3

Outcomes and assessment included in the meta-analysis

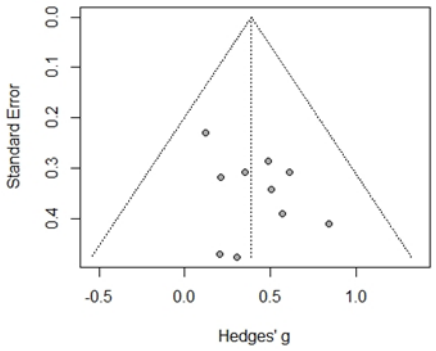
Global cognitive status
Montreal Cognitive Assessment (MoCA)
Mini Mental State Examination (MMSE)
Demtec
Addenbrooke's Cognitive Examination (ACE)
Attention
Digit span forward
Brief test of attention (BTA)
Paced Auditory Serial Addition Test (PASAT)
Working memory
Face-Name-learning-Test (GNL)
Digit span backward
Demtec- Digit span reverse
Verbal memory
California Verbal Learning Test (CVLT)- Short and long delay free recall
Hopkins Verbal Learning Test- Revised (HVLT-R)- Short and long delay free recall
Selective Reminding Test (SRT)
Demtec- Verbal short and long-term memory
Memo Test- Verbal short and long-term memory
Verbal episodic memory- A sentence recall task, a word list recall task
Consortium to Establish a Registry of Alzheimer’s Disease Plus (CERAD +)- Wordlist Learning and recall
Logical Memory subtest of the Wechsler Memory Scale- III
Visual memory
Modified Taylor figure- delayed recall
Rey-Osterrieth Complex Figure Test (ROCFT)- Immediate and delayed recall
Brief Visuospatial Memory Test-Revised (BVMT-R)- Short and long delay free recall

Verbal fluency
The F-A-S Phonemic Verbal Fluency Test
Semantic- Animals
Demtec- Animals
Controlled Oral Word Association Test (COWAT)
Phonemic and Semantic Verbal Test
Executive functions
Behavioural Assessment of the Dysexecutive Syndrome (BADS)
Tower of London (ToL)
Stroop Color Word Interference- Words-Colors
Stroop Color Word Interference- Interference
Zoo Map
Trail Making Test- Part B (TMT-B)
Visuospatial and visuoconstructive abilities
Rey-Osterrieth Complex Figure Test (ROCFT)- copy
The Line Orientation subtest from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
Judgement of Line Orientation (JLO)
Processing speed
Symbol Digit Modalities Test (SDMT)
Trail Making Test- Part A (TMT-A)
The Salthouse Perceptual Comparison Test (SPCT)
Useful Field Of Vision (UFOV)
Stroop Color Word Interference- Word
Stroop Color Word Interference- Colors
Depressive symptoms
Geriatric Depression Scale (GDS-15)
Beck Depression Inventory II (BDI-II)
Quality of life
Parkinson’s Disease Questionnaire (PDQ- 39)

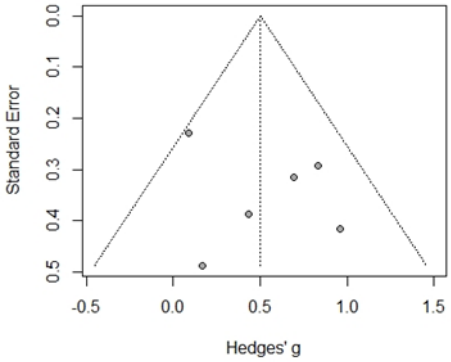
Figure S1

Funnel plot asymmetry of publication bias

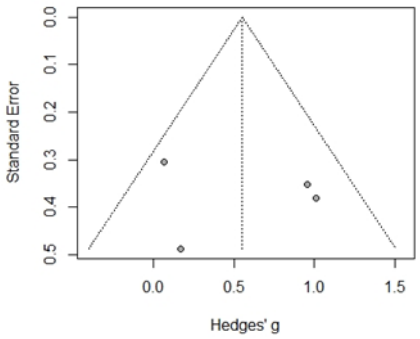
Overall cognition



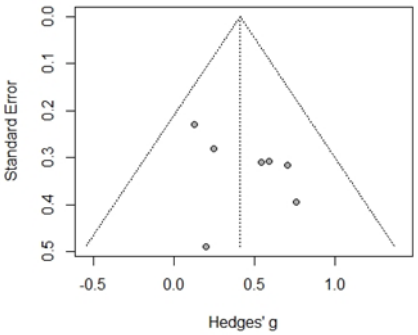
Working memory



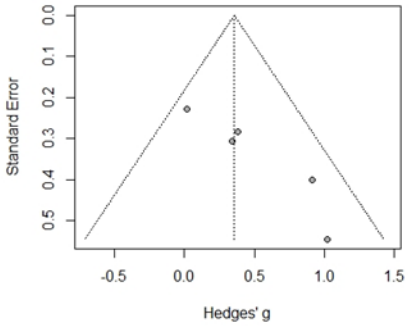
Global cognitive status



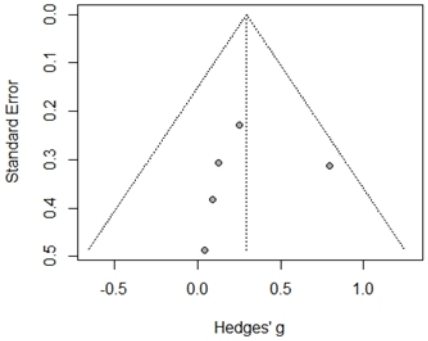
Verbal memory



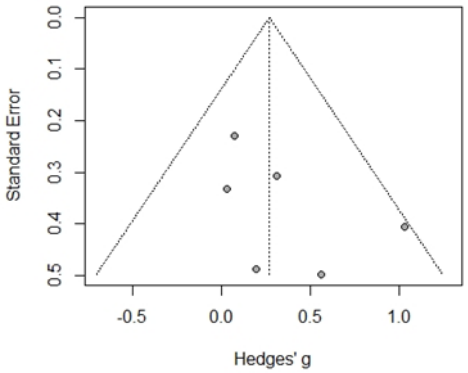
Attention



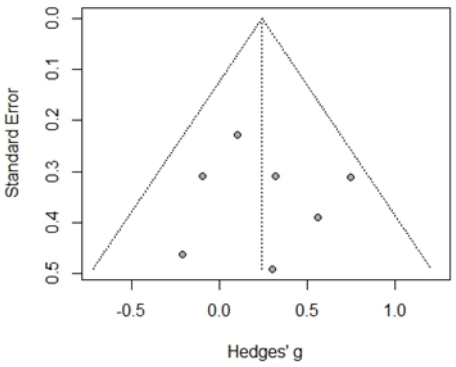
Visual memory



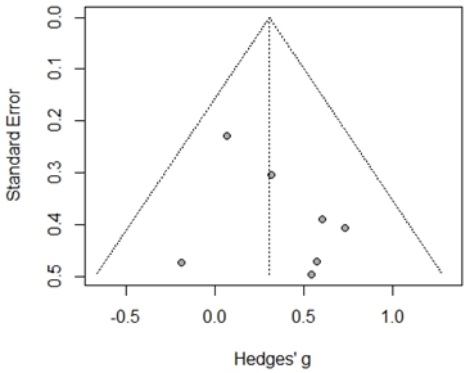
Verbal fluency



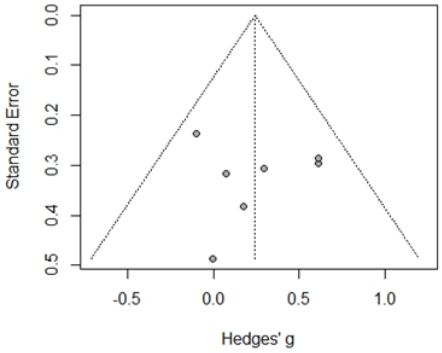
Processing speed



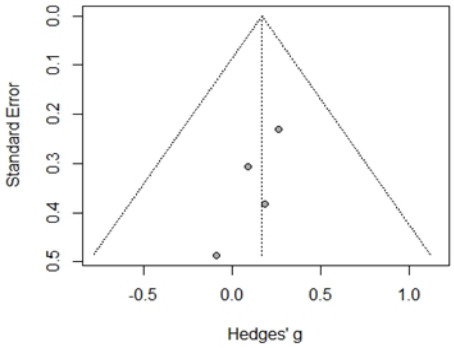
Executive functions



Depressive symptoms



Visuospatial and visuoconstructive abilities



Quality of life

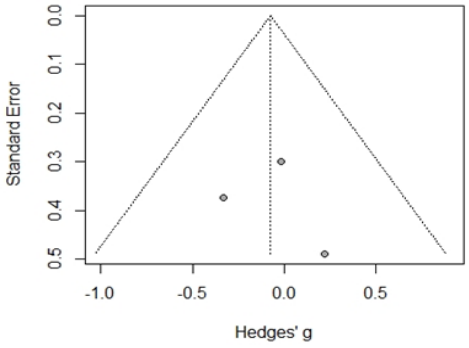
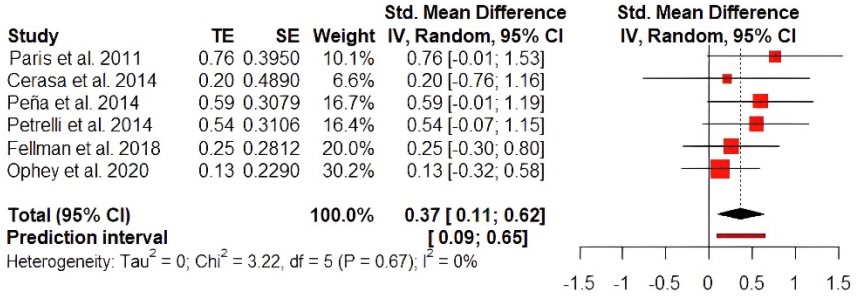


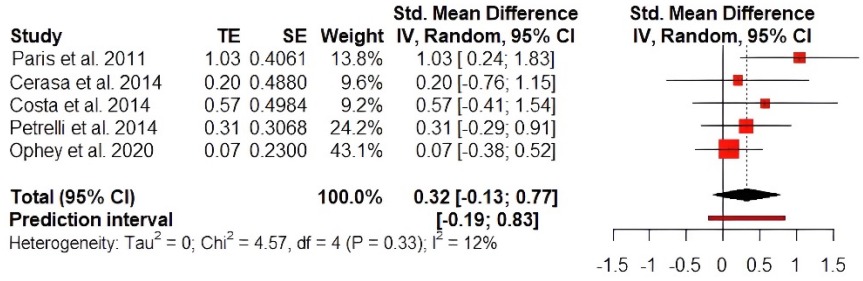
Figure S2

Forest plot of sensitive analysis: Effect sizes of randomized controlled trials

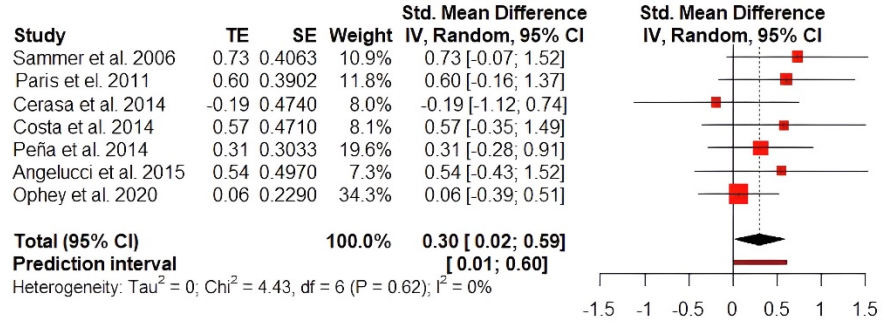
Verbal memory



Verbal fluency



Executive functions



Processing speed

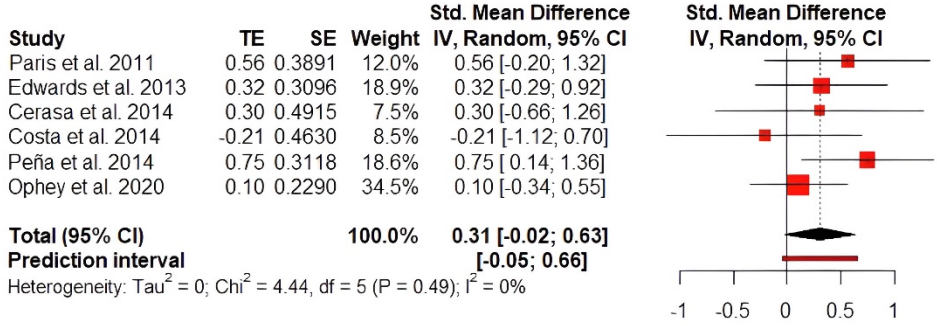
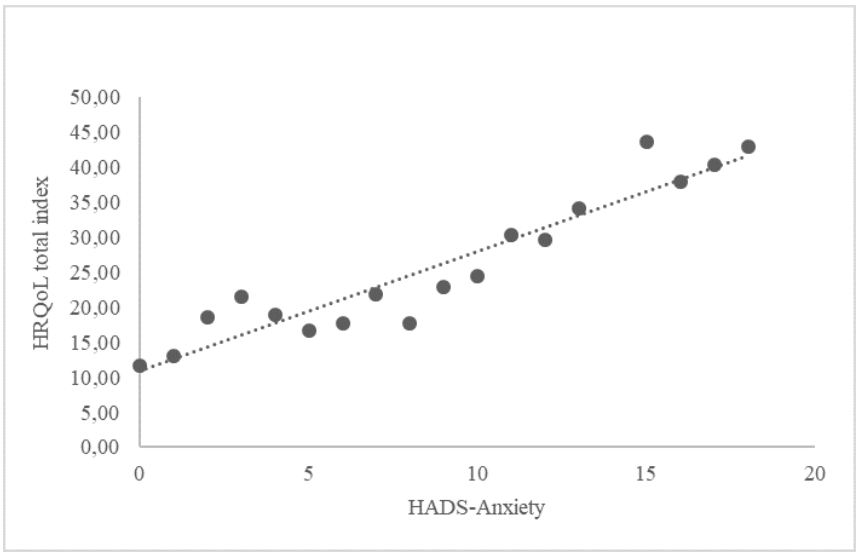
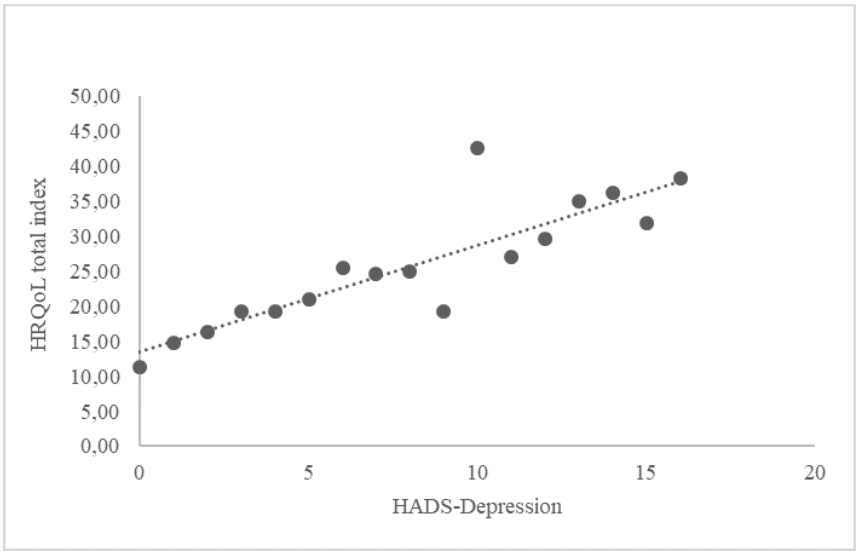
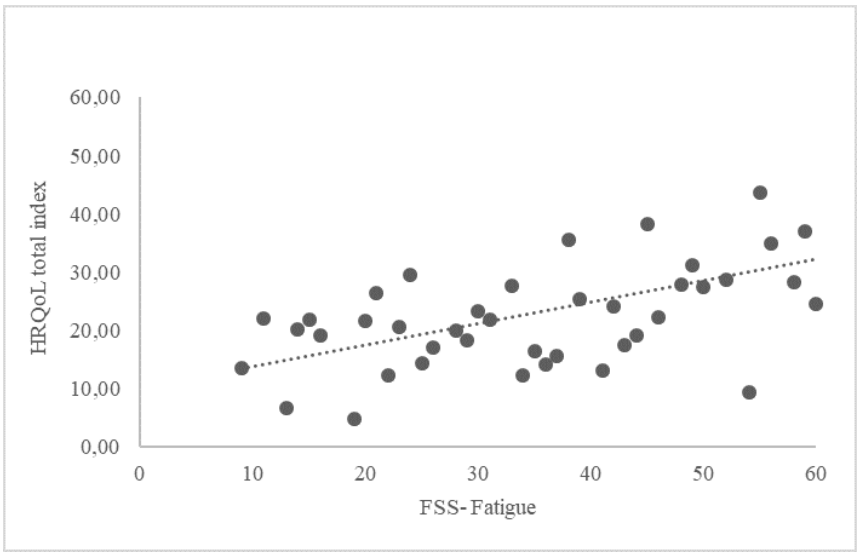


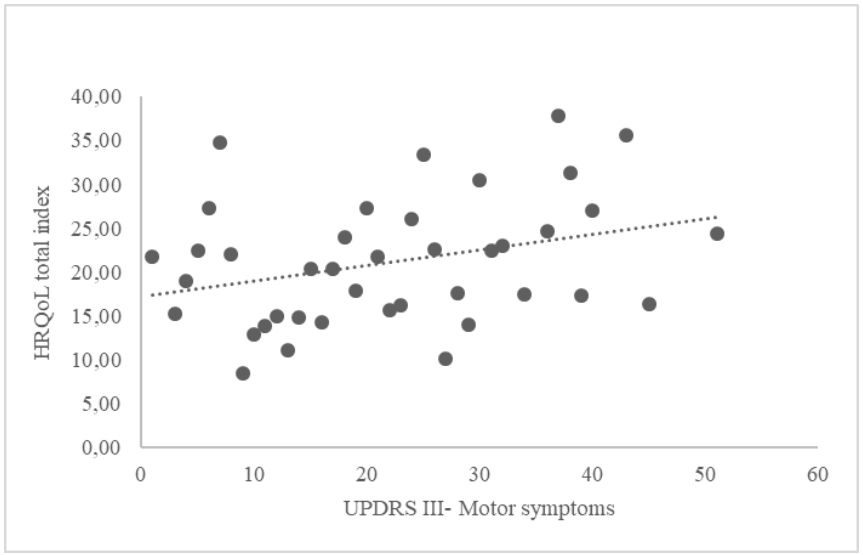
Figure S3

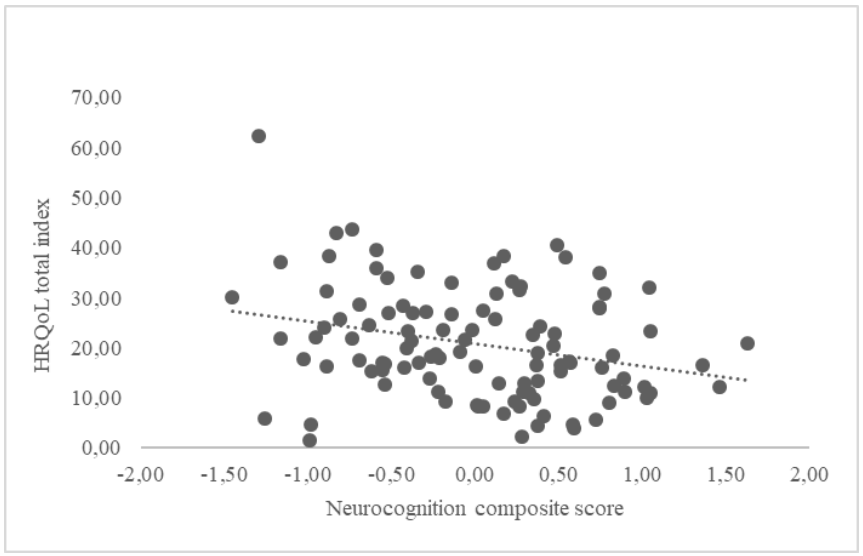
Spearman's rho significant correlation analyses of the HRQoL total index











Legend: HRQoL= Health-Related Quality of Life; HADS= Hospital Anxiety and Depression Scale- Anxiety and Depression scores; FSS= Fatigue Severity Scale; UPDRS III= Unified Parkinson's Disease Rating Scale- motor part.