University of Catania

Ph.D. Course in Neuroscience

Ph.D Thesis - XXXVI° cycle

Tele-Rehabilitation plus Virtual Reality APP to effectively improve cognitive and social functions in patients with Parkinson's Disease

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1. Parkinson’s Disease

1.1 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder of the central nervous system after Alzheimer's disease (AD) [1]. It was first described by James Parkinson in *An Essay on the Shaking Palsy* [2] as a movement disorder mainly characterized by rest tremor, postural instability and slow movements.. However, it is only in recent years that growing attention has also been given to the non-motor symptoms of PD including depression, cognitive decline, sleep disorders, psychosis [3].

1.2 Epidemiology and risk factors

PD is the most common neurodegenerative movement disorder with a prevalence of about 1-2% in the population older than 65 years [4]. In Europe, PD affects around 108-256/100,000 inhabitants, while 193.7/100,000 are affected in Italy [4]. It has been estimated that about 5% of all PD patients are younger than 50 years while about 70% are older than 65 years. The number of cases is predicted to double by 2030 due to the growing aging of the general population [5]. Mortality is unchanged in the first decade after disease onset, but increases with age, up to double that of the general population. The disease is more frequent in males than females with a 2:1 ratio, although women usually present a faster progression and higher mortality [6].

In addition to aging, which promotes neurodegenerative phenomena, several environmental factors have been associated with PD, including pesticides, herbicides, rural life, and solvents in PD occurrence [7]. Moreover, obesity, insulin resistance, hypertension, cholesterol, and some infections (i.e., HCV and Helicobacter pylori), have been also proposed as possible “risk factors” of PD [8].

On the other hand, although literature data are still not conclusive, several factors have been proposed as “protective”, including tobacco smoking, tea and caffeine consumption and urate [9,10].

PD is mainly a sporadic disorder and hereditary forms represent only about 5-10% of cases [11]. However, an about three-fold higher risk of PD has been reported in first-degree relatives of PD patients [12].

1.3 Neuropathology

The main pathological hallmarks of PD the loss of of the pigmented dopaminergic neurons of the midbrain substantia nigra, *pars compacta* and the presence of intracellular deposition of α-synuclein (Lewy bodies) in the dopaminergic neurons. It is estimated that more than 60% of dopaminergic neurons have already been lost at the time of diagnosis. The substantia nigra plays a fundamental role in the circuit of the basal ganglia which, with the *cerebellum*, are involved in the planning and programming of movements and motor learning. Basal ganglia are also involved in regulating behavior and emotional states (figure 1).

The basal nuclei include the neostriatum (the *caudate nucleus*, *accumbens*, *septi*, and *putamen*), the *paleostriatum* (internal *globus pallidus* GPi and external globus pallidus GPe and the reticulate part of the *substantia nigra* SNr), the *archistriatum* (composed of the *amygdala* and ventral nuclei)and the related nuclei (consisting of the *subthalamic nucleus*, compact part of the s*ubstantia nigra* SNc, *claustrum*, and *pedunculopontine nucleus*) [13].

In the basal ganglia circuit, putamen and caudate nucleus represent the afferent regions, receiving inputs from the cerebral cortex, while the efferent regions (GPi and SNpr) send outputs to the cortex through thalamic nuclei.

The afferent region (mainly putamen) and the efferent one (GPi and SNpr) are linked through a direct link pathway (from striatum to GPi) and an indirect link pathway (from striatum to GPi, passing through-GPe and STN).

In physiological conditions, dopamine regulates both direct and indirect pathways, balancing the GABAergic-inhibitory output and the activation of excitatory thalamus-cortical fibers.

The loss of dopaminergic neurons in the SN leads to an over-activity of the indirect pathway and to an inhibition of thalamic neurons and cerebral cortex, resulting in marked impairment of motor control.

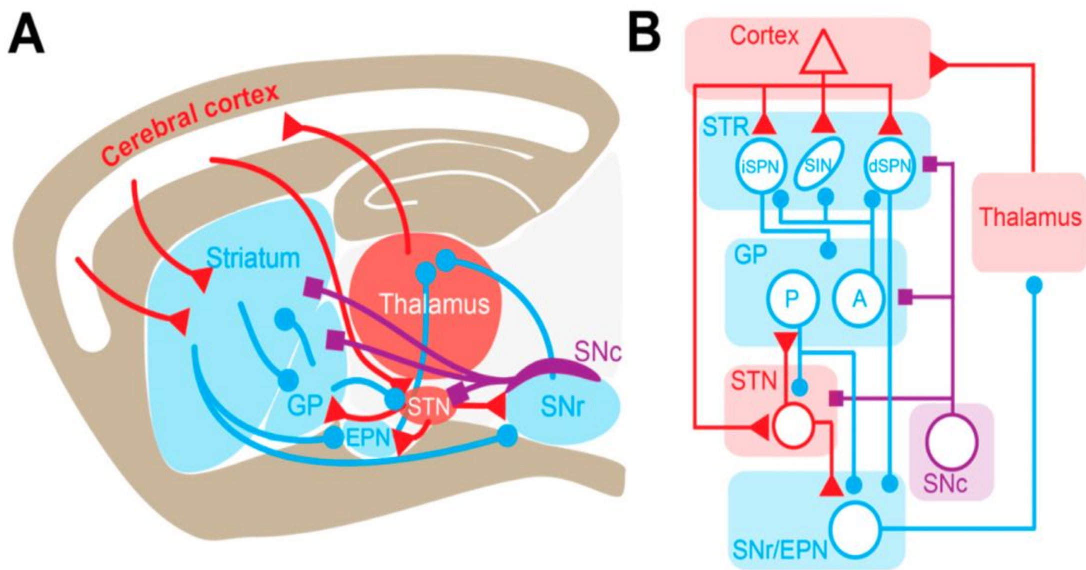


Figure 1: Basal ganglia circuit in PD. In Mallet N, Delgado L, Chazalon M, Miguelez C, Baufreton J. Cellular and Synaptic Dysfunctions in Parkinson's Disease: Stepping out of the Striatum. Cells. 2019 Aug 29;8(9):1005.

1.4 Pathophysiology

PD is characterized by the loss of dopaminergic neurons associated with the diffuse accumulation of the protein *α-synuclein*. The *α-synuclein* forms (protein aggregates) which tend to accumulate and form intracellular inclusions. The intermediate products of this aggregation process are toxic oligomeric and protofibrillar forms that alter mitochondrial, lysosomal, proteasomal functions, biological membranes and cytoskeleton. These processes cause an alteration of synaptic function and neuronal degeneration. According to Braak and Braak hypothesis [14], the loss of dopaminergic neurons begins in the dorsal motor nucleus of the glossopharyngeal, vagal, and anterior olfactory nucleus, then progresses to the brainstem and, in later stages, to the mesocortex, allocortex, and, finally, to the neocortex.

1.5 Clinical Diagnosis and Evolution

The diagnosis of PD is clinical and based on a neurological examination the presence of bradykinesia, rest tremor and rigidity and the absence of other signs representing a red flag for atypical parkinsonism. Idiopathic PD is characterized by a relatively slow progression and a clear response to dopaminergic drug therapy, which may lose its effectiveness during the natural course of the disease. To standardize and systematize the diagnosis of PD, specific diagnostic criteria have been elaborated in clinical and research fields. The application of these criteria can be useful in standardizing the diagnostic process, particularly in the early stages of the disease, when the diagnosis is more uncertain.

The most recent diagnostic criteria are the Movement Disorders Society (MDS) diagnostic criteria [15]. The MDS-PD criteria distinguish two levels of diagnostic certainty:

- Clinically proven PD: there is a high specificity, it can be assumed that at least 90% of patients have PD;
- Clinically probable Parkinson's disease: balancing sensitivity and specificity, the category presumes that 80% are identified as Parkinson's disease cases.

To promote diagnostic accuracy, neuroimaging can also be useful, although studies have highlighted that experienced physicians can diagnose Parkinson's disease with greater accuracy [16]. Among the structural imaging methods, brain TC and conventional MRI are used, in clinical practice, to exclude potential causes of secondary parkinsonism (i.e. white matter disease, inflammatory diseases, infectious, normal pressure hydrocephalus and tumors [17,18].

Moreover, brain MRI allows to detect the loss of volume of specific cortical and subcortical regions. In addition, transcranial parenchymal ultrasound can be used to evaluate the presence of signal changes in the parenchyma, particularly in the midbrain, in patients with PD. Finally, functional neuroimaging methods (PET, SPECT, fMRI) allow to study the activity and integrity of areas of interest at the cortical and subcortical level. In particular, The SPECT with 123I-FP-CIT ligand (DAT-SPECT scan) has been proposed as a sensitive early diagnostic marker for Parkinson’s disease, useful for a preliminary differential diagnosis with non-parkinsonian tremor disorders, or vascular parkinsonism [19] and for the evaluation of disease progression [20].

1.6 Clinical features

1.6.1 Motor symptoms

PD is a motor movement disorder mainly characterized by bradykinesia, rest tremor and rigidity with an asymmetric onset (figure 2).

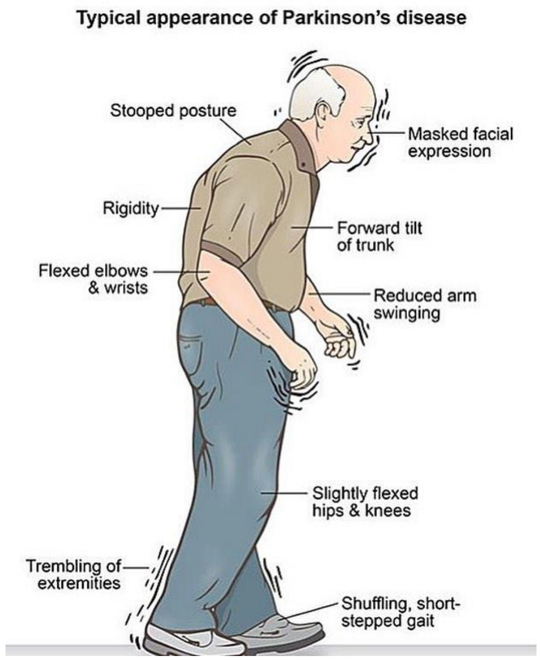


Figure 2: Common symptoms in PD. https://www.parkinson.org/.

Resting tremor typically appears firstly on the upper limb, presents a slow frequency (4-6 Hz) and tends to disappear during activities and sleep.

Bradykinesia is defined as the "slowness" of initiation of voluntary movements with a progressive reduction in speed and amplitude of repetitive actions particularly evident during fine motor tasks (i.e. writing, buttoning the shirt).

Rigidity is perceived as an increased resistance to passive mobilization of the limbs often worsened by voluntary movements of the contralateral limb (Froment's sign). As the disease progresses, other motor symptoms may appear:

- Balance disorders as the reflexes to maintain balance are impaired, increasing the risk of falling;

- Gait disturbances and walking with small steps. The patient has a flexed trunk and arms and loses the ability to turn 180°. Sudden freezes (freezes) may also occur in the more advanced stages of the disease;

- Hypomimia and less expressive face.

The most used scales for the assessment of PD severity are the Hoehn and Yahr (HY) scale and the MDS- Unified Parkinson's Disease Rating Scale (UPDRS). The HY was created by Margaret Hoehn and Melvin Yahr [21]. It comprises 5 stages, as shown in Figures 3 and 4.

Stage 1.0: Unilateral involvement only.

Stage 1.5: Unilateral and axial involvement.

Stage 2.0: Bilateral involvement without impairment of balance.

Stage 2.5: Mild bilateral involvement with recovery on retropulsion (pull) test.

Stage 3.0: Mild to moderate bilateral involvement, some postural instability but physically independent.

Stage 4.0: Severe disability, still able to walk and to stand unassisted.

Stage 5.0: Wheelchair bound or bedridden unless aided.

Figure 3: Stage of HY. Clarke CE, Patel S, Ives N, Rick CE, Woolley R, Wheatley K, Walker MF, Zhu S, Kandiyali R, Yao G, Sackley CM. Clinical effectiveness and cost-effectiveness of physiotherapy and occupational therapy versus no therapy in mild to moderate Parkinson's disease: a large pragmatic randomized controlled trial (PD REHAB). Health Technol Assess. 2016;20(63):1-96.

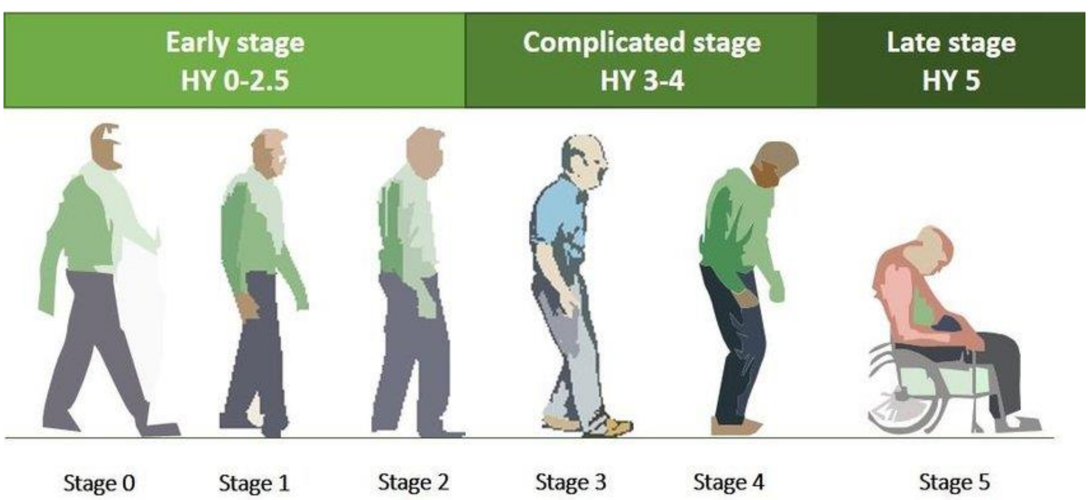


Figure 4: Stage of HY. Dr. Simon Stott, Deputy Director of Research, The Cure Parkinson's Trust. https://www.parkinsonsnsw.org.au/understanding-the-five-stages-of-parkinsons/.

The MDS-UPDRS is a revision of the Unified Parkinson's Disease Rating Scale (UPDRS), developed in 1980, and revised by the MDS. The MDS-UPDRS evaluates multiple aspects of Parkinson's disease, including motor and non-motor symptoms of daily life and possible complications. MDS-UPDRS is divided into four parts. The first part evaluates the non-motor symptoms of daily life. The second part evaluates the motor symptoms of daily life. The third part includes the objective clinical evaluation, carried out by the professional, with respect to the key motor symptoms of the disease (figure 5). Motor complications are evaluated in the last part. The total number of items is 65, with a 5-point Likert scale (from 0 to 4). A score of 0 indicates normality, while in a more serious situation, a score of 4 is assigned. The scale is used in clinical settings and research [22].

Figure 5: UPDRS - III part.in "Understanding the Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) Vaughan K. Collins,Rachel N. Massart* OTS, Kristen A. Pickett Ph.D. References UPDRS – III.*

1.6.1. Non-motor symptoms

Non-motor symptoms are various and include behavioral and affective disorders, dementia, autonomic disorders, sleep disturbances and sensitivity disorders. Many non-motor symptoms occur during the disease, some may even present earlier than the onset of the motor disorder.

Non-motor disorders may be present not only during the disease course, from the earlier to the later stages, but also in the prodromal phase. Among the non-motor symptoms occurring in the prodromal or early phases of PD, hyposmia, REM sleep disorders, excessive daytime sleepiness, depression and anxiety, constipation and erectile dysfunction are probably the most frequent (figure 6). It has been hypothesized that these disorders are caused by the early involvement of autonomic neurons located in the spinal cord, heart, gastrointestinal and urinary tracts [23].

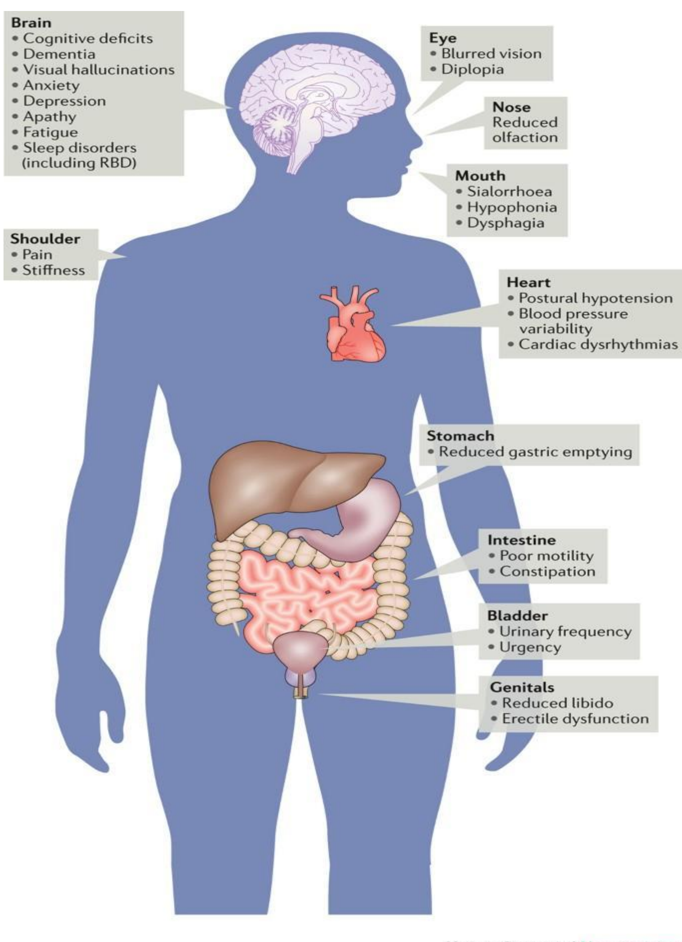
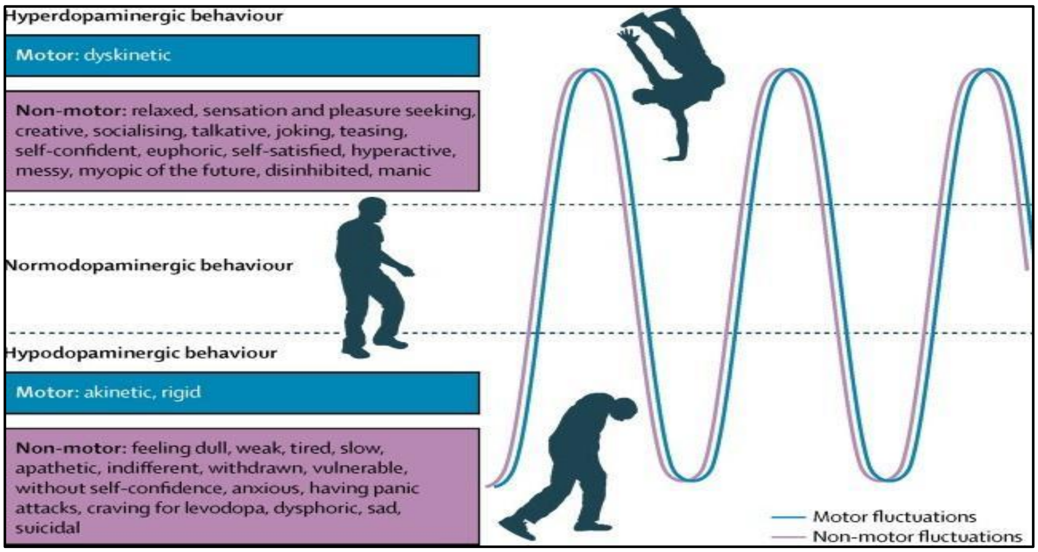


Figure 6: Non-motor symptoms in PD, in Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci. 2017;18(7):435-450. doi: 10.1038/nrn.2017.62.

In addition to the pathological changes that occur in the nervous system, it must also be considered that many non-motor disorders are the consequence of treatment with dopaminergic agents (figure 7). For example, pharmacological effects on the mesolimbic system can cause impulse control disorders, while effects on the autonomic system can cause disorders such as orthostatic hypotension, nausea, and constipation [24].



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2. Cognitive features in PD

2.1. Cognitive decline in PD

Cognitive decline is one of the most frequent non-motor symptoms of PD. Previous studies have reported that in PD there is an up to 6-time increased risk of developing cognitive decline than in non-parkinsonian population [1].

Notably, although cognitive decline was previously considered peculiar of the later stages of PD, more recent findings demonstrated that cognitive decline can affect about 40% of PD patients since the early stages of the disease [2,3]. Considering the detrimental effect of cognitive decline on PD and their caregiver's quality of life, its prevention and management must be a priority for clinicians and researchers.

The spectrum of cognitive impairment in PD ranges from subjective cognitive decline (SCD) and mild cognitive impairment (PD-MCI) to overt dementia (PDD).

The term "Subjective Cognitive Decline" (SCD) refers to a "self-perceived deterioration in cognitive abilities but characterized by normal age-adjusted, sex-adjusted and education-adjusted performance on specific and standardized cognitive tests". SCD is a frequent condition in PD patients and has been associated with an increased risk of PD-MCI and PDD occurrence [4].

PD-MCI is considered as an intermediate cognitive stage between normal cognition and dementia. Interestingly, previous studies have suggested that MCI can occur even at the earlier stage of PD and represent a risk factor for later PDD occurrence [2,3]. The prevalence of PD-MCI is about 26.7% with a range from 18.9% to 32.8% and the frequency increases with age and disease duration [5]. The MDS Task Force has proposed new diagnostic criteria for PD-MCI that include two levels of diagnostic operability [6]. In summary, Level I includes: 1) diagnosis of PD based on UK PD Brain Bank criteria, 2) a gradual decline in cognitive abilities reported by the family member or patient or observed by the healthcare professional, 3) cognitive deficits evidenced by administration of a short battery of neuropsychological tests or a global rating scale, 4) the cognitive impairment does not significantly interfere with the normal performance of daily life activities. Level II includes a more extensive cognitive assessment, is more reliable in detecting cognitive decline and includes 1) at least two neuropsychological tests exploring each cognitive domain (attention and working memory, executive functions, memory, language, and visuospatial processing), 2) the deficit must be considered in two tests exploring one cognitive domain or in a test in two cognitive domains (single-domain MCI and multi-domain MCI), 3) cognitive impairment should be considered if scores are below normal or if there is evidence of a deficit in serially administered tests or if there is a significant decline in the premorbid cognitive form [7]. Impaired cognitive function in non-demented PD patients consists of a broad spectrum of clinical deficits of varying severity affecting the amnestic and non-amnestic domains [8].

Finally, PDD occurs predominantly in the advanced stages of the disease with a prevalence estimated in a longitudinal study of approximately 80% in patients with a disease duration longer than 20 years [9]. In the general population, PDD accounts for 3-4% of the forms of dementia [10]. Several studies suggested that older age, motor symptoms severity [11,12]. Additional reported risk factors are the akinetic-rigid phenotype, and psychosis [13,14]. In 2007, the Task Force of Movement Disorders Society defined the clinical diagnostic criteria for possible and probable PDD and proposed a practical approach to diagnosis [15]. Key criteria include a diagnosis of PD, the presence of an insidiously progressive dementia syndrome in the context of established PD, impairment in more than one cognitive domain, and it involves the reduction of autonomy in carrying out the activities of daily life [15,16].

2.1. Cognitive Rehabilitation in Parkinson's Disease

Considering the high frequency of cognitive decline in PD even in the early stages of the disease, the identification of new therapeutic opportunities in the treatment of PD related cognitive decline is of undoubtable importance.

To date, there are no approved and effective drug therapies for PD-MCI. Concerning PDD, the use of acetylcholinesterase inhibitors in PDD patients has been considered supported due to the beneficial effect on global cognitive scales, behavioral disturbances and daily autonomy scales [17,18]. There is no evidence to support the use of donepezil, galantamine, and memantine in PDD [19].

Moreover, the effect of dopaminergic drugs on cognitive functions is still not well known [20]. As far as non-pharmacological interventions are concerned, cognitive rehabilitation programs would seem to be useful in mild cognitive decline. The purpose of cognitive rehabilitation is to reduce the deficit of damaged cognitive functions increasing the abilities of daily activities. In general, cognitive training programs have the aim of improving specific cognitive domains, such as attention, visuospatial function, working memory, and executive function, which are the cognitive components essential for carrying out the tasks of everyday life [21].

Cognitive rehabilitation uses restorative techniques and compensatory techniques. The restorative techniques aim to improve cognitive function, to restore functionality as close to normal levels. Compensatory techniques are based on the assumption that impaired function cannot be restored by exercise alone and provide strategies that organize information to improve recall and learning. Alongside traditional cognitive rehabilitation with the use of pencil and paper, innovative techniques such as virtual reality (VR) and telerehabilitation have been developed in the last thirty years, which can also be used jointly [22].

2.2. Telemedicine and Telerehabilitation

The constant population aging is leading an increasing incidence of age-related neurodegenerative diseases, characterized by cognitive decline (i.e. Parkinson's disease - PD and Alzheimer's disease - AD). The need to adapt the healthcare system to the multiple emerging needs, therefore, appears evident, to improve assistance and ensure continuity of care [23]. Indeed, during the SARS-COV-2 pandemic, the possibility of using innovative technologies to provide home healthcare services has been underlined [24-26]. In particular, telemedicine has allowed the continuity of care and territorial assistance, without the physical presence of the therapist/clinician and the overload of hospitalized health structures, also favoring the reduction of costs of the National Health Service [27,28]. Telemedicine is a method of providing health care services, using information and communication technologies (ICT), in which the health professional and the patient are distant, allowing problems to be overcome of patient mobility and reducing costs [29,30]. Its use can range from providing specialist advice on self-management and monitoring patients with chronic conditions, such as PD. The advantages of this practice are many:

- ➢ Deliver appropriate interventions as efficiently and quickly as possible;
- ➢ Increase access to health services by the population;
- ➢ Allow monitoring with a higher rate of patients;
- ➢ Make the patient himself more involved together with the family and the caregiver in the treatment of the disease;
- ➢ Decrease health care costs, both public and private;
- ➢ Improve patient outcomes.

One field of telemedicine is telerehabilitation. Tele-rehabilitation represents an emerging and innovative approach that can represent a valid support during the home rehabilitation process for the recovery and/or compensation of compromised cognitive and behavioral abilities and for the improvement of the patient's quality of life in his family and social environment. In recent years, the use of telerehabilitation has been shown to lead to clinical improvements comparable to the conventional face-to-face rehabilitation programs [31,32]. Moreover, telerehabilitation is useful for patient's assessment, monitoring, education, intervention, and supervision. The most important advantage of telerehabilitation is probably the ability to reach people who live in very remote areas. Other benefits include the ability to speed up the discharge process while maintaining treatment compliance and reducing hospital visits and delays in patient discharge. Several studies confirm that telerehabilitation can be a valid alternative to standard rehabilitation, as it manages to guarantee an improvement in the various clinical aspects of the disease [33].

Therefore, innovative solutions, such as telemedicine, can play a crucial role in ensuring continuity of care. From a clinical point of view, these solutions become indispensable when geographical and socioeconomic barriers prevent patients from accessing primary clinics, offering everyone the possibility of remote monitoring and rehabilitation. After discharge from the hospital, patients can continue to care at home under the synchronous or asynchronous supervision of speech therapists, psychologists, or doctors. To achieve this goal, a multidisciplinary team should monitor patients, addressing the cognitive, medical, and psychological aspects of both patients and healthcare professionals. Remote supervision, facilitated by doctors and/or therapists (synchronous or asynchronous), and a virtual assistant using specific algorithms can guide patients through their cognitive rehabilitation.

A notable advantage of telerehabilitation in clinical practice also lies in its ability to adapt tools to the needs of the individual patient, allowing rehabilitation in the patient's home environment. This reduces the stress of traveling or queuing at the hospital, ensuring access to rehabilitation sessions in optimal cognitive and motor conditions. As a result, therapeutic sessions can be prolonged, promoting greater patient compliance with the treatment plan. Patients undergoing cognitive telerehabilitation often perceive positive therapeutic results and performance improvements thanks to the constant feedback provided by technological devices

However, these telemedicine devices also impose limitations on their use. Indeed, the challenges related to the widespread use of such devices at home may include: i) the absence of an assistant to supervise the performance of the exercises, particularly for the most compromised patients who require additional therapy; ii) limited experience with technological interfaces and PCs by both patients and healthcare professionals; iii) the lack of structural technical requirements such as the absence of a PC or an internet connection [34].

In any case, cognitive training based on telerehabilitation plays an important and constantly evolving area as it allows the possibility of administering cognitive training at home and at affordable costs.

2.3. E-Rehabilitation through smartphone Apps and Virtual Reality

Less expensive and effective telerehabilitation technologies have recently spread, which integrate playful aspects with educational elements. These digital devices also allow interactive virtual simulation, integrating remote rehabilitation with virtual reality, to develop skills to be applied in the real world, with exercise in a simulated and protected environment. Hence, experiential learning, made possible by these, could potentially enhance behavioral change [35]. In this context, a recent interesting field of application of Telemedicine/e-health has concerned smartphone apps. Recent evidence has highlighted how mHealth through smartphones and tablets can be a useful tool for implementing effective and cost-effective health interventions, especially in the field of tele cognitive rehabilitation. The devices have multiple functionalities, such as sensors, Internet access, geolocation data, notifications, and clinical apps [36]. Furthermore, smartphones/tablets can provide support comparable to dedicated medical devices, without the weight and embarrassment of assistive devices [37]. Various authors have demonstrated that the use of some smartphone Apps can improve the patient's health, thanks to the use of gamification, colorful aesthetics, points systems, social competitions (e.g. ranking), avatars, game rewards, missions of the history, which engage the user and improve physical activity [32,38]. Moreover, the feasibility and efficacy of mHealth have been demonstrated both in older individuals [39-43] and in patients with neurodegenerative disorders [44-47]. Studies have reported that the use of mHealth training has been able to boost cognitive skills, such as processing speed, prospective and episodic memory, and executive functioning [39,44-47], making smartphones and tablets valuable tools for improving cognitive performance. Therefore, the use of mHealth can improve cognitive abilities and allow the generalization of outcomes in daily life, even in the presence of neurodegenerative disorders [44-47].

The effects of telerehabilitation are increased when used in conjunction with VR, which allows concrete, ecological and realistic experiences, with individual control over different sensory-motor, cognitive and social domains, usually difficult to reproduce in a clinical context [28,31,38]. The exercises performed in a virtual environment create "increased feedback" which allows the patient to develop "awareness of the results" of the movements performed and "awareness of the quality" of the movements themselves with positive repercussions at a behavioral, cognitive, and motor level. Indeed, multisensory feedback and the repeated implementation of tasks with sensory resistance promote brain plasticity processes [48]. VR allows the activation of mirror neurons with the integration between perception, cognition, and action, reinforcing the effects of the training and the sense of self-efficacy of the subject [48]. The simulation of real-life scenes, through playful elements, increases patient involvement and the possible generalizability of learning in real life [48,49].

VR provides different degrees of "immersion" and "presence". The immersion consists in the objective perceptual experience of the system characteristics and virtual task (physical sensation of being in a virtual world); while, “Presence” consists of a more subjective aspect concerning the "perceived" and characteristics of the user (involvement and activation resulting from the activity) [50]. Moreover, VR has the capability to generate a profound sense of embodiment, where users feel fully immersed and connected to the virtual environment, coupled with a heightened sense of agency, empowering them to interact and influence the digital surroundings. The term "agency" in this context refers to the perceived control and influence that users feel they have within the virtual space, allowing them to manipulate and shape their digital experiences. This heightened sense of agency enhances the overall engagement and interactivity, contributing to a more immersive and compelling virtual reality experience. In this way, the VR-APP is a serious non-immersive game that allows a good level of user involvement. It has been shown that serious non-immersive VR games consent the user to face cognitive and motor challenges through interactive elements, which allow experiential learning in an engaging environment. These aspects consent people with neurological disorders to participate in repetitive, adaptive, significant and stimulating exercises, with possible positive effects on rehabilitative outcomes, even if the rehabilitation is at the patient's home [51- 53]. Hence, VR app could provide an interesting and effective way to support telerehabilitation in neurological patients [54,55].

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2. Article 1:

Feasibility and Usability of Non-Immersive Virtual Reality tele-cognitive APP in cognitive rehabilitation of patients affected by Parkinson's Disease.

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Abstract

Background: cognitive impairment is one of the most common non-motor features of Parkinson's disease (PD). The aim of the present study was to evaluate the feasibility and acceptability/usability of a protocol of non-immersive virtual reality tele-cognitive APP performed in a "remote way" in a sample of Italian patients with PD. **Methods:** non-demented patients with mild PD were included in the study. Patients performed the cognitive rehabilitation in a remote way, at home (3 training sessions lasting 20 minutes/week for 6 weeks) using the Neuronation App, downloaded for free on the patients' smartphone. The usability and feasibility of the tele-cognitive rehabilitation program were assessed with the System Usability Scale (SUS) and the Goal Attainment Scaling (GAS). **Results:** Sixteen patients (9 men and 7 women; mean age 58.4 ± 8.3 years; mean disease duration 4.6±2.1 years) were included in the study. At the end of the study, the mean SUS was 83.4 ± 11.5. The GAS score recorded at baseline was significantly higher (38.5 ± 2.4) than the GAS score recorded at the end of the study (65.6±4.2; p-value < 0.001). **Conclusion:** in our sample, "good" feasibility and usability of a six-week cognitive rehabilitation protocol based on the non-immersive virtual reality tele-cognitive APP NeuroNation were recorded. Our data supported the usefulness of cognitive rehabilitation performed in a remote way in PD patients.

Keywords. Cognitive Rehabilitation, feasibility, Mobile Health, Parkinson's disease, Smartphone App, usability.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized by both motor (rest tremor, bradykinesia, rigidity) and non-motor symptoms (i.e. depression, sleep disorders, cognitive decline) [1].

Cognitive impairment, ranging from mild cognitive impairment to dementia, represents one of the most common and disabling non-motor symptoms of PD, can be recorded since the early stage of the disease [2-4], and has been associated with a high risk of institutionalization [5]. On this ground, the individuation, and application of useful rehabilitation/reinforcement cognitive protocol that could represent a strategy to delay the occurrence or the worsening of cognitive deficits are receiving growing interest [6]. Hence, previous studies have highlighted the beneficial role of cognitive rehabilitation, from traditional methods "paper and pencil" based to the more innovative tools including virtual reality (VR) and PC-based methods, in PD patients [7,8].

However, cognitive rehabilitation protocols performed in a hospital setting 2-3 times a week may not be easy to apply for patients with movement disorders, especially during this SARS-CoV2 pandemic period, in which most frailty subjects have been advised to avoid not strictly necessary hospital income [9,10]. In this context, rehabilitation protocols performed in a “remote way” could represent a valid alternative to the traditional face-to-face rehabilitation to overcome mobility problems and reduce the cost for the healthcare system [11,12]. In fact, several easy and free digital devices allowing a non-immersive interactive virtual simulation useful to enhance cognitive performances in a simulated and protected environment are available [13]. Moreover, it should be noted that previous studies reported that the clinical efficacy of telerehabilitation could be considered as not inferior to the traditional rehabilitation programs. Thus, it seems of interest to evaluate the potential beneficial role of telerehabilitation based on the free downloading of brain-training apps and VR games performed in a remote way in PD. The aim of the present study was to evaluate the feasibility and acceptability/usability of a cognitive telerehabilitation plus VR in a sample of Italian patients with PD.

Material and Methods

Study Population

Non-demented PD patients diagnosed according to the Movement Disorders Society (MDS) diagnostic criteria [14], who attended the “Parkinson’s disease and Movement disorders” center of the University Hospital “Policlinico-San Marco” of Catania, between March to November 2021, were enrolled in the study. Inclusion criteria were: a) aged between 40 and 80 years; b) at least 5 years of schooling; c) Hoehn and Yahr disease stage < 2.5.

The exclusion criteria were: a) presence of psychiatric disorders (major depression, psychosis, anxiety disorders); b) dementia, diagnosed according to the MDS diagnostic criteria [15].

Ethics

The study was approved by the local Ethical Committee and was in accordance with the

1964 Helsinki Declaration. Each study participant provided informed consent.

Clinical and neuropsychological assessment

All the enrolled patients were evaluated by movement disorders specialists with a standard neurological examination. PD severity was evaluated in an "off" state with the Unified Parkinson Disease Rating Scale – Motor Examination (UPDRS-ME) and the Hoehn and Yahr (HY) scale. Levodopa Equivalent Daily Dosage (LED) was calculated.

In order to exclude patients suffering from dementia, the Montreal Cognitive Assessment (MoCA), the Activities of Daily Living (ADL), and the Instrumental Activities of Daily Living (IADL) have been performed.

VR tele-cognitive APP

From the smartphone "play store" area, a free downloaded non-immersive VR tele-cognitive APP called NeuroNation - Brain Training (Synaptikon GmbH, Berlin) has been installed on a patient's smartphone. NeuroNation is an online brain training program offering extensive brain fitness training with a combination of personalized tasks and gamification. The APP program includes 27 tasks with 250 levels to exercise memory, executive functioning, attention, logical thinking, and thinking speed. The APP customized the task based on patients' personal preferences, strengths, and cognitive potential. Audio-video feedback to encourage performance motivation and self-assessment during brain training is provided.

Protocol

<u>Baseline visit (face-to-face visit):</u> NeuroNation has been downloaded on the patients' smartphone and the level of difficulty has been set according to patient characteristics estimated considering the performance obtained (number of errors and time needed) in four time-limited (1 minute) trials improving various cognitive domains.

<u>Subsequent six weeks</u>: patients performed the training remotely at home with the following scheduled sessions: 3 training sessions/week lasting 20 minutes for 6 weeks (total number of sessions: 18). The APP reminds the training using an alarm clock at the

agreed time (9.00 A.M.), three times a week (Monday, Wednesday, and Friday). The time for each cognitive domain was standardized among the participants.

At the end of each week, the APP proposed a test to ascertain the cognitive level, providing the patient with a performance report. The examiner received the report from the patient every week via message. In addition, a weekly teleconsultation to resolve concerns or difficulties has been carried out.

Outcome measures

The usability and feasibility of the tele-cognitive rehabilitation program were assessed with the following questionnaire performed at the end of 6-week of treatment:

1. System Usability Scale (SUS): this scale provides a “quick and dirty” reliable tool for assessing user acceptance (usability and perception of outcome) usability of hardware, mobile devices, APP, and websites. It consists of 10 items based on the subjective experience of usability. The items are rated on a five-point Likert scale ranging from "strongly agree" to "strongly disagree". Higher scores indicate better usability, while scores < 50 indicate “difficulties” in usability [16,17]; scores > 60 and < 80 are considered “good and promising”; scores of 90 are considered “exceptional”.

2. Goal Attainment Scaling (GAS): this scale is used to evaluate the achievement of objectives. The GAS assesses the patient's perception of the goals achieved during the intervention. Each goal is agreed upon with the patient and is evaluated on a 5-point scale, based on the perceived degree of achievement: -2= much worse; -1= a little worse; 0= expected level; 1= a little better; 2= much better [18,19]. The goal of the present protocol was the "improvement of cognitive abilities".

Statistical analysis

Statistical analyzes were performed using STATA 16.0 software packages (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC. StataCorp. 2017). Descriptive statistics were analyzed and expressed as mean (standard deviation) for continuous variables, as appropriate; frequencies (%) were used for categorical variables. A paired T-test was performed to compare continuous variables, and the χ^2 Test was performed to compare frequencies.

Results

Sixteen patients (9 men and 7 women; mean age 58.4 ± 8.3 years; mean education 12.9±3.8 years; mean disease duration 4.6±2.1 years) were included in the study and completed the study. No drop-out was recorded. The mean MoCA score was 26.3±2.4. The mean UPDRS-ME was 25.1±7.3 and the Hoeh and Yahr stage was 1.8±0.4. All the enrolled patients were treated with levodopa; LED was 294.7±118.0. No significant differences were found comparing men and women in terms of age (respectively 59.2 ± 8.4 *versus* 57.4 ± 8.8, p-value 0.684) and education (respectively 12.1 ± 4.2 *versus* 14.0 ± 3.3, p-value 0.346).

The mean SUS was 83.4 ± 11.5. Moreover, a statistically significant difference between the GAS score recorded at baseline (38.5 ± 2.4) and the GAS score recorded at the end of the study was recorded (65.6 ± 4.2; p-value < 0.001).

Discussion

The present pilot study evaluated the feasibility and acceptability/usability of 6-week of cognitive telerehabilitation using smart VR training in a sample of non-demented patients with PD. The novelty of our study is the use of a telerehabilitation system based on digital rehabilitation strategies (Mobile Health), set and programmed to empower the patients making him/her autonomous. According to our findings, the protocol "NeuroNation" presented a “successful” and usability with the patient’s perception of “improvement of cognitive abilities”.

These results allow us to support promising applications of non-Immersive Virtual Reality tele-cognitive apps performed in a remote way, especially in situations where social distancing is required.

During the COVID-19 pandemic, in fact, the possibility to support patients with telerehabilitation protocols via Mobile Health, independently of their geographical area of life, could represent a non-indifferent opportunity, considering its accessibility and highly motivational power related to the integration of playfulness-gamification [20-22].

Finally, mHealth is flexible, as its use is independent of time and place and integrated into the daily life of patients [23,24]. It should be considered that previous studies have reported that patients who consider therapy to be a useful and motivating systems show greater therapeutic adherence and involvement in therapy, especially in distant rehabilitation [25,26]. Moreover, it has been demonstrated that the use of Mobile Health can improve functional outcomes, promoting the quality of life of patients, especially in PD [26,27]. Interestingly, in our sample, the benefit of the Tele-Rehabilitation on quality of life may be supposed as per the patient's frequent request to use the app on a daily basis.

Study limitation and conclusion

The study has some limitations. The small sample size may not be sufficient to generalize our findings. Moreover, a possible selection bias due to the inclusion of patients with only mild PD without psychiatric comorbidities cannot be ruled out. However, even if only patients with Hoeh and Yahr stage <2.5 were enrolled, long disease duration did not represent an exclusion criterion, and not all the enrolled subjects could be considered "early PD". However, the present study was a usability and feasibility pilot study, performed in a selected population of PD patients, preceding the application of the tele-cognitive rehabilitation protocol in a larger efficacy study.

We believe that further studies using larger samples should be promoted, also evaluating changes in cognitive and emotional functioning.

In conclusion, our pilot study suggests that cognitive telerehabilitation using a smart -VR APP could be an effective way to provide PD patients with home cognitive rehabilitation.

The authors declare no Conflict of Interests for this article.

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4. Article 2

Can Mobile Health Apps with Smartphones and Tablets be the new frontier of cognitive Rehabilitation in Older individuals? A narrative review of a growing field.

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Abstract.

Introduction: A recent interesting field of application of Telemedicine/e-health involved smartphone Apps. Although research on m-Health began in 2014, there are still few studies using these technologies in healthy elderly and in neurodegenerative disorders. Thus, the aim of the present review was to summarize current evidence on the usability and effectiveness of the use of mHealth in older adults and patients with neurodegenerative disorders. **Methods.** This review was conducted by searching for recent peer-reviewed articles published between June 1, 2010, and March 2023 using the following databases: Pubmed, Embase, Cochrane Database, and Web of Science. After duplicate removal, abstract and title screening, 25 articles were included in the full-text assessment. **Results.** Ten articles assessed the acceptance and usability, and 15 articles evaluated the efficacy of eHealth in both older individuals and patients with neurodegenerative disorders. The majority of studies reported that mHealth training was well accepted by the users, and was able to stimulate cognitive abilities, such as processing speed, prospective and episodic memory, and executive functioning, making smartphones and tablets valuable tools to enhance cognitive performances. However, the studies are mainly case series, case-control, and in general small-scale studies and often without follow-up, and only a few RCTs have been published to date. **Conclusions.** Despite the great attention paid to mHealth in recent years, the evidence in the literature on their effectiveness is scarce and not comparable. Longitudinal RCTs are needed to evaluate the efficacy of mHealth cognitive rehabilitation in the elderly and in patients with neurodegenerative disorders.

Keywords: cognitive domains, E-rehabilitation, neurological disease, older adults, smartphone APP.

Introduction

In 2021, in Europe, the prevalence of people aged more than 65 years was around 20.8% [1], and the percentage is expected to increase reaching 28.1% by 2050 [2]. The constant aging of the population is determining an increasing incidence of age-related neurodegenerative disorders, characterized by a cognitive decline (i.e. Parkinson's disease - PD and Alzheimer's disease- AD). Thus, the need to adapt the healthcare system to the multiple emerging needs, to improve assistance and guarantee the continuity of care is evident [3].

Moreover, during the SARS-COV-2 pandemic, the possibility of using innovative technologies to provide healthcare services at home has been emphasized [4-6]. In particular, telemedicine allowed the continuity of care and territorial assistance, without the physical presence of the therapist/clinician and the overload of hospitalized healthcare facilities, also favoring the reduction of the costs of the National Health Service [7,8]. A recent interesting field of application of Telemedicine/e-health involved smartphone Apps. Hence, recent evidence has highlighted that mHealth through smartphones and tablets can be a useful tool for implementing effective and economical healthcare interventions, especially in the field of tele cognitive rehabilitation. In fact, the devices have multiple functionalities, such as sensors, internet access, geolocation data, notifications, and clinical apps [9]. Furthermore, smartphones/tablets can provide support comparable to dedicated medical devices, without the burden and embarrassment of assistive devices [10]. However, despite the high diffusion of these technologies, their use in clinical practice is still poor [11]. Although research on m-Health began in 2014, there are still few studies using these technologies in healthy elderly and in neurological populations [12-14].

Indeed, it has been shown that the use of some smartphone Apps may improve patient's health, due to the use of gamification, colorful aesthetics, point systems, social competitions (e.g. leaderboard), avatars, game rewards, story missions, which involve the user and improve physical activity [15,16].

Considering that the interest in using the App in cognitive assessment and rehabilitation is growing [17-20], the aim of the present review was to summarize current evidence on the usability and effectiveness of the use of mHealth in older adults and in patients with neurodegenerative disorders.

Search strategy

This review was conducted by searching for recent peer-reviewed articles published between June 1, 2010, and October 2022 using the following databases: Pubmed, Embase, Cochrane Database, and Web of Science. The goal of the research strategy was to track progress in using m-health for cognitive domains in older adults with and without neurodegenerative disease. To this end, the comprehensive search was conducted using the following terms: "Cognitive Rehabilitation" AND "Smartphone" OR "Mobile App"; AND/OR "older adults "and" neurodegenerative disease".

Inclusion criteria were: (i) study participants aged older than 65; (ii) m-health approach applied to cognitive rehabilitation; (iii) English language; and (v) published in a peer-reviewed journal. We excluded articles describing theoretical models, methodological approaches, algorithms, basic technical descriptions, and validation of experimental devices that do not provide a clear translation into clinical practice. In addition, we excluded: (i) animal studies; (ii) studies focusing only on other innovative approaches (such as exergaming, or serious games without smartphones or tablets), or (iii) on assessment or monitoring.

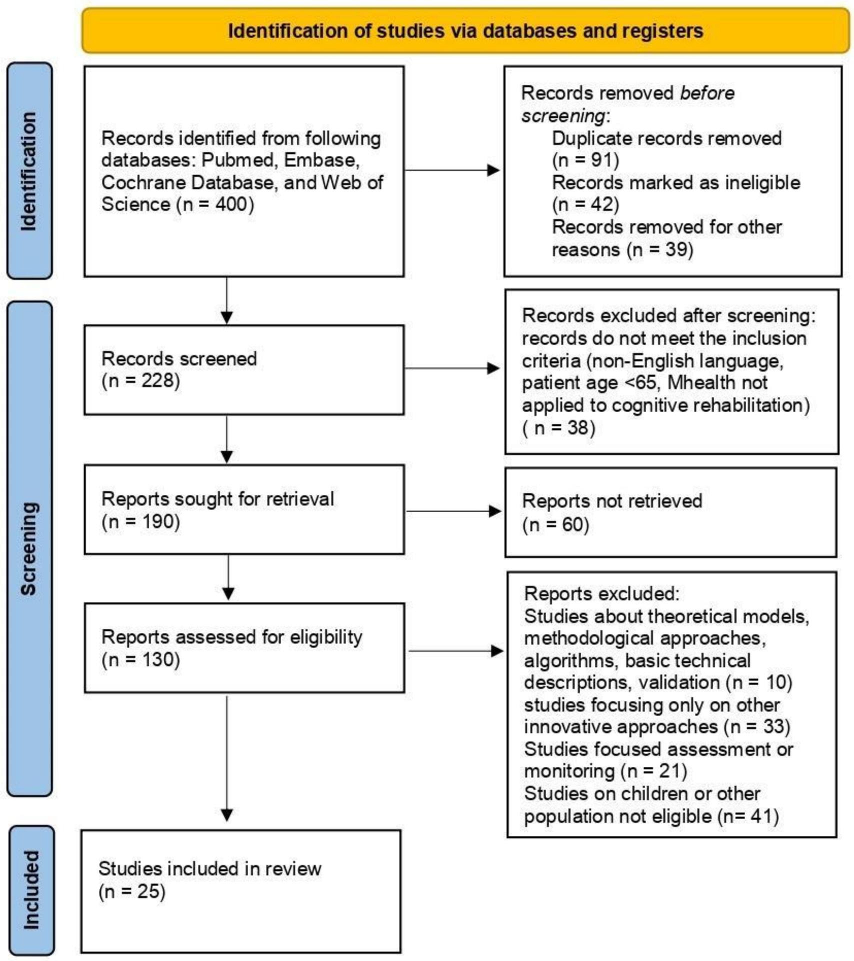
Titles and abstracts were screened independently. Relevant articles were then fully assessed. Disagreements over the article selection have been solved by discussion and with the supervision of a senior researcher.

The list of articles was then refined for relevance, revised, and summarized, with the key themes identified from the summary based on the inclusion/exclusion criteria. The following information was considered: authors, year and type of publication (eg, clinical trials, pilot study); characteristics of the participants involved in the study, and purpose of the study.

Results

The database search produced a total of 400 titles. After duplicate removal and abstract and title screening, 25 articles were included in the full-text assessment. A flowchart of study selection is presented in Figure 1. The main findings of the selected articles are reported in Table 1.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table 1 shows the principal studies concerning telerehabilitation via mHealth.

Type	Authors	StudyDesign	Sample characteristics	Device and training	Major findings
Acceptance and usability	Vaportzis et al. (2017)	RCT	43 older adults	Tablet training weekly 2-hour class for 10 weeks	Tablet training was well-accepted and could boost processing speed.
	Heinz et al. (2013)	Focus group	30 older adults	3 separate focus groups (an independent apartment complex, a rural community, and exercise program participants)	Older adults were willing to use new technologies if the utility of the tools was high and enabled them to overcome feelings of inadequacy.
	Petrovčič et al. (2019)	Exploratory study	617 older adults	Cycle of Technology Acquirement by	How the patient uses the smartphone on a daily living and the breadth of smartphone functionality influences

				Independent- Living Seniors (C-TAILS) model phone interview	the patient's ability to use assistive apps
	Chan et al. (2016)	Explorator y study	54 older adults	extensive iPad training 15 hr/week for 3 months	iPad apps could increase episodic memory and processing speed
	Vaportzis et al. (2017)	Focus group	18 older adults	Tablet training weekly 2-hour class for 10 weeks	Learning using a tablet was considered “useful”. The major concern of patients was the lack of clarity in instructions and support.
	Vaportzis et al. (2018)	Mixed methods study	43 older adults 14 healthy older adults	Tablet training weekly 2-hour class for 10 weeks	Participants became more confident with tablets and enjoyed downloading applications.
	Menéndez Álvarez- Dardet et al. (2020)	Explorator y study	212 Spanish older adults	active PC Not specified	Conflicting results. Possible age- related findings.
	Benge et. al. (2020)	Explorator y study	53 older adults with cognitive impairment 44 care partners 204 control	Smartphone Daily use	Smartphone apps might be a feasible intervention for some patients.
	Maggio et al. (2022)	Feasibility study	16 PD patients	Neuronation Brain training 3 times a week for six weeks	The tool has good usability and feasibility
Effectivene ss in the elderly	Jang et al. (2021)	RCT	389 non- demented elderly	Application- based Cognitive Training at Home (ACTH) for 12 months	Global cognition improvement in non-demented elderly individuals.
	Vaportzis et al. (2017)	RCT	43 older adults	Tablet training weekly 2-hour class for 10 weeks	Tablet training was well-accepted and could boost processing speed.
	Chan et al. (2016)	Explorator y study	54 older adults	extensive iPad training 15 hr/week for 3 months	iPad apps could increase episodic memory and processing speed
	Heinz et al. (2013)	Focus group	30 older adults	3 separate focus groups (an independent apartment complex, a rural community, and exercise program participants)	Participation in engaging activities characterized by new learning promoted the improvement of various cognitive skills, such as memory and executive functioning
	Xavier et al. (2014)	Longitudin al	6442 older adults	internet Not specified	Digital literacy could reduce cognitive decline among people aged 50-89.
	Yuan et al. (2019)	Explorator y study	3230 older adults	Smartphone Not specified	Higher smartphone use was positively associated with increased cognitive functions. Gender differences were found in the effect of smartphone use on visuospatial skills and memory.
	Tun et al. (2010)	Explorator y study	267 adults	computer Not specified	Frequent computer use can promote good cognitive function, particularly for executive control, from adulthood to old age, especially for subjects with lower cognitive ability.
	Silber et al. (2016)	Experiment al study	27 older adults	Computer Not specified	Less daily computer use wass associated with smaller brain volume in regions of memory.

	Zilberman et al. (2016)	Pilot study	8 older adults	8-week educational tablet training program	Participants who were actively engaged in a structured group with individual support were more likely to transfer skills into their environments and daily routines to promote performance and occupational performance satisfaction.
Effectiveness in patients with neuro-degenerative disorders	Scullin et al. (2022)	RCT	52 older adults with mild dementia	digital voice recorder app or a reminder app 4-week randomized controlled trial	Seniors with cognitive impairments improved memory strategies through smartphone training, which enhanced prospective memory.
	Kraepelien et al. (2020)	RCT	77 PD patients	internet-based cognitive behavioral therapy 10 weeks	Smartphone training was useful as an adjunct to standard medical treatment and improved the cognitive functioning of individuals with PD.
	Wu et al. (2019)	Experimental study	112 older elderly 127 MCI 84 AD	computer and a touchscreen device Daily use	Participants who did not use technologies daily had reductions in global cognitive function, processing speed, short-term memory and executive function.
	Aghanavesi et al.(2017)	Experimental study	19 PD patients 22 healthy controls	Smartphone Not specified	Using smartphone, it is possible to intervene effectively and evaluate the skills of PD subjects.
	Nicosia et al. (2022)	Experimental study	268 normal older adults 22 individuals with mild dementia	smartphone 4 times per day over 7 consecutive days	Smartphone training was reliable and valid and represents a feasible tool for boosting cognitive domains.
	El Haj et al. (2021)	Experimental study	22 patients with mild AD	smartphone-based calendars 3 weeks period	Smartphone applications may be useful for boosting prospective memory in AD
	Pang et al. (2021)	Experimental study	42 patients with AD	smartphone-based calendar training and walking exercise 12 weeks	Smartphone-based training improved cognitive function and have the potential as non-pharmacological interventions to boost cognitive functioning in women suffering from subjective cognitive decline.

**LEGEND: AD=Alzheimer Disease; RCT=Randomized Controlled Trial; PD=Parkinson Disease*

Acceptance and usability

Ten articles were included: 8 articles enrolling healthy elderly [21-31] and 2 articles enrolling patients with neurodegenerative disorders (1 article assessing elderly with cognitive impairment [32], and 1 article assessing patients with Parkinson's disease-PD [14]). Out of these, only the study performed by Vaportzis et al. [21], enrolling 43 seniors and reporting a good acceptance and usefulness of tablet training was an RCT. However, data on "familiarity" with smartphones and tablets remains controversial [21-32]. Heins et al. carried out a study on 30 elderly patients, reporting that the use of technology was "viewed positively" since it helped maintain independence and quality of life [22]. Moreover, older individuals without cognitive decline showed interest in using their smartphones/tablets as a cognitive aid (e.g. reminders, alarm clocks, calendars). In addition, patients with cognitive impairment were found to have adequate acceptance and usability of devices to facilitate cognitive functioning [14,31]. On the contrary, other studies have pointed out that younger patients had better outcomes through the use of m-health devices than older ones [25,26], probably due to a lack of confidence in electronic devices. The characteristics of some devices, such as internet signal problems, and poorly understood interface, can create difficulties of use in the elderly, especially with cognitive deterioration. Indeed, in studies performing a training section before proposing the use of devices for cognitive support-rehabilitation, a good acceptance and usability of smartphones, and even more tablets, were reported [24, 27-31]. Bier et al. found that subjects with and without cognitive impairment had generalized the skills learned during training interventions to other smartphone and tablet functions, using other apps in daily life [31]. Confirming this data, Imbeault et al., reported that cognitively impaired subjects, in addition to the cognitive stimulation app, installed other apps such as diaries, or recipe apps to improve self-esteem [25]. Furthermore, we previously reported good feasibility and usability of a 6-week cognitive rehabilitation protocol based on the non-immersive virtual reality telecognitive app in non-demented PD patients [14].

Effectiveness of telerehabilitation via mHealth in the elderly

Eight articles were included, of which 2 RCT studies: Vaportzis et al. [21] reported that table training improved processing speed; Jang et al. enrolled 389 non-demented elderly volunteers and reported that home cognitive training via smartphone improved cognitive performances in terms of global cognitive functioning, language, and memory [33]. In a study enrolling 30 elderly individuals, Heintz et al. reported that participation in engaging activities characterized by new learning promoted the improvement of various cognitive skills, such as memory and executive functioning [22]. Xavier et al. in a longitudinal study enrolling more than 6400 elderly individuals, demonstrated that increased Internet/email use was associated with significant improvement in memory performances [34]. Other studies have shown that mHealth enables improvements in executive functioning, such as processing speed and mental flexibility, in individuals with and without dementia. In particular, Chan et al. [27] conducted a study on 18 elderly individuals with no computer knowledge, reporting that, after training on tablet use, an improvement in episodic memory and processing speed was observed. Confirming these data, Yuan et al. noted that older adults without cognitive impairment through smartphone use showed more significant improvements in all cognitive domains, especially executive functions, than non-smartphone users [35]. Moreover, Tun & Lachman in a study of 2671 adults demonstrated that computer use can stimulate executive functions, especially the ability to switch attention and alternate attention [36]. Similarly, Kesse-Guyot et al. in a longitudinal cohort study found that older people using mHealth devices showed increases in episodic memory and executive function [37]. Furthermore, it has been observed that the knowledge acquired through mHealth training can be maintained for a long time, both in subjects with and without cognitive impairment [38,39-42]. Interestingly, the Intelligent Systems for Assessing Aging Change study on longitudinal aging has shown that the reduced use of technologies (PCs, tablets, smartphones) was associated with a smaller hippocampal volume and worse performance on memory and functioning executive in older adults with cognitive impairment [38].

Effectiveness of telerehabilitation via mHealth in patients with neurodegenerative disorders

Seven articles [43-50], including 2 RCT studies [43,44] were included. Scullin et al. sin a study on 52 elderly people with mild dementia reported that smartphone training could stimulate memory, especially prospective memory, by learning new strategies [43]. Kraepelien et al. enrolled 77 PD patients and pointed out that smartphone training was helpful as an adjunct to standard medical treatment to improve cognitive functioning [44]. Indeed, it has been shown that mHealth training could have better cognitive outcomes from using smartphones and tablets [43-50]. Wu et al. in a study of elderly people with MCI observed that the control group, who had not used technologies, presented a reduction of global cognitive functioning, processing speed, short-term memory, and executive function [45]. Indeed, Aghanavesi et al. in a study on PD patients demonstrated that through the use of smartphones, it was possible to effectively intervene in cognitive skills [46]. These findings were also supported by Nicosia et al. [47]. The authors conducted a study on 268 cognitively normal seniors (aged 65-97 years) and 22 individuals with mild dementia showing that smartphones have the potential to intervene in the first phases of AD improving short-term memory, processing speed, and working memory [47]. These results were confirmed by El Haj et al. who highlighted the positive effect of using smartphone-based calendars on prospective memory in AD [49]. Similar findings were reported by Pang and

Kim, performing a study on smartphone-based calendar training and walking exercise regimen in 42 postmenopausal women with subjective cognitive decline [50].

Discussion

Several studies supported the feasibility and efficacy of mHealth in both older individuals [21-31,33-42] and patients with neurodegenerative disorders [32,43-50]. Moreover, studies reported that the use of mHealth training was able to stimulate cognitive abilities, such as processing speed, prospective and episodic memory, and executive functioning [21,43-50] making smartphones and tablets valuable tools to enhance cognitive performances.

Some authors have shown that the use of mHealth could improve cognitive abilities and allow the generalization of outcomes in daily life, even in the presence of neurodegenerative disorders [19,20,31].

Unfortunately, it should be noted that, despite the growing interest in this topic, literature data on the use of mHealth in older adults with or without neurodegenerative disorders is still scarce. It should be noted that the majority of selected studies were case-control carried out on small-sample and that methodological differences such as the study population (healthy elderly *versus* cognitively impaired), and type of apps do not allow the comparison across the studies. Furthermore, few RCTs have been performed- In fact, to the best of our knowledge, only 2 RCTs on the effectiveness of smartphone training on older adults, and 2 RCTs related to the efficacy of smartphone tools in neurodegenerative disorders are available [28,43-45]. However, literature data suggest that it would be useful to carry out specific training to increase the use of technologies, favor the effects of cognitive rehabilitation in older individuals with and without cognitive decline [28,43-45], improve "familiarity" with technological tools [48], reducing anxiety about technology or technophobia [25].

In conclusion, the present review underlines that despite the great attention paid to mHealth in recent years, especially after the COVID-19 pandemic. Longitudinal RCTs are needed to evaluate the efficacy of mHealth cognitive rehabilitation in healthy elderly and in patients with neurodegenerative disorders.

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5. Article 3

Effectiveness of Telerehabilitation plus Virtual Reality (Tele-VR) in cognitive and social functioning: a randomized clinical study on Parkinson's Disease

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Abstract

Introduction. Telemedicine could represent an emerging and innovative approach to support cognitive and behavioral rehabilitation reducing the overload of healthcare facilities, favoring home care therapy. The aim of the present study was to assess the potential efficacy of Tele-VR apps in enhancing cognitive performance and improving social skills in patients with Parkinson's disease (PD). **Methods.** Thirty-four patients with PD were included in the study. Patients were assigned to one of the following treatment groups: the Experimental Group 1 (EG1) underwent a Tele-VR program via two cognitive rehabilitation applications (app) on smartphones (Neuronation-Brain Training and Train your Brain); the Experimental Group 2 (EG2) received a Tele-VR program through one cognitive rehabilitation app (Neuronation-Brain Training) and one socio-cognitive rehabilitation App (The Sims) on smartphones; Active

Control Group (aCG) performed a program using pencil and paper exercises (Not-VR). **Results.** At the end of the study, compared to the baseline, aCG and EG1 presented an improvement in the executive-attentive and visuospatial cognitive domains. The EG1 increased mood and subjective memory performance perception. Finally, in the EG2 group, a significant improvement was recorded in all cognitive domains and social cognition skills (theory of mind). **Conclusion.** Rehabilitation with smartphone apps could be more useful than Not-VR rehabilitation in improving cognitive and social cognition skills in patients with PD. The combination of cognitive-social cognition training could improve the cognitive and affective domains, also aiding in the long-term maintenance of cognitive outcomes.

Keywords. E-rehabilitation, cognitive domains, Parkinson's disease, cognitive rehabilitation.

Introduction

In the last decade, telemedicine has represented an emerging and innovative approach to support motor and cognitive rehabilitation [1,2]. Telemedicine reduces the overload of healthcare facilities, decreasing the costs of the national health service by favoring home care, which is particularly important following the COVID-19 pandemic [1-3]. Indeed, Telemedicine can be implemented at the patient's home, thus reducing the wait times for hospital visits, leading to shorter treatment initiation times and ensuring continuous monitoring that can be challenging to achieve through in-hospital care [1,2]. The beneficial effect of telerehabilitation increases in combination with virtual reality (VR) [3,4]. VR allows realistic experiences, using sensorimotor, cognitive, and social domains. Simulating real-life scenes through playful elements, the tool increases patient rehabilitation compliance [3,4]. A recent field of Tele-VR regards the use of smartphones. Smartphone applications (app), in fact, can be used every day, allowing the subject to easily access therapy at home, thus enabling "healthcare in the pocket" [5]. These benefits of VR may be useful in the rehabilitation of patients with Parkinson's disease (PD), who are at risk of developing cognitive impairment [6]. To date few studies on the usefulness of cognitive rehabilitation, and no studies on social skills rehabilitation using smartphone VR-app in PD patients are available.

The aim of the present study was to assess the potential efficacy of Tele-VR apps in enhancing cognitive performance and improving social skills in patients with PD.

Material and Methods

Study Population

Cognitively unimpaired patients affected by PD diagnosed according to the Movement Disorders Society (MDS) diagnostic criteria [7,8], who attended the "Parkinson's Disease and Movement Disorders" center of the University Hospital "Policlinico-San Marco" of Catania, between March and November 2021, were enrolled in the study.

We enrolled only patients aged between 40 and 80 years, with at least 5 years of schooling (Primary School) and with a Hoehn and Yahr stage < 2.5. PD patients with psychiatric disorders or dementia were excluded.

Ethics

The study was approved by the local Ethical Committee and was in accordance with the 1964 Helsinki Declaration. Each study participant provided informed consent.

Clinical assessment

PD severity was evaluated during the "off" state, after at least 12-hours of levodopa withdrawal with the "Unified Parkinson Disease Rating Scale– Part III Motor Examination" (UPDRS-ME) and the "Hoehn and Yahr" (HY) scale; the Levodopa Equivalent Daily Dosage (LED) was calculated.

Study procedures

PD patients were randomly allocated in three different groups using a block randomization. The Experimental Group 1 (EG1) underwent a Tele-VR program via two cognitive rehabilitation apps on smartphones; the Experimental Group 2 (EG2) received a Tele-VR program via one cognitive rehabilitation app, and one social-cognitive rehabilitation App; the Active Control Group (aCG) underwent a Not-VR program, using paper-pencil exercises performed independently at home and presented to the therapist for evaluation at the end of the training (after 6 weeks).

At baseline (T0), all patients underwent a clinical and neuropsychological assessment, as well as tutorial training tailored to their specific rehabilitation needs. After the baseline, patients started the rehabilitation protocol 3-times a week for 6 weeks. During the rehabilitation program, the three groups (EG1, EG2, aCG) received a weekly phone call from the rehabilitator for possible doubts or questions.

A complete neuropsychological assessment was performed after 6 weeks (T1, end of the rehabilitation program) and after 3 months from the end of the rehabilitation process (T2, follow-up visit).

VR tele-cognitive app

The EG1 and EG2 training was carried out through a remote rehabilitation system using a non-immersive VR app downloaded for FREE from the Google Play Store on smartphones. Each rehabilitation session, lasting 30 minutes (15 minutes for the app) was performed 3 times a week for 6 weeks. These non-immersive VR Apps allow the patients to feel “present” in a playful and virtual environment, where enhanced feedback helps them to be aware of their performance. Furthermore, using a telemedicine approach, the apps send the therapist real-time reports on the results achieved.

Experimental group 1 (EG1)

For EG1, two cognitive apps, NeuroNation - Brain Training (Synaptikon GmbH, Berlin) and Train Your Brain (Grove FX) were used. NeuroNation - Brain Training (Synaptikon GmbH, Berlin) offers science-based brain training, which enhances cognitive performance across multiple cognitive domains. The program shows data on cognitive performance through personalized summary sheets. Train Your Brain (Grove FX) consists of concentration, spatial thinking, and reasoning skills exercises. The training type, set by the rehabilitator at the beginning, lasted 15 minutes and was carried out after the NeuroNation training. These Apps allowed remote rehabilitation at the patient's home.

Experimental group 2 (EG2)

PD patients in EG2 received a Tele-VR program via a cognitive rehabilitation app (Neuronation-Brain Training), the same used for the EG1, plus the socio-cognitive app The Sims™ Mobile. The Sims™ Mobile (ELECTRONIC ARTS) is a non-immersive VR app in which the patient overcomes social challenges (initiating and conducting dialogues, managing finances, work, and home) with audiovisual feedback. The training with The Sims (lasting 15 minutes) was carried out after the NeuroNation Brain Training app.

The feasibility, acceptability, and usability of this Tele-VR rehabilitation program, administered 3-times a week for six weeks, have been previously assessed and “good” usability and an “excellent” perception of improvement were recorded [9].

Active Control Group (aCG)

For the aGC, worksheets of cognitive exercises were used, aimed at the cognitive and emotional-social components, with exercises of various kinds (puzzles, memory). These exercises were performed 3-times a week (30 minutes for rehabilitation sessions) for 6 weeks.

Outcome measure

During all the scheduled visits (T0, T1 and T2) all the enrolled subjects underwent the following neuropsychological evaluation: Mini-Mental State Examination (MMSE); Montreal Cognitive Assessment Scale (MoCA); Frontal Assessment Battery (FAB); Rey Auditory Verbal Learning test –(RAVLT), immediate and delayed recall; Stroop color-word test; Trail Making Test part A and part B (TMT-A/B); Phonemic Verbal Fluency (Verbal fluency letter test - COWAT); Raven's Colored Progressive Matrices (RCPM); Clock drawing test (CDT); Copy of figures; Memory Assessment Clinics-questionnaire (MAC-Q); Hamilton Rating Scale for Depression/Anxiety (HRS-D); Verbal Reasoning Assessment Test (VRT); The Short Empathy Quotient Scale (EQ-short); Faux pas Test - Adult Version; Toronto Alexithymia Scale (TAS).

Statistical analysis

Statistical analyses were performed using STATA 16.0 software packages (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC. StataCorp. 2017). Descriptive statistics were analyzed and expressed as mean and standard deviation for continuous variables and number and percentage for categorical variables. The Shapiro-Wilk normality test was performed. Differences between means were evaluated with the ANOVA and the paired t-test for repeated measures in case of normal distribution and Kruskal-Wallis and the Wilcoxon matched-pairs test for repeated measures in case of not-normal distribution. A post-hoc analysis, False Discovery Rate (FDR) corrected was performed. The χ^2 Test was performed to compare frequencies. A significance level of the statistical tests was established with $p < 0.05$.
A first statistical analysis comparing the performance obtained at T0, T1, and T2 visits by each group of treatment (intra-group comparison) was performed. Subsequently, an inter-group comparison was carried out analyzing the mean differences (T1-T0) of the scores obtained at

the MMSE, MoCA, FAB, and Faux Pas, considered as a prototype of tests globally assessing cognitive abilities and social cognition skills.

Results

Thirty-four patients (23 men; mean age 63.3±8.6 years) completed the study. No statistically significant differences were recorded comparing the three groups (aCG, EG1, EG2) in terms of sex, age, education, disease duration, UPDRS-ME, and LED (table 1).

At the baseline neuropsychological assessment, all patients scored within the normal range on all tests administered. At the "comprehensive" neuropsychological assessment, no statistically significant differences were recorded comparing the cognitive performances of the three groups except for the TMT-A in which aCG performed worse than EG1 and EG2. aCG group performed worse than the other two groups in a test assessing social skills (Faux pas test- p-value 0.070) and in the sub-score difficulties in identifying feelings of the TAS-20 (p-value 0.049).

Concerning the intra-group comparison, the aCG presented, after 6 weeks of rehabilitation, a statistically significant improvement in the executive-attentive domain (FAB, Stroop) and visuospatial and praxis skills (CDT and copy of figures test). The improvement in praxis skills and executive-attentive domains persisted also at the T2 follow-up visit, after 3 months from the end of the study (table 2). The post-hoc analysis confirmed the significance.

Pertaining to the EG1 group, at the end of the 6 weeks of VR rehabilitation, a statistically significant improvement at the following tests was recorded: MoCA, FAB, Rey-IR, Stroop time, FAS, WCST, TMT-A, VRT-absurdities. For almost all the neuropsychological tests, the improvement was confirmed also at the T2 follow-up visit. In the post-hoc analysis, only the improvement in the executive-attentive domain (FAB, Stroop test, FAS, WCST, and TMT-A) was confirmed. A significant improvement in mood (HAM-D) and subjective memory performance perception (MAC-Q) was recorded (table 2).

In the EG2 group, at the end of the rehabilitation program and at follow-up, a significant improvement in almost all the cognitive (MoCA, FAB, RAVLT-Immediate recall, RAVLT-delayed recall, RAVEN, FAS, CDT, VRT-TOT, MAC-Q) and social cognition tests (FAUX pas test, HAM-D, EQ-SS) were recorded. At the post-hoc analysis, the improvement in the episodic memory (RAVLT, immediate and delayed recall), executive-attentive (FAB, RCPM, FAS, WCST, TMT-A), visuospatial (copy of figures), and social cognition (Faux pas test) was confirmed (table 2).

Finally, when the mean differences (T1-T0) of the scores obtained by the three groups at the MMSE, MoCA, FAB, and Faux Pas were compared (inter-group comparison), both the EG1 and the EG2 presented a significantly higher improvement than the aCG at the MoCA. Furthermore, both the EG1 and the EG2 presented a higher improvement at the FAB score than the aCG, although the difference was statistically significant only for the EG2 (Table 3).

Discussion

In the present study, patients receiving VR training sessions showed improvements in both cognitive, emotional, and social outcomes. At the intra-group comparison, at the end of the study, the aCG presented an improvement in executive-attentive and visuospatial domains while the EG1 and EG2 groups showed a significant improvement in almost all socio-cognitive domains. Not least, in the EG1 and EG2, the subjective perception of memory performance and mood benefited from the Tele-VR rehabilitation programs. Interestingly, at the inter-group comparison, both the EG1 and EG2 presented a significantly higher improvement at the MoCA and FAB than the aCG.

Previous studies have underlined that the use of smartphone apps can encourage patients to perform rehabilitation through playful graphics and increasing levels of difficulty [6,9-11]. Studies on the feasibility and effectiveness of mHealth have shown that Apps are able to stimulate cognitive skills, such as processing speed, memory, and executive functioning both in older individuals [10] and in patients with neurodegenerative disorders [11].

In agreement with literature data [6,10,11], in our sample, the patients receiving training with the apps (cognitive alone or cognitive/social in combination) presented a significant improvement in all the neuropsychological tests. Notably, although the EG1 rehabilitation protocol did not include social skills training, the EG1 obtained positive effects also on this cognitive domain, theory of mind (ToM) in particular. ToM is a cognitive ability related to social cognition; it drives automatic and voluntary behaviors modulating the behavioral responses in social environments [12]. Social cognition may be impaired in PD, due to the involvement of frontostriatal circuits, which also play an important role in socio-cognitive function [13]. PD patients could have deficits in emotion recognition, especially for negative

emotions such as sadness, anger, and fear. Additionally, patients with PD may present executive dysfunction associated with difficulties in the theory of mind [12]. In this context, it seems that rehabilitation with smartphone apps could be useful in improving social cognition skills.
In our sample, the combination of cognitive training with social cognition-specific training enhanced cognitive and affective domains, favoring long-term maintenance of cognitive outcomes. This aspect is very interesting because the debate regarding the correlation between cognitive domains and social cognition skills is still open. In any case, a correlation between executive functioning and social cognition is hypothesized, due to the involvement of the lateral frontal lobes in both cognitive domains [13]. In agreement with these hypotheses, in our sample, the rehabilitation of social cognition skills led to a more generalized improvement, not only strictly related to the social cognition skills test.

Moreover, in the present study, patients receiving Tele-VR achieved an improvement in mood. This result is in line with other studies that have reported the beneficial effect of mHealth in improving mood, probably for the release of endorphins and dopamine consequent to the playful scenarios of VR triggering positive emotions and feelings of well-being [13].
The main limitation of the study is the relatively small size of the sample which could limit the generalizability of the results. Sample size is limited due to various factors, such as participant availability and eligible resource constraints; however, our sample may be adequate to acquire preliminary insights and pilot data, to carry out more extensive future studies. Moreover, probably for a randomization bias, at baseline, patients of the aCG group presented worse performance than the EG1 and EG2 groups at the Faux pas test and at the TMT-A. However, all the enrolled subjects performed within the range of normality in all the tests of the comprehensive neuropsychological evaluation.
Finally, the enrollment of patients with normal cognitive abilities did not allow us to explore the beneficial role of Tele-VR using smartphone Apps in PD patients with cognitive decline.

To our knowledge, this is the first study investigating the effects of cognitive and social skills training using a semi-immersive VR system via smartphone app in a sample of patients with normal cognition. We observed that rehabilitation with smartphone apps could be more useful in improving social-cognitive skills in PD patients. Indeed, the combination of cognitive and social training could improve the cognitive and affective domains, while aiding in the long-term maintenance of outcomes.

Further studies are needed to confirm our findings and to assess the potential beneficial role of Tele-VR using smartphone Apps in PD patients with Mild Cognitive Impairment.

Conflicts of interest

The authors report no conflicts of interest.

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Dr. Maggio M.G. carried out this study during the Ph.D. course in Neuroscience at the University of Catania.

Authors' contribution

(1) Research project: A. conception, B. Organization, C. Execution and design; (2) Statistical Analysis: A. Design, B. execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

MGM: 1A, 1B, 1C, 2A, 3A,3B

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CEC: 2A, 2B, 2C

RCS: 1B, 3B

FD: 3B

MZ: 3B

AN: 1A, 1B, 1C, 2A, 2C, 3A,3B

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Table 1. Demographic and clinical characteristics of the sample

	Total sample (n.34)	aCG (n.10)	EG1 group (n.12)	EG2 group (n.12)	p-value
Sex, men (%)	23 (67.6)	9 (90.0)	8 (66.7)	6 (50.0)	0.1§
Age, years (mean±SD)	63.3±8.6	66.8±6.5	59.7±9.7	63.8±8.3	0.5§
Education	12.3±4.2	11.7±5.2	13.1±3.5	12.0±4.1	0.5§
Disease duration	4.6±2.3	3.5±2.2	4.8±2.5	5.4±1.9	0.7§
UPDRS-ME	27.6±10.4	33.8±8.3	27.9±12.7	22.1±6.3	0.08§
LED	363.0±174.8	450.0±191.5	373.4±177.0	280.2±126.1	0.077°

Legend: Abbreviations: aCG: active control group; EG: experimental group. UPDRS-ME: Unified Parkinson’s Disease Rating Scale-Motor Examination; LED: Levodopa Equivalence Dosage. Bold p-value <0.05. §: ANOVA-test; °: Kruskal-Wallis test.

Table 2. Baseline and follow-up neuropsychological assessment

Clinical assessment	Active Control Group			T0 *vs* T1 p-value	T0 *vs*T2 p-value	Experimental Group 1			T0 *vs* T1 p-value	T0 *vs* T2 p-value	Experimental Group 2			T0 *vs* T1 p-value	T0 *vs* T2 p-value
	T0	**T1**	**T2**			**T0**	**T1**	**T2**			**T0**	**T1**	**T2**		
MAC-Q	24.2±2.4	22.2±3.7	23.8±2.7	0.204§	0.642§	23.1±7.2	19.6±3.1	21.2±5.1	**0.02°**	**0.005°**	25.1±4.5	21.3±3.2	21.9±2.9	**0.014§**	**0.025§**
HAM-D	7.8±6.7	7.1±2.9	7.4±4.3	0.084°	0.071°	8.0±5.2	5.0±4.2	3.7±3.0	**0.041§**	**0.001§**	9.1±5.8	6.3±4.4	6.1±5.0	**0.028§**	**0.010§**
MMSE	27.3±2.1	27.7±1.1	27.6±1.5	0.386§	0.522§	28.2±1.5	28.9±0.9	28.7±0.8	0.056§	0.213§	28.3±1.5	28.9±1.3	28.5±1.2	0.125°	0.500°
MoCA	24.0±2.3	23.6±2.4	23.4±2.0	0.545§	0.382§	26.6±1.8	28.2±1.6	27.1±2.1	**0.007§**	0.599§	25.1±3.3	27.7±1.5	27.6±1.3	**0.002§**	**0.014§**
FAB	15.7±2.0	15.7±2.2	15.7±1.9	**0.040°**	**0.010°**	16.2±1.0	16.8±0.9	16.9±0.8	**0.027§**	**0.005§**	15.6±1.3	16.4±0.8	16.7±0.9	**0.005§**	**0.001§**
Rey-IR	32.6±8.2	31.7±4.9	30.8±4.9	0.627§	0.303§	35.3±8.2	40.3±8.7	43.0±12.3	**0.035§**	**0.025§**	30.0±6.7	35.5±6.7	36.1±6.7	**0.002°**	**0.002°**
Rey-DR	6.1±2.8	7.0±1.9	6.5±2.8	0.234§	0.565§	8.3±2.4	9.4±2.4	9.9±3.2	0.097°	0.106°	6.2±2.1	7.9±2.1	8.0±2.4	**0.027°**	**0.004°**
Stroop, time (sec)	24.3±18.5	22.8±18.0	24.9±18.1	**0.025°**	0.120°	21.3±8.6	16.3±6.2	14.5±7.6	**0.022§**	**0.001§**	18.4±11.9	13.2±6.4	12.7±6.6	**0.020°**	0.110°
Stroop, error (n.)	2.9±4.8	0.4±0.5	0.5±0.9	**0.002°**	**0.001°**	0.3±0.6	0.6±1.4	0.5±1.0	0.750°	0.625°	0.7±1.1	0.2±0.7	0.2±0.7	0.125°	0.062°
Raven	25.7±3.6	26.2±3.4	25.8±3.9	0.343§	0.811§	29.0±2.9	29.8±3.0	30.4±3.8	0.221§	0.064§	28.7±3.7	31.3±4.1	30.8±1.8	**0.003°**	**0.007°**
FAS	24.4±9.2	24.5±6.9	24.5±5.9	0.964§	0.982§	35.4±9.6	43.5±12.8	48.8±19.4	**0.001°**	**0.002°**	30.6±11.4	38.9±9.9	39.1±9.9	**0.002§**	**0.002§**
WCST, Cat	3.1±1.6	3.6±1.8	3.1±1.5	0.322§	1§	3.7±1.9	5.4±0.8	5.0±1.1	**0.007°**	**0.031°**	3.7±2.1	5.2±0.9	4.9±1.2	**0.004§**	0.078§
WCST, PE	9.3±8.4	10.5±8.0	10.2±7.6	**0.014 °**	**0.023°**	6.2±4.6	1.8±2.1	2.7±2.8	**0.002°**	**0.002°**	6.2±7.3	2.7±5.2	2.9±5.2	**0.002§**	**0.001§**

CDT	1.2±1.1	0.6±0.8	0.5±0.8	**0.001°**	**0.001°**	0.2±0.6	0	0	0.500°	0.500°	0.7±0.9	0	0	**0.025§**	**0.025§**
Copy of figures	9.7±1.8	10.3±1.7	9.9±1.9	**0.023§**	0.393§	10.4±1.1	11.1±1.0	10.9±1.1	0.054°	0.156°	10.1±1.0	11.2±0.8	11.2±0.5	**0.011§**	**0.001§**
TMT-A	61.4±25.2	63.6±25.2	66.0±21.7	0.661§	0.310§	35.3±24.1	28.2±15.3	29.0±17.4	**0.049°**	**0.011°**	49.4±16.3	43.9±20.9	41.7±19.6	**0.027§**	**0.009§**
TMTt-B	119.5±42.7	120.5±39.4	122.3±41.5	0.904§	0.684§	79.4±39.4	62.1±31.3	63.5±27.9	0.065§	0.116§	90.0±45.1	73.7±39.9	75.7±46.5	**0.012§**	0.050§
TMTt-B-A	62.0±56.0	62.4±54.8	75±57.4	0.967§	0.415§	44.3±34.8	26.2±21.2	29.6±20.8	0.171§	0.067§	43.6±26.5	32.8±25.8	32.0±27.7	**0.006§**	**0.032§**
VRT															
Absurdities	11.9±3.4	10.9±3.2	10.4±3.5	0.270§	0.103§	11.2±2.5	11.7±2.2	12.3±1.9	0.454§	0.090§	12.2±2.1	12.7±1.5	12.9±1.4	0.250°	0.500°
Intruders	10.1±3.4	10.9±3.1	10.4±3.0	0.515°	0.230°	11.4±2.7	11.8±2.5	11.5±3.2	0.500°	0.457°	11.6±2.6	11.4±3.3	12.6±1.6	0.906°	0.093°
Relationshi	8.6±2.9	9.3±3.3	9.2±3.2	0.172§	0.239§	11.0±2.8	11.5±3.3	11.4±2.4	0.364§	0.910§	10.1±2.9	11.8±1.8	10.6±2.9	**0.038§**	0.526§
Differences	12.2±3.3	12.5±2.4	12.7±2.5	0.105°	0.296°	12.7±1.8	13.5±1.2	13.2±1.5	0.171°	0.718°	13.3±0.7	13.9±0.4	13.8±0.8	**0.031°**	0.187°
Idiomatric expressions	10.3±3.8	11.1±2.8	10.8±2.8	0.980°	0.460°	12.1±2.1	12.7±1.9	13.2±1.4	0.307§	0.060§	12.9±0.9	12.9±0.9	12.5±1.3	0.586§	0.137§
Family relationship	6.9±3.8	8.2±4.1	7.3±4.0	0.274§	0.721§	9.1±3.7	10.9±2.3	9.5±4.0	0.095§	0.776§	6.9±5.5	10.9±3.9	11.0±2.6	**0.031°**	**0.003°**
Classifications	12.2±2.5	12.3±2.3	12.5±2.2	0.500°	0.156°	13.3±1.4	13.4±2.2	13.8±0.9	0.375°	0.062°	13.2±1.7	13.6±1.0	13.9±0.4	1°	0.250°
VRT-Tot	73.5±14.2	74.9±13.6	72.5±14.3	0.594§	0.589§	81.7±10.2	83.8±9.3	84.9±10.5	0.180§	**0.016§**	81.7±9.9	86.8±8.9	85.7±9.9	**0.003°**	**0.025°**
Faux	52.0±19.5	55.7±18.5	51.6±18.6	0.225§	0.916§	64.9±9.6	73.6±4.3	70.8±5.7	**0.004§**	0.051§	65.8±8.6	73.2±6.1	72.6±6.8	**<0.001§**	**<0.001§**
EQ-CE	6.6±2.6	6.1±1.8	6.5±2.2	0.615°	0.361°	6.5±1.4	7.1±2.4	6.7±2.8	0.267§	0.726§	6.2±2.6	7.2±1.6	7.0±1.7	0.153§	0.312§

EQ-ER	5.7±2.3	6.2±1.8	5.9±1.9	0.322§	0.743§	6.8±2.7	7.0±2.1	7.7±1.7	0.836§	0.211§	6.3±2.5	7.9±1.5	7.9±1.6	0.082§	0.126§
EQ-SS	5.6±3.0	5.6±3.0	6.0±2.8	0.140°	**0.039°**	6.6±2.5	7.7±1.8	6.9±2.6	0.150§	0.666§	5.8±2.6	7.7±1.8	7.8±1.9	0.071§	**0.017**§
TAS-20															
TAS-20 DF	17.5±5.9					13.5±3.2					13.6±2.8				
TAS-20 IF	17.4±6.5					12.1±2.9					16.8±2.3				
TAS-20 EO	27.6±6.6					25.4±7.6					24.6±7.2				

Legend: Abbreviations: aCT: active control group; EG: experimental group;; vs: versus. MMSE: Mini-Mental State Examination; MoCa: Montreal Cognitive Assessment; FAB: Frontal Assessment Battery; RAVLT: Rey Auditory Verbal Learning test - Imm: Immediate and Del: Delayed recalll; SCWT: The Stroop Color and Word Test; RCPM: Raven's Colored Progressive Matrices; WCST: Wisconsin Card Sorting Test; CDT: Clock Drawing Test; TMT: Trail Making Test; HDRS: Hamilton Depression Rating Scale; HARS: Hamilton Anxiety Rating Scale. #number and percentage of subjects performing in the range of normality score. Bold p-value <0.05. §: paired t-test; °: repeated measures Wilcoxon test.

Table 3. Global cognitive abilities and social skills: Inter-group comparison.

	aCG	EG1	EG2	p-value aCG versus EG1	p-value aCG versus EG2
MMSE (T1-T0)	**0.4±1.5**	**0.7±1.1**	**0.6±1.2**	0.595	0.731
MoCA (T1-T0)	**-0.4±2.0**	**1.7±1.7**	**2.7±2.4**	**0.014**	**0.004**
FAB (T1-T0)	**-0.02±0.7**	**0.6±0.8**	**0.7±0.7**	0.07	**0.026**
Faux (T1-T0)	**3.7±8.9**	**8.7±8.4**	**7.3±4.6**	0.191	0.235

Legend: Abbreviations: aCT: active control group; EG: experimental group; MMSE: Mini-Mental State Examination; MoCa: Montreal Cognitive Assessment; FAB: Frontal Assessment Battery.

6. Conclusion

The studies conducted were aimed at assessing the feasibility, the accessibility and the effectiveness of a six week Tele-VR rehabilitation with APP on the patient's smartphone in cognitively unimpaired patients with PD.

After evaluating the evidence in the literature on the use of VR-APPs in older individuals rehabilitation, we focused on the usability and feasibility of the tool. The SUS scale was used to evaluate the usability of VR-APP smartphones and the Goal Attainment Scaling (GAS) was used to measure the patient's perception of goals achieved during the intervention.

The novelty of our study was the use of a telerehabilitation system based on digital rehabilitation strategies (Mobile Health), prepared and programmed to empower the patient by making him autonomous. According to our results, the protocol presented good usability and acceptability of the tool. Moreover, the patients declared to perceive "improved cognitive abilities".

Given the promising results, we dedicate ourselves to evaluate the effectiveness of the Tele-VR protocol, using APPs to increase cognitive abilities. In our sample, subjects who received training with APP (cognitive or cognitive/social in combination) presented a significant improvement in all neuropsychological tests. Notably, the improvement in social cognition tests was recorded not only in patients treated with VR APP based on social skills but also in patients treated with VR APP based only on cognitive APP

Additionally, according to previous studies, patients who received Tele-VR experienced an improvement in mood [1], possibly due to the release of endorphins and dopamine resulting from playful virtual reality scenarios that trigger positive emotions and feelings of well-being [2].

In conclusion, according to previous studies in patients with neurodegenerative disorders [13-15], in our studies Tele-VR rehabilitation presented a good feasibility and efficacy. .

Our data allow us to support the role of VR APPs implemented via smartphone/tablet as a valuable tool to improve cognitive performance.

Future studies with larger samples and longer follow-ups could be performed to confirm our findings.

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Appendix A:

Studies in the Field of Neuroscience and Rehabilitation published during my Ph.D in collaboration with other center

- **Maggio MG,** Bonanno M, Manuli A, Onesta MP, De Luca R, Quartarone A, Calabrò RS. Do Individuals with Spinal Cord Injury Benefit from Semi-Immersive Virtual Reality Cognitive Training? Preliminary Results from an Exploratory Study on an Underestimated Problem. Brain Sci. 2023;13(6):945.

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8. Statements

1. We know that what we are doing is nothing more than a drop in the ocean. But if the drop were not there, the ocean would be missing something (Mother Teresa).
2. Every great advance in science has issued from a new audacity of imagination (John Dewey).
3. Research is movement: what was true yesterday is no longer true today and will be changed again tomorrow (Piero Angela).
4. Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (World Health Organization).
5. I have not failed. I've just found 10,000 ways that won't work (Thomas A. Edison).
6. Not like someone who always wins, but like someone who never gives up (Frida Khalo).
7. The change towards technology-based practice and more specifically smartphone-based applications is an extremely relevant area for health professionals to effectively communicate and treat a variety of patient groups (Jin).
8. Using technology to deliver rehabilitation services has many benefits for not only the clinician but also the patients themselves. It provides the patient with a sense of personal autonomy and empowerment, enabling them to take control in the management of their condition (Brennan).
9. There is no failure except in no longer trying (Elbert Hubbard).
10. Failure is the most important ingredient in science (Stuart Firestein).