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Evaluation of the effectiveness of cognitive rehabilitation in the early stages of deterioration in neurodegenerative diseases

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Abstract

In the context of neurodegenerative diseases, patients with Mild Cognitive Impairment (MCI) convert to dementia at a greater rate than the cognitively intact individuals. The MCI construct was introduced also for Parkinson's Disease (PD), similarly to what happened in Alzheimer's Dementia (AD). Mild cognitive impairment in PD (PD-MCI) refers to cognitive deficits that appear in the early stage of the disease, that represent a risk factor for the development of Parkinson's disease dementia (PDD) and that are strongly associated with reduced quality of life both for patients and care-givers, leading to an increase in health-related costs.

At present, there is no established successful pharmacological treatment for cognitive impairment in PD. Non pharmacological intervention, such as cognitive training programs, may represent beneficial alternatives and/or adjunctive therapy to medications to delay the onset of the cognitive deficits or at least to maintain patients at their current level. Advances in the development of Information & Communication Technologies (ICT) has recently prompted the possibility to develop computer-based solution for the training of one or more cognitive functions. This approach could help overcome the limits of traditional paper-and-pencil cognitive intervention techniques. However, strong evidence about the effectiveness of cognitive intervention, using both computers and in-person interventions, is still insufficient.

The aim of this research is to evaluate the effectiveness of ICT tools in the training of cognitive deficits in subjects with neurodegenerative disorders. We conducted a prospective single-blind Randomized Controlled Trial (RCT) for computer-based cognitive training (CoRe system - acronym for Cognitive Rehabilitation)) of logical and executive functions for inpatients with PD-MCI single domain (executive) or multiple-domain with executive involvement.

Participants (41), after baseline cognitive assessment (T0), were randomized to receive standard rehabilitation (physiotherapy and physical treatment) plus cognitive training with CoRE (intervention group, G1 = 23) or standard rehabilitation only (control group, G2 = 18). The CoRe program consisted of 12 individual sessions (3 session/week), lasting 45 minutes. All the patients were evaluated after 4 weeks (T1) with the same neuropsychological battery; follow-up evaluations was scheduled after 6 months (T2). The scores of the neuropsychological tests were considered outcome measures of the study. Our hypothesis was that G1 had a higher probability of maintaining or improving its cognitive level than G2. Particularly, the primary outcome measures coincided with global functioning scores (MMSE and MOCA) and the secondary outcome measures coincided with executive tests. However, non-executive test scores were also considered in our analysis to assess whether the treatment effect could be transferred even into untrained domains. To perform the intended intra-group and inter-group evaluations Wilcoxon test was chosen. Intra-group tests were performed on paired data: for each neuropsychological test, the scores obtained by each patient at three set moments of the experiment (T0, T1, T2) were compared to detect the statistical significance of the changes. Inter-group tests were aimed at detecting significant differences in the neuropsychological tests scores variations (at T0, T1 and T2) between G1 and G2. Furthermore, for each patients a percentage change was calculated for each of the two primary outcome measures between the baseline and the next evaluations, in order to identify and

compare the number of patients who improved, retained or worsened their cognitive state in the two groups (Fisher's Exact test). Mean percentage change scores at MMSE and MOCA for G1 and G2 between the baseline and the next evaluations were calculated and compared (Wilcoxon test).

Among the 23 patients in G1, 6 dropped-out because they were discharged before the end of cognitive training. Between T0 e T1, G1 patients who completed CoRe training (17) showed a medium/large effect size improvement in the overall cognitive performance score measured by MOCA, in many executive tests and also in some memory tests; while the same cannot be said for control group that tended to remain stable in its performance. Furthermore, inter-group analysis confirmed that this improvement of G1 was statistically different from trend of G2. These results suggested a positive effect of cognitive training. However, the comparison between the two groups between T1 e T2 showed the trend was similar and no significant difference was observed in the trajectory of the two groups in this interval. So, after six month, G1 behaved as G2 despite treatment and no post-training improvement was maintained after the discharge. Finally, between T0 and T2, G1 showed a medium/large effect size improvement in several tests, also inter-group comparison revealed significant differences in favor of G1 in global cognitive functioning (MOCA) and in both logical-executive and mnemonic domains.

About the impact of cognitive training on overall cognitive functions, the mean percentage change scores calculated for each of the two primary outcome measures showed that between T0 and T1 there was no significant group difference at MMSE, while there was significant group difference in favor of G1 at MOCA. Similarly, between T0 and T2, the difference at MMSE was not significant (although at the limit of significance), while there was significant difference between groups in favor of G1 at MOCA. Furthermore, the percentage of patients that improved, remained stable or worsened in MOCA and MMSE, between the baseline and the next evaluations, was significantly different in the two groups. Regarding MMSE, no significant group differences was observed between T0 and T1, whilst the rate of patients who worsened in G2 was significantly greater than G1 between T0 and T2. Instead, regarding MOCA, the rate of patients who improved in G1 was significantly greater than G2 both between T0 and T1 and between T0 and T2.

This study suggested that the benefits of cognitive training were evident immediately afterward but not at the follow-up check six month later. However, comparing the baseline with the next post-training assessments, in G1 the global cognitive functioning measured by MOCA significantly improved as opposed to decline in the control group. This improvement was more consistent immediately after the end of the training and decreased over time, but even after seven months the performance was higher than the baseline. Finally, in G1 most patients improved their cognitive state compared to baseline, while in G2 most patients maintained their cognitive state stable between T0 and T1 and worsened between T0 and T2; these data confirmed that untreated patients were more likely to get worse over time. Therefore, this cognitive intervention seems to be a complementary treatment for patients with PD in the attempt of briefly stabilizing cognitive decline, delaying the downward trajectory.

1. Introduction

The prevalence of neurodegenerative diseases is expected to increase over the next years, in parallel to the aging of the world population (Mayeux et al., 2012), therefore it is important to identify new methods to prevent, delay or stop the neurodegenerative waterfall responsible for dementia conversion, thus improving the quality of life of affected people and their care-givers (Emery 2011). Mild Cognitive Impairment (MCI), introduced in the nineties (Petersen et al., 1997, 1999), represents an intermediate stage between normal aging and dementia. This construct is currently used to refer to symptomatic pre-dementia stage representing a risk factor for the development of dementia. The first definition considered MCI a precursor of Alzheimer's dementia (AD) only, but over the years there has been an evolution of the concept of MCI since the researchers observed that MCI represented an extremely heterogeneous condition for both its clinical and prognostic manifestations. In fact, the current conceptualization recognize multiple MCI subtypes, each of which may represent the prodromes of different dementia types. More recently similar nomenclature and criteria were proposed also for Parkinson's disease (PD) (Caviness et al., 2007). Although PD is predominantly characterized as a movement disorder, over the past years there has been an increasing awareness that the clinical spectrum of PD is much broader, also encompassing many non-motor domains, including cognition (Chaudhuri et al., 2006). Central to the non-motor symptoms are cognitive disturbance, whereby it is now recognized that PD with dementia (PDD) is a likely consequence of the disease (Aarsland et al., 2005). Prior to the establishment of a frank dementia syndrome and/or even in those who do not progress to PDD, more subtle and specific cognitive impairment is often reported at earlier stages of the disease and to define this condition the term "Parkinson disease with mild cognitive impairment" (PD-MCI) was introduced (Litavan et al., 2012).

With advances in medical and surgical interventions for motor symptoms, individuals with PD are living longer and facing greater disability related to cognitive impairments. Accordingly, there is a corresponding need to develop therapeutic strategies to address these cognitive impairments that increase caregiver strain and decrease quality of life over the course of the disease (Schrag et al., 2000; Visser et al., 2009). However, while research is continually accumulating in order to better understand the pathology and trajectory of cognitive changes, treatment options lag behind. At present, there is no established successful pharmacological treatment for cognitive impairment in PD (Orgeta et al., 2015; Emre et al., 2014). Drug therapy for cognitive impairment is therapy for AD (memantine and cholinesterase inhibitors) because so far there is no approved drug treatment for dementia non-Alzheimer's (Sorbi et al., 2012). Therefore, due to the limited drug treatment options and the negative impact of cognitive symptoms in PD, there may be a therapeutic role for non-pharmacological interventions targeting cognitive symptoms. In the literature, studies on intervention strategies targeting cognitive impairment much earlier in the disease process have increased. Recently, a large meta-analysis by Norton and colleagues (2014) demonstrated critical findings with respect to the justification for early intervention, showing that half of dementia cases worldwide may be attributable to modifiable risk factors such as vascular risk factors, depression, and cognitive inactivity. Given this, there is a growing number of

multifaceted studies now exploring the benefits of different non-pharmacological intervention in older people. With regard to the modifiable risk factors of cognitive inactivity, a cognitive intervention that is growing in popularity is Cognitive Training approach (CT) (Walton et al., 2017). CT programs which utilize the most well-developed programs have demonstrated the feasibility of these retraining interventions in either acquired or progressively deteriorating neurological conditions. In fact, cognitive studies showed that the brain displays certain plasticity even in advanced age (Berry et al., 2010; Jones et al., 2006). The older human brain still has the capacity to adapt to physical, cognitive and social environment challenges well facing a decline in sensory motor and cognitive ability (Goh 2011); neuroplasticity changes do not always imply an improvement in behavioral performance, rather these changes are usually associated with function preservation or a reduction in the rate of decline (Dinse 2015). While there is now extensive literature on the effect of cognitive intervention as a therapeutic strategy to prevent cognitive decline in healthy older people (Ball et al., 2002; Valenzuela and Sachdev 2009), in MCI and in dementia due to Alzheimer's disease (Andrieu et al. 2015; Rojas 2013; Neely 2009), there is limited evidence for the effectiveness of cognition-based interventions in PD (Sinforiani et al., 2004; Sammer et al., 2006, Paris et al., 2011; Mohlman et al., 2011). More recently, Walton and colleague (2017) suggested that in patients with PD-MCI, CT may either briefly stabilize cognitive decline, delay the downward trajectory, or attenuate the rate of decline leading to a less dramatic rate of change given that the advancing neuropathological progression in neurodegenerative disease like PD makes sustained long term improvement unlikely. Some studies focused on attention and executive impairments in PD-MCI patients using both computers and in-person interventions, suggesting that both approaches appear feasible. The most common approach to cognitive intervention is based on execution of paper-and-pencil exercises, but advances in the development of Information & Communication Technologies (ICT) has recently prompted the possibility to develop ad hoc modalities for evaluating and training one or more cognitive functions (Cherniack 2011; Geda et al., 2011; Zucchella et al., 2014). These computer-based solutions could help overcome the limits of traditional cognitive intervention techniques. In fact, computerized approach can automatically adapt to the trainee's daily performance, facilitate acquisition and recording of the user's data and evaluate the results or any combination of these functionalities. In addition, computerized cognitive training could be more engaging and motivating than paper-and-pencil exercises, but the poor familiarity of older people with technological devices could be a critical issue of this approach (Richardson et al., 2014). Besides strong evidence concerning the effectiveness of computer-based solution as clinical tools is still missing, together with a consensus on how, when and for what purposes these digital games should be employed

In general, cognitive intervention programs may represent beneficial alternatives and/or adjunctive therapy to medications for delaying the onset of the cognitive deficits, increasing the cognitive reserve, or at least maintaining patients at their current level (Burn et al., 2010; Poletti et al., 2011). However, there are no standardized guidelines regarding the types of strategies that offer the most beneficial outcomes, or the types of cognitive impairments or stages of cognitive decline for which treatment is most beneficial, that would guide application in PD (Cicerone et al., 2011). Well controlled, randomized larger scale investigations are needed for PD and other neurodegenerative diseases involving cognitive decline

that take into account the specific disease characteristics of the population (e.g., duration of motor severity, medications), the specific cognitive domains affected (e.g., executive dysfunction, visuospatial) and the effects of cognitive intervention on other domains such as activities of daily living. Furthermore, as in healthy populations, slower rates of decline in individuals without dementia necessitate longer observation periods to truly clarify whether such non-pharmacological interventions may be employed as " preventive" technique.

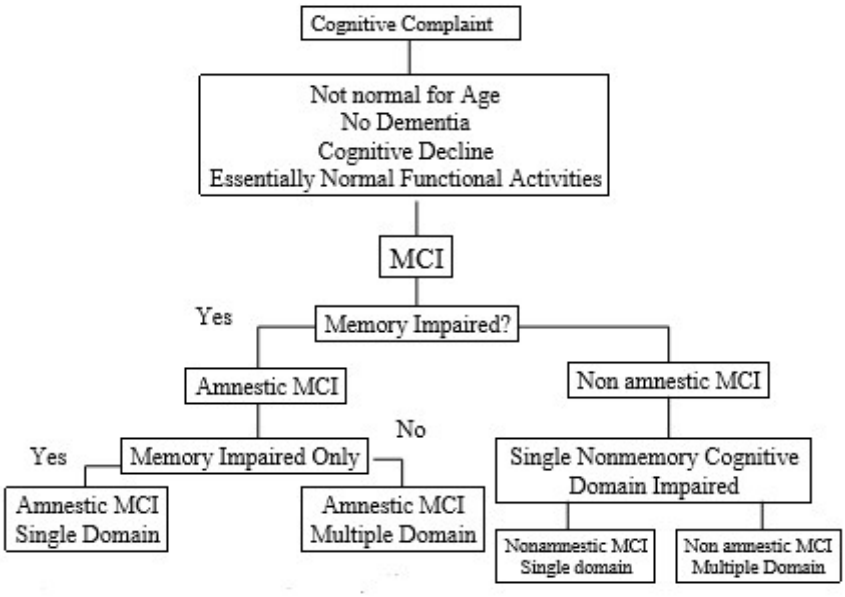
2. Early stages of deterioration in neurodegenerative diseases: Mild cognitive Impairment (MCI)

Over the decades various definitions have been proposed with the aim of describing the intermediate stage between normal cognitive and dementia. To date, the term MCI, introduced for the first time by Petersen in the nineties (Petersen et al., 1997, 1999), represents all the effects a diagnostic entity used to refer to the symptomatic pre-dementia phase representing a risk factor for the development of dementia. The diagnosis of MCI is based on the following clinical, cognitive and functional criteria:

- absence of dementia (DSM-V and ICD-10 criteria are not fulfilled) and simultaneous exclusion of normality;
- presence of cognitive decline, subjectively reported by the patient and/or a relative and confirmed by objective measures on specific neuropsychological tests;
- absence of significant functional impact (preserved basic activities of daily living or minimum decline of instrumental activities of daily living).

Over the years, there has been an evolution of the concept of MCI. The first definition proposed by Petersen (Original Mayo Clinic) (Petersen et al., 1999) considered MCI a precursor of AD, consequently the presence of memory deficits was an essential requirement for the diagnosis. The International Consensus Conference of 2003 (Expanded/Key Symposium) (Petersen et al., 2004; Winblad et al., 2004), instead, admits deficits in other cognitive domains in addition to the memory domain and considers MCI a prodromic form of different dementia types. This vision was recently shared and adopted by the National Institute on Aging and Alzheimer's Association (NIA-AA) (Albert et al. 2011) and the Diagnostic and Statistical Manual on Mental Disorders (DSM-V). Therefore, MCI represents an extremely heterogeneous condition for both its clinical and prognostic manifestations. Current conceptualizations of MCI recognize multiple subtypes centered on the presence or absence of memory impairment, namely amnestic (aMCI) and non-amnestic (naMCI), and on the number of compromised cognitive domains (MCI single domain vs MCI multiple domain) (Figure 1).

Figure 1. *MCI neuropsychological classification (source Morris and Petersen, 2005)*



More precisely, aMCI is characterized by circumscribed impairments in memory domain while naMCI by the presence of impairments in other domains (executive function, language, visual-spatial skills) in the absence of memory deficit. Getting information about the phenotype (aMCI vs naMCI) and the amount of cognitive domains involved (single vs multiple) is important to make assumptions about future outcomes. In fact, these MCI subtypes may represent the prodromes of different dementia types. In most cases, patients with aMCI often progress to AD with an annual rate of conversion of approximately 10-15 %, compared with healthy subjects of the same age, whose conversion rate is about 1-2% (Mitchell et al., 2009). When MCI appears as an involvement of one or more domains other than memory, the etiologically condition responsible of the disorder may be non-AD degenerative form.

The MCI construct was introduced also for PD, similarly to what happened in AD, to denote cognitive deficits that appear in the early stage of the disease and that represent a risk factor for the development PDD. PD is a common neurodegenerative disorder (approximately 1-2% of people aged 60 year and over is affected) (de Rijk 2000) characterized by motor (tremor, rigidity, bradykinesia) and non-motor symptoms (sleep dysfunction, cognitive-behavioral disorders, depression, anxiety, etc). Among non-motor symptoms, cognitive impairment is an important feature which is common in the early stage of the disease and even prior to onset of motor symptoms (Dubois 1997; Pont-Sunyer 2015). It has been shown that approximately 25% of newly diagnosed patients with PD have MCI (Aarsland et al., 2010). The most common cognitive impairments include executive dysfunction, visuo-spatial deficit, information processing speed deficit, and short-term memory deficit (Kehagia et al., 2010). Consequently, the term PD-MCI has been proposed and the Movement Disorder Society Task Force has produced consensus-derived PD-MCI clinical diagnostic criteria (Litvan et al., 2012) that include the following:

- subjective report of cognitive problems by the patient or caregiver;
- performance at least 1.5 standard deviations (SDs) below the age-corrected mean score in one cognitive domain;
- without impairments in activities of daily living that can be attributed to cognitive impairment.

These criteria are inspired by those of Petersen, but they have been modified to adapt to the PD. They do not define the PD-MCI subtype only on the basis of the presence/absence of amnesic involvement ("amnesic" vs. "non-amnesic"), but recommend specifying the cognitive domains involved; examples of the subtype definition could be "single domain PD-MCI" (eg. executive) or " multiple domain PD-MCI" (eg. memory, visual-spatial skills). An estimate 25% of PD patients have mild cognitive deficit in the absence of dementia (Aarsland 2010) and 25-30% of individuals with PD meet criteria for dementia (Emre et al., 2007). Furthermore the presence of PD-MCI increases the risk of developing PDD more frequently and faster than those with no cognitive deficits (Javin et al., 2006; Williams-Gray 2009; Barone et al. 2011). The annual conversion rate from PD-MCI to dementia ranges between 6 and 15%. Therefore PD-MCI may be a transitional state between normal aging and dementia, as is the case with some mild cognitive impairment and AD. However, there may be a PD-MCI that is non-progressive and does not convert to dementia. PD-MCI is associated with older age at disease onset, male gender, experiencing depression and having severe motor symptoms (Muslimović et al., 2005).

In conclusion, in the context of neurodegenerative diseases, patients with MCI convert to dementia at a rate greater than the cognitively intact individuals. PD-MCI can also be regarded as a risk state for dementia and changes to cognition are significantly associated with reduced of quality of life both patient (Lawson et al., 2014) and care-giver (Szeto et al., 2016) leading to increased health-related costs (Vossius et al., 2011). Therefore its early identification could offer opportunities for preventative interventions; it is important for researchers to explore options for interventions targeting cognitive deterioration in early stage of PD, much like the roles of speech, occupational therapy, and physiotherapy prior to significant motor or functional deterioration (Walton et al. 2017), in order to improve patient well-being and functioning as well as to delay further decline.

3. Pharmacological treatments

In addressing this argument, it should first be clarified that drug therapy for dementia is actually therapy for AD, because so far there is no approved drug treatment for dementia non-Alzheimer's (Sorbi et al., 2012). Drugs used for cognitive impairment in AD (cholinesterase inhibitors and memantine) are not able to alter the evolution of the disease because they are symptomatic drugs and also have a modest and limited effect over time**.** Unfortunately, like AD, other neurodegenerative syndromes such as PD, remain in a similar state regarding treatment options. At present, there is no established, successful pharmacological treatment for cognitive impairment in PD. In PDD, only modest improvements have been shown with medications, most prominently with cholinesterase inhibitors such as rivastigmine (Emre et al., 2004; 2014) being licensed for symptomatic treatment in mild to moderate PDD. Other agents such as memantine have also

been studied (Leroi et al., 2009; Emre et al., 2010); however, their utility in PDD is as yet unclear. In patients with milder levels of cognitive impairment, there are even fewer treatment options available (Seppi et al., 2011). In any case, current drug treatments targeting cognition are only modestly effective, are symptomatic rather than curative or slowing, and thus do not target underlying neuropathology. An additional problem with drug-based therapy for cognitive decline is the significant polypharmacy typical of this disease, with patients often taking multiple pharmacological agents both for motor and non-motor symptoms such as sleep and/or mood disturbance (Walton et al., 2017).

4. Non-pharmacological treatments: cognitive intervention

Cognitive intervention programs have recently been adapted for different neurological conditions (Cicerone et al., 2005), including also progressive neurological diseases. Cognitive intervention refers to behavioral interventions aimed at improving cognition in individuals who have experienced a decline in cognitive functioning (i.e. due to disorders of the central nervous system, traumatic brain injury, neurodegenerative disorders, and stroke), or enhancing and extending functioning in those who are cognitively intact (Acevedo and Loewenstein, 2007). These interventions may be administered in individual or group formats over several sessions and involve a range of activities including general mental activity, guided practice on cognitively demanding tasks, strategy use and computerized exercises (Mowszowski et al., 2010). Furthermore, cognition based interventions have been guided theoretically by restorative or compensatory approaches. The first one aims to improve functioning in specific domains, thus recovering impaired skills (examples of technique are spaced retrieval, repeated attention and memory tasks, vanishing cues and errorless learning). The second aims to develop new ways of performing tasks, bypassing deficient cognitive processes and teaching alternative approaches to achieve goals (e.g. categorizing, visualizing or paraphrasing information during learning as internal technique; using calendars or environmental cues as external technique) (Ylvisaker et al., 2002).

4.1 Cognitive intervention in neurodegenerative disease

In the literature, there is increasing evidence about the influences of environmental and lifestyle factors on cognitive functions and brain plasticity during aging (Park et al., 2013). These factors include education, engagement in professional and leisure activities, expertise and experience; these represent moderators of differences in cognitive aging and protective agents for the development of dementia (Kramer et al., 2004). In fact, it is now known that while cognitive inactivity is a key dementia risk factor (Norton et al., 2014), engagement in cognitively and socially stimulating activities can decrease neurodegeneration, cognitive decline, and dementia risk (Valkanova et al., 2014). This is described by the theory of cognitive reserve (Stern 2006; Barulli et al., 2013) as well as the scaffolding theory of aging (Reuter-Lorenz et al., 2014) both of which link engagement over the lifespan to cognitive trajectories in later life. Lifetime cognitive enrichment, or cognitive reserve, can also allow older adults with

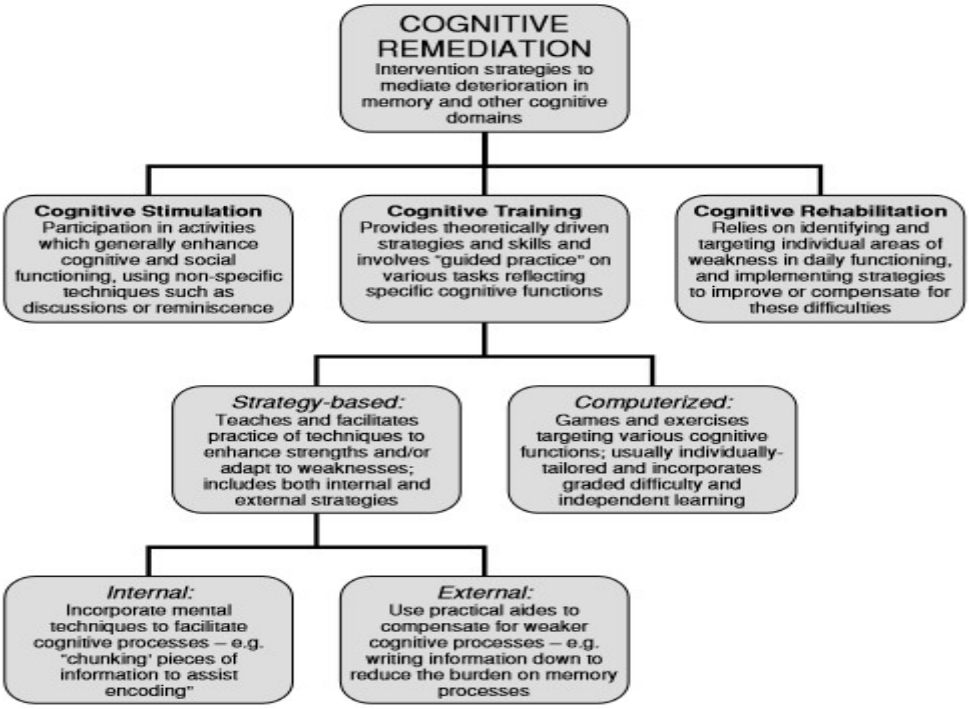
neurodegenerative pathology to resist any longer to neurodegenerative brain damage manifesting only mild symptoms (Brayen et al,. 2010; Meng et al., 2012). Given the involvement of such factors in the outcome of aging it is possible to assume that cognitive intervention may play a critical role in the promotion of cognitive vitality in normal aging and also in patients with cognitive impairments, in order to promote neuroplasticity and prevent/delay cognitive decline in older adult. Despite the growing interest about this topic, there is no unanimous agreement on the usefulness of cognitive interventions in progressive neurological disease (AD, MCI and related disorders) since we are facing pathologies where the underlying pathological process continues to inevitably evolve. In light of this, cognitive intervention to be effective must be proportionate to the degree of cognitive deterioration and consequently the approach to be taken must be different in relation to the different phases of the disease.

In the literature three different approaches to cognitive intervention in older adult can be distinguished (Clare et al., 2005; Bahar-Funchs et al., 2013): cognitive stimulation, cognitive rehabilitation and cognitive training .

- Cognitive stimulation refers to the involvement in group activities that are designed to increase cognitive and social functioning in a non-specific manner. Those include discussions, supervised leisure activities, list memorization with no particular support and more structured activities such as reality orientation or reminiscence.
- Cognitive rehabilitation involves individually tailored programs centered on basic skills to reduce functional impairment and increase engagement in daily adaptive activities.
- Finally, cognitive training (CT) involves teaching theoretically motivated strategies and skills in order to optimize cognitive functions such as processing speed, memory, attention, and executive function (Mowszowski et al., 2010). It involves strategies that exploit spared cognitive capacities to improve the impaired ones (i.e. some memory-training techniques rely on visual imagery to support episodic memory) and that optimize cognition (i.e. spaced retrieval or self-cuing memory optimization strategies). CT can also result in improving meta-cognition (i.e. the knowledge that participants have about memory mechanisms and their own memory), and cognitive self-efficacy (i.e. the notion that participants can exert some control over their cognition). Proper CT programs must rely on theoretically valid training techniques that take into account the pattern of impaired and intact capacities (Belleville et al., 2008).

The Figure 2, proposed by Mowszowski and colleagues (2010), shows a schematic representation of the three cognitive intervention approaches used in older adults with progressive neurological disease; the authors used the general term “cognitive remediation” to refer to behavioral intervention strategies aimed to mediate deterioration in memory and other cognitive domains.

Figure 2. *Cognitive remediation terminology (source Mowszowski et al 2010)*



Programs of cognitive stimulation and cognitive rehabilitation are more suitable for demented patients. In particularly, cognitive stimulation may be more effective in patients with severe cognitive impairment (Woods et al., 2009; Treiber et al., 2011) since their cognitive deficits may preclude them from active participation. In these cases, the intervention is based on residual capacity helping the patient and caregiver to live with the disease and to maintain a certain degree of autonomy in daily life as long as possible. Instead cognitive rehabilitation programs are more effective in demented patients with moderate cognitive impairment in order to reduce the functional impact of the disease on daily life activities, through specific activities tailored to the pattern of impairment of individual patients (Adam et al., 2000; Lekeu 2002) . There has been some debate as to which approach should be favored in persons with MCI. CT might represent a powerful approach in persons with MCI, because they are at risk of developing dementia and, at the same time, they still have an adequate level of functioning in daily activity and they retain a large range of cognitive capacities to learn and apply sets of new strategies; for all this reasons, patients with MCI represent an ideal target for CT (Belleville et al., 2008). Moreover, CT is thought to strengthen neural networks of attentional and control processes via neuroplasticity, as a result of responding to experience or environmental stimulation (Raz et al., 2006; Shaw et al., 1994). Its efficacy in MCI has been the most often tested, as shown below, and the results of studies on healthy older and MCI suggest that CT can be implemented as an early intervention technique (Mowszowski et al., 2010). If designed properly, CT program could optimize the cognitive functioning of persons with MCI, reduce their handicap and alleviate the anxiety resulting from their cognitive difficulties and failures. Thus, efficient intervention programs could yield paramount benefits in terms of cognitive capacities and quality of life (Belleville et al., 2008). CT can use either paper and pencil or multimedia computer software. For many years, the

most common approach has been based on execution on paper-and-pencil exercise, but this technique, although most familiar to older patients, involves some disadvantages. Management and analysis of performance data is particularly complex and requires the therapists to manually annotate answers and response times in order to evaluate the temporal evolution of each patient's performances. The stimuli choice also represents a problem: the number of stimuli that can be administered during descriptive exercises or memory-based tasks is limited, and the probability of showing the same ones to a patient in a short span of time is very high. This very likely could lead not only to a learning effect which could damage the rehabilitation, but also to boredom, frustration and reduction of the patient's compliance towards the therapy. Advances in the development of ICT has recently prompted the possibility to develop ad hoc modalities for evaluating and training one or more cognitive functions (Cherniack 2011; Geda et al., 2011; Zucchella et al., 2014). A recent review (Garcia-Casal et al., 2017) highlighted the superiority of cognitive intervention programs based on information technology than the traditional ones on cognition and depression, but in the absence of a significant impact on activities of daily living. These computer-based solutions, also called Seriuos Games (SG), could help to overcome the limits of traditional cognitive intervention techniques. Computerized CT involves game-like exercises that target core cognitive abilities using engaging motivational cues and on-time feedback, thus functioning figuratively as a “brain gym.” Most programs use a staircase adaptive design, whereby task complexity and response time demands change frequently during and across sessions, in accordance with changes in individual performance in order to avoid over- or understimulation. In addition, several computerized CT programs adapt training content (i.e., targeted domains) to individual needs, providing more training time in areas of relative weakness. This is of particular interest in conditions characterized by a pattern of specific cognitive changes (Walton et al., 2017). This is the underlying idea for the development SG which are digital applications specialized for purpose other than entertaining (Robert et al., 2014). The elderly population (above 50 years) represent now a considerable portion of digital gamers which is predicted to increase; for this reason, SG may represent a motivating and relatively cheap method to prevent/delay the onset of cognitive or sensory- impairments There is evidence that SG can successfully be employed to train physical and cognitive abilities in elderly people (Anguera et al., 2013; Wiemeyer and Kliem, 2012). Recently, some studies have started to investigate the effectiveness of SG in people with AD, MCI, and related disorders. McCallum and Boletsis (2013) performed a literature review of the experimental studies conducted to date on the use of SG in neurodegenerative disorders. In particular, the results of the 15 reported studies suggested that cognitive games (i.e., games which target cognitive improvement) can improve a number of cognitive functions, such as attention and memory (Stavros et al., 2010; Rosen et al., 2011) and visuo-spatial abilities (Yamaguchi et al., 2011). Walton end colleague (2017) suggested that computerized CT may not be beneficial at the PDD stage, while it may be efficacious at the early phases of the disease, or where MCI is present. Despite these promising results, a number of studies showed that elderly people and people with neurodegenerative disorders have problems in using many of the SG currently available on the market. Their difficulties include problems in getting familiar with the game technology and embarrassment about using the tools designed for the game. Therefore, the poor familiarity of older people with

technological devices could be a critical issue of this approach (Legouverneur et al., 2011; Richardson et al., 2014).These difficulties derive from the fact that most of the SG currently employed have been developed for entertainment purposes (e.g., the Nintendo Wii Fit, Wii Sports, and Big Brain Academy) and with a “typical healthy user” in mind. To overcome this problem, SG targeting specifically cognitive disorders in neurodegenerative diseases (like AD and other related disorders) are starting to emerge (Benveniste et al., 2010; Nor Wan Shamsuddin et al., 2011), along with guidelines ensuring their usability among the targeted populations (Robert et al., 2014; Fua et al., 2013; Bouchard et al., 2012). Robert end colleague (2014) showed that SG are considered adapted to people with MCI and reported some practical recommendations for the development and use of SG in people with Alzheimer’s disease and related disorders and frailty collected during the workshop “Innovation Alzheimer 2013”.
In order to acquire more academic and professional credibility and acceptance, researchers need to start collecting incremental data over numerous studies to test and evolve usability and usefulness of SG as clinical tools targeting people with dementia-related disorders.

4.2 *Evidence for Cognitive Intervention Efficacy*

Since the nineties, many studies assessed the efficacy of cognitive intervention in healthy older adults, (Yesavage *et al*., 1990; Verhaeghen *et al*., 1992; Stigsdotter and Backman, 1995) suggesting beneficial effects on cognitive vitality in aging. A seminal study in this area is the ACTIVE study - Advanced CT for Independent and Vital Elderly - (Ball et al., 2002). This study implemented strategy-based memory, reasoning or speed-of-processing training versus a no-contact control condition in 2832 adults, over ten 60-minute sessions, and demonstrated significant improvement from baseline in the targeted cognitive ability for each intervention group. Longitudinal analysis also indicated sustainability over two years where effects were maintained in each targeted domain. At five-year follow-up the team reported significant functional decline in all participants but this decline was not as marked in the group that received training. No significant impact was found on functional activities on a two-year follow-up. This was probably due to the high level of functioning of the healthy older adults enrolled in the study as no functional decline was apparent over the two-year follow-up (Willis et al., 2006). Finally, a recent analysis (Unverzagt FW et al., 2012) did not find a difference between trained and control participants in incidence of dementia at 5-year follow up. The ACTIVE results provided the impetus for a number of studies seeking to utilize CT as a possible strategy for attenuating cognitive decline in aging and neurodegenerative disease. Valenzuela and Sachdev (2009) conducted a meta-analysis of seven Randomized Controlled Trials (RCTs) and demonstrated large effect sizes indicating improvement across cognitive outcomes including memory, processing speed, working memory and instrumental activities of daily living in healthy older adult following CT. A recent meta-analysis (Gross et al., 2012) in healthy older adults (35 studies, 3797 participants), reported a moderate effect size improvement on memory in post-training compared to controls after memory strategy training; but this meta-analysis was not limited to RCTs. Lampit and colleague (2014) published a systematic review and meta-analysis

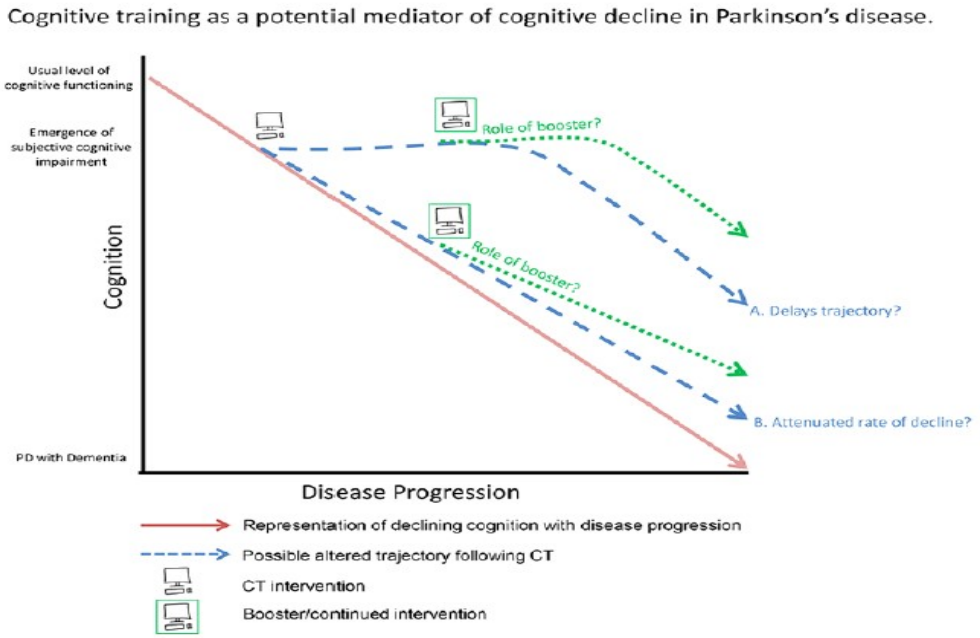
encompassing 51 RCTs of computerized CT in 4885 healthy older adult and reported modest improvement in overall neuropsychological performance at immediate follow-up to training. However, they found that improvement differs across cognitive domains and intervention design; in particular, positive effects were found only in trials of supervised (group-based) training, provided for at least 30 minutes per session and not more than 3 times per week.

Generally positive findings in healthy older adults have suggested that CT programs represent a preventive strategy against cognitive decline in later life. However, broad conclusions are limited by vast differences in methodological rigor, study design and nature of each CT program as demonstrated even in the above mentioned trials. Anyway, the finding that CT can delay cognitive and functional decline in healthy older adults has tremendous consequences for its potential application to MCI. In recent years, there has been an increase number of studies assessing the effect of CT in MCI. A review (Bellville et al., 2008) reported that six out of seven studies demonstrate cognitive improvement following CT; however, different methodological approaches were present in their training programs. In detail, Gunther and colleagues (2003) tested a computer-assisted cognitive training program in 19 patient with aMCI and reported positive and long term effect (five month after the end of training) on objective measures; but they did not include a control group. Further studies (Cipriani et al., 2006; Rozzini et al., 2007; Talassi et al., 2007) published encouraging results about the effectiveness of computer intervention program (involved exercises covering a broad range of cognitive abilities – memory, attention, perception and language) in aMCI patients. Of these three, Cipriani et al. (2006) showed a significant improvement in behavioral memory at three-month follow-up and Rozzini et al. (2007) reported enduring effect in a one-year randomizes study that compared MCI patients receiving pharmacological therapy and CT vs pharmacological therapy only or neither. Belleville and colleagues (2006) developed a multi-factorial intervention program tailored to improve episodic memory, in patients with MCI; the study reported a significant positive effect of the intervention on objective measures of episodic memory in both healthy older adults and persons with MCI who took part in the training. Also Olazaran et al. 2004 reported positive effects of cognitive intervention, but in this study the treatment include general cognitive activity rather memory strategies. Finally, Rapp et al. (2002) did not demonstrate improvement in objective memory measure despite subjective improvement in memory reported by participants after training. A small RCT of a combined intervention reported significant reduction in incident dementia in people with MCI (Buschert et al., 2012). Diamond and colleague (2015) utilized both computerized and memory strategy training in older adults “at risk” of dementia (80% with MCI), and observed medium effect size improvements in episodic memory, as well as independent effects in mood and sleep quality. Lastly, also Coyle et al (2015), in a recent systematic review, found evidence for efficacy of computerized and virtual reality cognitive training in MCI.

Most studies have considered patients with aMCI, whereas it is now known that MCI is a heterogeneous condition involving various cognitive domains and various different subtypes, that equally expose to the risk of developing dementia, have been identified, as in the case of PD-MCI. Therefore, it is desirable to plan CT programs incorporating multiple cognitive domain. In this regard some studies (Belleville et al., 2007; Moro et al., 2015) suggested that designing interventions

that also involve executive control may be appropriate for persons with MCI, as it has been shown that executive control is impaired in this population.
Many studies have been published in order to explore the efficacy of CT in PD over the past years; of which 7 RCTs encompassing 272 patients were available for a meta-analysis (Leung et al., 2015). Though still small, the current body of RCT evidence indicates that CT is safe modestly effective on cognition in patients with mild to moderate PD and suggests the presence of cognitive improvement after training particularly in working-memory, executive functioning and processing speed. However, the authors suggested that larger RCTs are necessary to examine the utility of CT for secondary prevention of cognitive decline in this population. Another area requiring further research relates to longitudinal outcomes and to the possible time-course effects after CT. Figure 3 shows a schematic representation of potential outcomes from CT in PD; in fact, it is currently unknown how a CT intervention affects long term on cognition in PD. Walton and colleague (2017) proposed that CT may either stabilize cognitive decline—delaying the downward trajectory, or attenuate the rate of decline leading to a less dramatic rate of change. In this regard, Petrelli and colleagues (2015) observed that patients who participated in 6-week CT program maintained their overall cognitive functions 1 year after intervention, while those in the control group showed significant decline. Though hindered by a small sample and large number of dropouts, this trial provides hope that CT can be beneficial in the long term for patients with PD to prevent cognitive decline and onset of PD-MCI.
In conclusion, these studies suggest the feasibility of CT programs also in the early stage of neurodegenerative diseases, suggesting that CT may be used as a prevention technique. However methodological variability suggests that further RCTs are warranted.

Figure 3. *Schematic representation of potential outcomes from cognitive training (CT) in Parkinson's disease (PD). It is currently unknown how a CT intervention affects long term on cognition in PD. We propose the following options: (1) Cognitive decline is delayed, possibly preventing dementia onset for an unknown period of time; (2) The trajectory of cognitive decline is slightly altered, again possibly delaying dementia onset. Finally, the role of boosters or long-term continued CT may lead to longer lasting or exaggerated effects on either of these outcomes (source Walton et al., 2017)*



4.3. Mechanisms of CT Efficacy

Neuroplasticity refers to the ability of the brain to undergo structural and functional change in response to internal and external stimuli. The traditional view of the brain as a “static” structure has been recently revised on the basis of numerous studies which show that neuronal connections and circuits undergo continual modification and reorganization.

The body of evidence for possible neurobiological benefits of CT is substantially smaller than that for cognitive effects, arguably because the complexity and cost of in vivo neuroimaging might have deterred researchers and funding bodies from such investigations until the basic questions of efficacy are elucidated (Walton et al., 2017). Nevertheless, in literature some RCTs in healthy elderly and MCI suggest that the main neuroimaging modalities (structural, functional and metabolic magnetic resonance imaging) are able to detect neurobiological change after several month of CT and relate them to cognitive change (Belleville et al., 2012; Park et al.,2013). These results support the presence of neuroplasticity also in older adults in response to CT. Structural changes, in term of regional increases in cortical thickness and white matter changes like fractional anisotropy increase, are observed in healthy older adult after 8 weeks of memory training compared to control (Engvig et al., 2010; 2012). Additionally, some studies also showed functional changes as possible indicators of improvement in response of CT. Particularly, in older adults compared to a control group, Chapman and colleagues (2015) found some global and regional alterations of blood flow in resting state networks that are associated with cognitive change following CT. Velenzuela and colleagues (2003), using metabolic image to uncover brain neurochemical changes, observed increases in creatine and phosphocreatine signals in the hippocampus after memory training in experimental group compared to control group. Belleville et al. (2007) found that memory training has been associated with neurobiological change in patient with MCI. Furthermore, Backman et al. (2011) showed, in a young healthy sample, increased striatal dopamine release following working memory training and this finding may be of relevance in dopamine-dependent PD samples. Recent studies suggest that lifetime cognitive enrichment can allow to maintain normal clinical functioning also in PD (Lucero et al., 2015; Hindle et al., 2014). In particular, to accurately determine the impact of the cognitive reserve on the brain, Lucero and colleagues (2015) also considered the underlying neuropathology in addition to the cognitive measures; their results suggest that in PD, educational attainment (ie, a cognitively challenging lifestyle) may allow patients to clinically overcome underlying pathology in the brain. It is therefore plausible that cognitively stimulating activity as delivered through CT may also, under the right conditions, lead to functional neural changes in patients with PD. To date, few studies have been dedicated to investigate the neural underpinnings of CT effects in PD. In patients with PD-MCI, Costa and colleague (2015) found that brain-derived neurotrophic factor serum level (BDNF) is significantly associated with cognitive performance and it has been suggested as a possible biomarker for evaluating cognitive change. In addiction, another study (Angelucci et al., 2015) showed that BDNF levels increase in response to CT in patients with PD. Two other studies have utilized functional magnetic resonance imaging and have linked CT-induced cognitive changes to altered BOLD response (Nombela et al., 2011; Cerasa et al.,

2014). All these studies were significantly limited by small sample size, therefore future research should look to investigate these mechanisms further.

5. Aim

The aim of this research is to evaluate the effectiveness of ICT tools in the training of cognitive deficits in subjects with neurodegenerative disorders. During these three years of activity we finalized the CoRe system (acronym for Cognitive Rehabilitation) (Alloni et al., 2015), an ontology-based software tool that allows several degrees of personalization and the possibility to generate, in theory, an unlimited number of different patient-tailored exercises. This implementation of CoRe is dedicated to the training of logical-executive functions (logical reasoning, strategy, planning, problem-solving and hypothetical deductive reasoning skills) with particular focus on PD, in which the logical-executive disorders are most common. Therefore, a RCT for computer-based cognitive training of executive functions was conducted in inpatients with PD-MCI single domain (executive) or multiple-domain with executive involvement.

6. Materials and Methods

6.1 Participants and measures

PD patients hospitalized at the Neurorehabilitation Unit of IRCCS National Neurological C. Mondino Institute were enrolled into the study.
Inclusion criteria were:

- diagnosis of idiopathic Parkinson's disease according to UKPDBB criteria (Hughes et al., 1992) and Hoehn & Yahr scale ≤ 4 (Hoehn et al., 1967);
- presence of PD-MCI single-domain (executive) or PD-MCI multiple-domain with executive involvement (Litvan et al., 2011);
- age between 50 and 85 years;
- education level ≥ 5 years.

Exclusion criteria:

- pre-existing cognitive impairment (e.g. aphasia, neglect);
- severe disturbances in consciousness;
- severe sensory disturbance or motor disturbances that do not allow the patient to control the trunk or to maintain the sitting position;
- concomitant severe psychiatric or neurological conditions,
- patients with Deep Brain Stimulation.

All the patients were treated with dopamine agonist or L-DOPA; this therapy was stable for 3 months and there have been no variations during the training period. The disease severity was evaluated by Hoehn & Yahr Scale and Unified Parkinson's Disease Rating Scale (UPDRS). The PD-MCI diagnosis was formulated on the basis of neuropsychological evaluation (baseline cognitive assessment, T0) performed by means the following standardized tests assessing different domains:

- global cognitive function: Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Montreal Montreal Overall Cognitive Assessment (MOCA) (Nasreddine et al., 2005);
- memory: verbal (Verbal Span, Digit Span) and spatial (Corsi's block-tapping test – CBTT) span (Spinner et al., 1987); verbal long-term memory (Logical Memory Test immediate and delayed recall) (Carlesino et al., 1995), (Rey's 15-word test immediate and delayed recall) (Caffarra et al., 2002); spatial long-term memory (Rey Complex Figure delayed recall – RCF-dr) (Laiacona et al., 2000);
- logical-executive functions: non-verbal reasoning (Raven's Matrices 1947 – RM47) (Carlesimo et al.,1995); categorical abstract reasoning (Weigl's Sorting test) (Spinner et al., 1987); frontal functionality (Frontal Assessment Battery – FAB) (Apollonio et al., 2005); semantic fluency (animals, fruits, car brands), phonological fluency (FAS) (Carlesimo et al., 1995);
- attention: visual selective attention (Attentive Matrices) (Carlesimo et al., 1995); simple speed processing and complex attention (Trail Making Test parts A - TMTa and part B - TMTb) (Giovagnoli et al., 1996); selective attention/susceptibility to interference (Stroop test) (Amato et al., 2006);
- visuospatial abilities: Rey Complex Figure copy – RCF-copy (Laiacona et al., 2000).

The same battery was also used during follow-up visits, 4 weeks (T1) and 6 months (T2) after the end of cognitive training. During these follow-up assessments, parallel versions of tests were applied where available, in order to control for potential learning effect. All the test scores were corrected for age, sex, and education and compared with the values available for the Italian population.
The study was approved by the local Ethics Committee and conducted in accordance with the Helsinki Declaration of 1974; all the participants provided written Informed Consent.

6.2 Study design and procedures

We conducted a prospective, single-blind, randomized/controlled study. All the patients enrolled into the study underwent baseline cognitive assessment (T0) by means of the above mentioned tests. Patients with PD-MCI single-domain (executive) or multiple-domain (with executive functions involvement) were randomized to receive standard rehabilitation (physiotherapy and physical treatment) plus cognitive intervention with CoRe software (intervention group - G1) or standard rehabilitation only (control group - G2). The randomization list was generated using a simple randomization method with "random number generator" software (www.regione.emilia-romagna.t/in_info/enerator). Patients who perform cognitive intervention were subjected to 12 individual sessions, lasting 45 minutes, of computer-aided exercises generated by the software CoRe to train logical and executive functions; the total duration of training was 4 weeks (3 sessions/week). All the patients were evaluated after 4 weeks (T1) with the same neuropsychological battery; follow-up evaluations was scheduled after 6 months (T2).

6.3 The CoRe System

This section describes the main features of CoRe system. CoRe allows a therapist to easily generate a computerized version of exercises usually administered with paper-and-pencil during face-to-face rehabilitation sessions. Besides, it records the patient's performance parameters during the execution of the session, so that the subject's assessment can be performed automatically by the system itself. This feature has two main consequences: first, it drastically reduces the time usually required to the therapist for the data analysis and, second, it introduces the option to automatically adjust the difficulty of the exercises based on the results of the assessment. The personalization of the exercises plays a vital role in preventing fatigue and boredom, since, as stated above, perceiving the rehabilitation as a stressful situation could very likely reduce the subject's compliance.

Some preliminary tests have been conducted on healthy volunteers and on a small patients sample to verify both the overall functionality and usability of the system. In particular, CoRe was tested in 38 healthy subjects (20 were above and 18 below the 60-year age threshold) with different education levels (<=5 years, 5 to 8 years, 13 to 18 years, >18 years) and different degree of familiarity with a PC assessed by Usability Scale (SUS)-based questionnaire; The degree of familiarity with a PC was discretized in 5 classes: "none", "almost none", "average", "good" and "excellent", to be picked based on self-assessment by the subject. They underwent a simulated rehabilitation sitting in presence of a therapist for support. A SUS-based evaluation questionnaire, also including an open question requiring general comments and suggestions, was administered to the users at the end of the simulated sitting. The analysis of the results revealed an overall positive score for the system, and allowed the identification of specific problems (e. g., many users considered the visualization of the execution time at the end of an instance a source of anxiety; similarly, a negative feedback was considered discouraging by some subjects) and subsequent refinement of the system accordingly (e.g., the execution time is now hidden from the user and only available to the therapist; the visualization of the feedback is now optional and can be deactivated by the therapist for use with poorly skilled and/or particularly sensitive users).

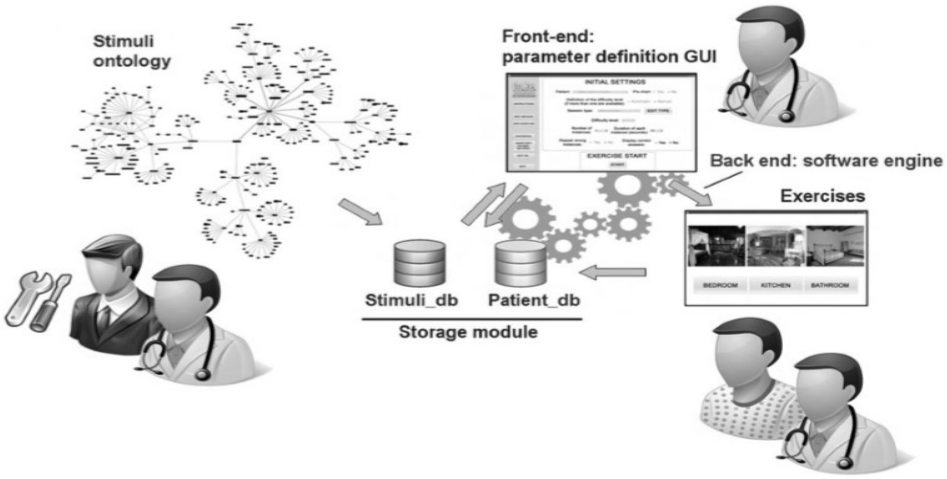
In addition, a pilot study was conducted on a small sample of PD patients (n = 15) from the IRCCS C. Mondino Foundation. The participants were subjected to 12 sessions in 1-month time range. The feedback obtained has been confirmed general appreciation and positive reaction to the system. From a qualitative point of view, patients use CoRe in different ways: when no cognitive impairment is present, they may exercise autonomously, when it is present, they may need the help of a therapist. Consequently new strategies and solutions have been introduced to make CoRe as compliant to the patients' needs as possible (e.g. clear and synthetic deliveries for each exercise; interactive examples for each task). More information about the details of these usability studies can be found in previous papers (Alloni et al., 2015; 2017).

6.3.1 The system architecture

As shown in Figure 4 CoRe features four modules:

- the ‘‘front end’’, in form of a graphic user interface (GUI) allowing the therapist to compose personalized treatment plans by selecting the exercises and by setting the parameters needed to generate each exercise (the difficulty level, number and maximum duration of the stimuli to be shown, etc.);
- the storage module, that is two databases. The first one is used to store the patients’ personal information (patients’ profiles) and performance parameters. The second one stores all the stimuli (texts, sounds and images) made available for the execution of the sessions. It is populated starting from a stimuli ontology, as illustrated in the next section;
- the ‘‘back end’’, a software engine able to generate customized exercises based on the input received from the GUI and, if the therapist chooses the option for automatic difficulty setting, on the patient’s performance;
- the exercises: each of them is an independent submodule. Most of them are computerized versions of existing pen-and-paper exercises. Others have been created to meet specific requirements made by the therapists and exploit PC functionalities that would be particularly difficult to reproduce with a classic, computer-free, approach. For example, the ‘‘Image and sound’’ exercise (see chapter 3 for a detailed illustration).

***Figure 4**. A schema illustrating the structure of CoRe and the intended users of each module: the setup GUI (front-end), meant to be used by the therapist; the exercises, generated by the software engine (back-end) and executed by the patient with the therapist’s support. Data are saved in the storage module, based on an ontology created and populated by the developer in collaboration with the therapist. (source Alloni et al., 2015)*



Once the parameters have been set, the session is started; during the dynamic generation of the executable exercise, performance data of the patient are retrieved to determine the proper difficulty level (in case the settings required automatic definition). The other database is accessed to retrieve stimuli that match the requirements. Besides retrieval operations, the databases can also be accessed for updates. While deletion of records is not allowed, it is possible to exclude a stimulus from the array of available elements, just by setting its ‘‘inclusion’’ flag (an attribute common to all the records of the stimuli database) to

false through the GUI. The great number of stimuli (texts, images and sounds) available in our system allows great variability in execution, something that cannot be achieved with pen and paper exercises. In fact, it is almost impossible for a patient to see multiple instances of a session based on the same stimuli. This helps keeping a high level of attention and involvement, thus reducing the risk of boredom.
The exercises can be performed either by using the touch-screen or the mouse. Literature data suggests that the touch screen is easier to learn and more intuitive to the mouse for users with minimal computer experience or cognitive impairment (Chernick 2007).

6.3.2 The stimuli ontology

Some of the exercises featured in the system are based on just the correct recognition of the stimuli proposed while others also require the user to identify relationships defined between stimuli. From a technical point of view, the most effective way of building such system – that is, one able to generate relation-based exercises correctly – is by organizing all the stimuli in an ontology, which describes every element through a set of attributes, and its relations with other entities. For example, the attribute ‘‘difficulty level’’ (‘‘low’’, ‘‘medium’’ and ‘‘high’’) associated with every single concept of the structure and related to the concept itself, may be considered initially to retrieve stimuli according to the patient’s scholarship (even if exercises will then be adjusted according to performance data). ‘‘Is-a’’ relations between stimuli can instead be used for classification tasks, while other, user-defined relations can be used to generate several types of exercises, as is the case with the following example, based on the ‘‘lives_in’’ relation: DOG is related to KENNEL as BIRD is related to? □ Hole □ Nest □ House. A detailed description of the ontology is beyond the scope of this paper and can be found in Leonardi et al. (2011). Here we only remark, as shown in Figure 3, that the stimuli DB is actually created starting from the ontology. The taxonomy is saved as an XML file whose content (concepts and relations) can be automatically transferred to the database, thanks to an ad hoc software ‘‘translator’’. Addition of new stimuli or new relationships occurs exclusively through the ontology interface, in such a way to guarantee a homogeneous description of all stimuli and to maintain the overall consistency of the stimuli DB. A specific section of the ontology is related to personalization of the exercises. This is a different concept with respect to adaptation of the difficulty of exercises according to the patient’s performance.

6.3.3 The CoRe exercises

The implementation of CoRe is aimed at the rehabilitation of executive functions (logical reasoning, strategy, planning, problem-solving and hypothetical deductive reasoning skills) with particular focus on Parkinson's disease, in which the logical-executive disorders are more prominent. We implemented 10 exercises, namely Word coupling: eight words are displayed on screen. The patient must associate them in four couples, identifying the relations that exist between the stimuli;

1. Pick the element: a matrix of random text elements (letters or numbers) is displayed. The patient must identify and select the requested element;

2. Find the intruder: five words are displayed, four of which belong to the same category. The patient must identify the common category and consequently select the only intruder;
3. Unscramble the sentence: scrambled words are displayed. The patient must select them in the right order to form a sentence;
4. Unscramble the images: same as above, the patient must put the scrambled images in the right order to form a short story;
5. Functional planning: a verb describing an activity is displayed. The patient must select from a list the element related to that activity (e.g. if the action is ‘‘writing’’ and the elements are ‘‘candle’’, ‘‘doorknob’’, ‘‘pen’’ and ‘‘notebook’’, the patient will have to select the latter two);
6. Image and sound: a sound is played, whose duration can be either ‘‘long’’ or ‘‘short’’. Meanwhile an image is displayed, whose dimensions can be ‘‘big’’ or ‘‘small’’. The patient must evaluate whether duration and dimensions ‘‘match’’ (that is, big image+long sound or small image+short sound, according to a criterion explained before the execution) or not;
7. Find the category: three images are displayed. The patient must identify the common category to which all of them belong;
8. Logical sequences: a logical sequence of elements (numbers or images) with a blanked out element is displayed. The patient must identify, among several options, the correct one to complete the series;
9. Logical analogies: the textual version of a mathematical proportion is shown, with one of the four terms blanked out (e.g.: FELINE is related to TIGER as is related to EAGLE). The patient must identify the relation and therefore select the right element among the proposed options (in the proposed example, given the options FISH and BIRD the patient will select the latter).

6.3.4 The CoRe outcomes

CoRe stores all the information related to the execution of the exercises shown, as well as the results obtained by the patients, in dedicated tables in *Patient_db.* The most important data recorded are the followings:

- *date* of the execution;
- name of the *exercise*;
- a value between 0 and 1 that measures the response *accuracy* (ACC);
- the number of *clicks* made by the patient before giving the correct answer (or before the time out);
- the *response time* (RT) i.e. the time in milliseconds needed to complete the exercise;
- *maximum time* (TO) in millisecond allowed for the exercise execution before the automatic interruption;
- *difficulty level* (DL);
- *repetition*: a boolean attribute that indicates whether, during the execution of the exercise, a repetition is expected in case of wrong answer;
- a string storing the *stimuli* shown to the patient, to allow a posteriori reconstruction of each instance;
- an integer corresponding to the number of *aids or tips* provided by the therapist to the patient;

- a character representing the motivation for early interruption of exercises. Different events are mapped with different keys (i.e. “Q” for problems related to the patient and “X” for other reasons independent from the patient). System malfunctions are mapped with a null value.

The analysis of these information is important to understand how the rehabilitation is progressing and how to schedule future sittings. The global evaluation of the patient performance is a complex task that includes four different aspects, each one requiring its own scoring:

1. A score related to the type of the exercise S_t = 0.75*WA/100+0.25*T/Tmax
   S_t is used to represent the intrinsic difficulty level of the exercise: major importance is given to the correct answer (weight 0.75) rather than the response time (weight 0.25). The formula parameters have been valued using the results of the usability study on healthy volunteers reported in above. In particular, WA is the average percentage value of wrong answers for the considered exercise; T is the average execution time and Tmax is the maximum time required to complete an exercise.
2. A score related to the difficulty level S_{lvl} = DL/nDL, where nDL is the total number of difficulty levels for the exercise
3. A score related to the response time S_{rt} = (TO-RT)/TO
4. A score related to the accuracy S_{acc} = ACC

Note that S_t , S_{lvl}, S_{rt} and S_{acc} have values from 0 to 1. We then defined the overall score WS, ranging from 0 to 100, giving equal weight to the four specific scores:

$$WS=25* S_t + 25* S_{lvl} + 25* S_{rt} + 25* S_{acc}$$

The weighted score allows to assess both the overall outcome of a sitting and the global trend of the rehabilitation, providing a unique qualitative value that summarizes the patient's performance whatever the battery of exercises the therapist gave to him.

6.4. Statistical analysis

The scores of the neuropsychological tests were considered outcome measures of the study. Our hypothesis was that G1 had a higher probability of maintaining or improving its cognitive level than G2. In particularly, the primary outcome measures coincided with global functioning scores (MMSE and MOCA) and the secondary outcome measures coincided with executive tests. However, non-executive test scores were also considered in our analysis to assess whether the treatment effect can be transferred even into untrained domains.

To perform the intended intra-group and inter-group evaluations Wilcoxon test was chosen. Considering the small sample size currently available, normality tests can not be expected to give reliable results, so Wilcoxon test is to be preferred since it does not require the assumption of normal distribution of the data. Intra-group tests were performed on paired data: for each neuropsychological test, the scores obtained by each patient at three set moments of the experiment (T0, T1, T2) were compared to detect the statistical significance of the changes. Inter-group tests were aimed at detecting significant differences in the neuropsychological tests scores variations (at T0, T1 and T2) between G1 and G2. Effect Size index

(Cohen's d) was calculated to measure the magnitude of the treatment effect for each significant differences.

Furthermore, a procedure described by Binetti et al. (2013) was used to define the response to training on overall cognitive functions: for each patients a percentage change was calculated for each of the two primary outcome measures (MMSE and MOCA) between the baseline and the next evaluations immediately after training ([(T1 score minus T0 score)/(T0 score)] x 100) and six month after the end of the training ([(T2 score minus T0 score)/(T0 score)] x 100). Patients with a percentage change score of ≥0 were defined as clinical responders (>0 were considered as improving and =0 as being stable); all other patients were defined as non-responders (Petrelli et. al., 2015). A Fisher's Exact test (F) was used to compare the number of responder and non-responder patients both in G1 and in G2 for the two primary outcome measures between T0 and T1 and between T0 and T2. Mean percentage change scores at MMSE and MOCA for G1 and G2 between the baseline and the next evaluations was calculated and compared (Wilcoxon test).

The results are considered significant for p-values lower than 0.05. Statistical analyses were performed using R (https://www.**r**-project.org/).

7. Results

Forty-one patients with diagnosis of idiopathic PD were enrolled, respectively 23 in the intervention group (G1) (16F/7M, mean age 71.18 ± 7.04, mean education 9.06 ± 4.51) and 18 in the control group (G2) (7F/11M, mean age 69.33 ± 7.72, mean education 7.67 ± 3.50). Among the 23 patients in the G1, 6 did not complete the cognitive training because they were discharged before the end of the training. Pre- and post- intervention data and follow-up evaluation after six month are available for all the remaining 17 patients. As regards the G2, there was no drop-out and all patients have completed pre- and post- intervention assessment and the 6-month follow-up. Thirty-six patients were evaluated and excluded because they did not meet the inclusion criteria of the protocol; the absence of cognitive impairment, the presence of MCI without executive involvement or PDD profile or deep brain stimulation were the main reasons for exclusion.

The demographic and clinical characteristics are shown in Table 1. The mean scores (M) and standard deviation (SD) for each group and test are shown; no statistical differences between the groups, either in terms of personal data or in terms of the cognitive scores, at T0 were observed. Table 2 reports mean and standard deviation of cognitive scores at T0, T1 and T2. Table 3 shows the results (p-values of the Wilcoxon tests) of the intra-group and inter-group comparisons of the neuropsychological tests scores obtained at T0, T1, T2.

Table 1. *Demographic data and T0 neuropsychological scores (Group 1 and 2)*

	Intervention Group (G1)		**Control Group (G2)**		
	M	**DS**	**M**	**DS**	***(W)p***
AGE	71.18	7.04	69.33	7.72	0.36
SCHOOL ATTENDANCE (years)	9.06	4.51	7.67	3.50	0.36
DISEASE DURATION (years)	7.18	3.19	10.67	7.36	0.15
HOEHN & YAHR SCALE	2.8	0.96	2.9	0.47	0.46
UPDRS	37.82	13.93	36.50	12.82	0.74
T0					
MMSE	25.32	2.26	25.35	2.68	0.96
MOCA	20.82	3.34	19.17	3.49	0.16
DIGIT SPAN	4.32	0.32	4.13	0.90	0.70
CBTT	3.74	1.12	3.81	0.82	0.96
VERBAL SPAN	3.62	0.55	3.42	0.48	0.32
REY-ir	33.99	7.05	29.33	7.39	0.06
REY- dr	6.25	2.89	5.86	2.04	0.49
LOGICAL MEMORY TEST-ir	4.06	2.61	4.66	2.41	0.60
LOGICAL MEMORY TEST-dr	4.62	2.67	5.39	2.19	0.50
RM47	23.32	5.95	21.02	4.70	0.33
WEIGL'S TEST	6.41	2.77	5.85	2.06	0.57
FAB	13.21	1.86	12.58	2.06	0.27
TMT A	144.47	61.51	121.71	53.90	0.20
TMT B	236.71	104.09	216.94	119.21	0.61
ATTENTIVE MATRICES	39.93	11.77	38.95	9.07	0.70
STROOP TEST TIME interference	28.26	19.95	21.52	11.07	0.43
STROOP TEST ERROR interference	8.56	6.55	5.88	5.05	0.28
FAS	27.25	10.66	24.38	9.30	0.39
SEMANTIC FLUENCY	32.71	5.79	29.15	8.61	0.06
RCF copy	26.54	8.11	24.01	9.00	0.43
RFC-dr	13.54	5.61	10.51	6.49	0.15

Abbreviation: M = mean; SD = standard deviation; (W)p = Wilcoxon test p values; ir = immediate recall; dr= delayed recall

Table 2. *Mean and standard deviation of neuropsychological scores at T0, T1 and T2 (Group 1 and 2)*

	Intervention Group (G1)			Control Group (G2)		
	T0	**T1**	**T2**	**T0**	**T1**	**T2**
	M (DS)	*M (DS)*	*M (DS)*	*M (DS)*	*M (DS)*	*M (DS)*
MMSE	25.92 (2.26)	25.61 (2.02)	25.59 (1.99)	25.35 (2.68)	25.38 (2.09)	24.49 (2.08)
MOCA	20.82 (3.34)	20.52 (2.78)	22.58 (2.95)	19.17 (3.48)	19.11 (3.32)	17.61 (4.08)
DIGIT SPAN	4.32 (0.32)	4.61 (0.62)	4.27 (0.30)	4.13 (0.90)	4.11 (0.47)	3.79 (0.90)
CBTT	3.71 (1.12)	4.10 (0.82)	3.90 (0.60)	3.81 (0.82)	3.77 (7.00)	3.56 (0.50)
VERBAL SPAN	3.62 (0.55)	3.86 (0.62)	3.69 (0.49)	3.42 (0.48)	3.55 (0.78)	3.37 (0.58)
REY-ir	33.99 (7.05)	39.54 (9.06)	37.84 (9.03)	29.33 (7.39)	29.71 (6.24)	28.55 (5.27)
REY-dr	6.26 (2.89)	7.60 (2.02)	7.00 (1.60)	5.86 (2.04)	5.24 (2.06)	5.06 (2.00)
LOGICAL MEM-ir	4.06 (2.61)	5.36 (2.04)	4.72 (1.50)	4.66 (2.41)	4.37 (4.70)	4.37 (1.58)
LOGICAL MEM-dr	4.62 (2.67)	4.52 (1.38)	5.75 (1.50)	5.39 (2.19)	5.81 (1.52)	5.29 (1.69)
RM47	23.32 (5.95)	25.57 (3.92)	23.80 (4.81)	21.02 (4.70)	20.45 (4.44)	19.22 (6.21)
WCIGLSTEST	6.41 (2.77)	9.32 (2.64)	8.32 (1.98)	5.85 (2.06)	6.15 (2.41)	5.62 (2.29)
FAB	13.21 (1.80)	14.48 (2.25)	14.09 (1.53)	12.58 (2.06)	12.35 (1.68)	11.13 (1.37)
TMT A	144.47 (61.51)	108.82 (58.33)	121.94 (53.21)	121.71 (53.90)	124.82 (59.54)	145.64 (77.68)
TMT B	236.71 (104.09)	212.11 (74.28)	227.06 (94.76)	216.94 (119.21)	213.94 (112.63)	182.70 (122.70)
ATTENTIVE MATRICES	39.93 (11.77)	43.29 (5.89)	41.00 (9.07)	38.95 (9.07)	39.00 (7.97)	38.40 (9.64)
STROOP TIME interf	28.26 (19.95)	19.66 (13.13)	24.63 (15.84)	21.52 (11.07)	24.66 (11.44)	29.40 (14.50)
STROOP ERROR interf.	8.56 (6.55)	5.16 (4.20)	5.64 (4.55)	5.88 (5.05)	5.67 (4.34)	8.47 (10.77)
FAS	27.26 (10.66)	33.15 (11.10)	29.17 (8.71)	24.38 (9.30)	24.07 (7.67)	23.40 (7.24)
SEMANTIC FLUENCY	32.71 (5.70)	32.88 (4.58)	33.04 (5.72)	29.15 (0.61)	28.90 (0.45)	29.83 (5.50)
RCF copy	26.54 (8.11)	28.05 (6.95)	26.16 (7.34)	24.01 (9.00)	24.84 (8.82)	23.76 (8.20)
RFC dr	13.54 (5.61)	16.91 (4.39)	14.54 (5.54)	10.51 (6.49)	12.19 (5.33)	10.75 (7.26)

Abbreviation: M = mean; SD = standard deviation; ir = immediate recall; dr = delayed recall

Table 3. *P-values of the Wilcoxon tests for intra-group and inter group-comparison at T0,T1 and T2.Green cells represent results with positive correlation, while red cells represent negative correlation.*

	G1			G2			ΔG1G2		
	T0vsT1	T1vsT2	T0vsT2	T0vsT1	T1vsT2	T0vsT2	T0vsT1	T1vsT2	T0vsT2
MMSE	0.661	0.596	1.0	0.836	0.0002	0.019	0.684	0.066	0.060
MOCA	0.0005	0.016	0.017	0.821	0.001	0.001	0.00001	0.274	0.0002
DIGIT SPAN	0.258	0.129	1.0	0.850	0.054	0.031	0.196	0.887	0.032
CBTT	0.158	0.407	0.236	0.792	0.182	0.154	0.181	0.821	0.107
VERBAL SPAN	0.169	0.350	0.656	0.234	0.182	0.850	1.00	1.0	0.468
REY-ir	0.0006	0.084	0.006	0.237	0.182	0.329	0.0008	0.582	0.006
REY- dr	0.151	0.721	0.016	0.332	0.608	0.099	0.098	0.398	0.005
LOGICAL MEM –ir	0.010	0.083	0.236	0.724	0.319	0.234	0.007	0.427	0.145
LOGICAL MEM-dr	0.123	0.319	0.234	0.255	0.031	0.756	0.550	0.447	0.214
RFC-dr	0.071	0.106	0.170	0.087	0.217	0.513	0.6	0.829	0.679
RM47	0.021	0.017	0.623	0.225	0.346	0.048	0.012	0.386	0.078
WEIGL	0.003	0.113	0.003	0.325	0.019	0.684	0.007	0.972	0.001
FAB	0.029	0.287	0.068	0.601	0.004	0.001	0.029	0.189	0.0007
TMT A	0.020	0.187	0.029	0.569	0.036	0.027	0.001	1.0	0.003
TMT B	0.120	0.328	0.205	0.856	0.394	0.105	0.379	0.081	0.972
ATTENTIVE MATRICES	0.208	0.697	0.513	0.553	0.092	0.447	0.596	0.518	0.562
STROOP TIME interf.	0.018	0.074	0.365	0.093	0.087	0.018	0.001	0.822	0.001
STROOP ERROR interf.	0.022	0.096	0.573	0.182	0.061	0.010	0.023	0.768	0.007
FAS	0.007	0.008	0.343	0.516	0.015	0.378	0.019	0.107	0.164
SEMANTIC FLUENCY	0.923	0.588	0.390	0.293	0.666	0.582	0.516	0.529	0.816
RCF copy	0.53	0.299	0.393	0.660	0.168	0.522	0.829	1.0	0.868

Abbreviation: ir = immediate recall; dr= delayed recall

Between T0 and T1

- within-group analysis:

G1 showed statistically significant improvement at MOCA (z = 3.47, p = 0.0005, d = 0.87), Rey's 15-word test immediate recall (z = 3.42, p = 0.0006, d = 0.68), Logical Memory Test immediate recall (z = 2.57, p = 0.010, d = 0.55), RM47 (z = 2.30, p = 0.021, d = 0.44), Weigl's Test (z = 2.93, p = 0.003, d = 1.07), FAB (z = 2.17, p = 0.029, d = 0.61), TMTA (z = 2.32, p = 0.020, d = 0.59), Stroop Test time interference (z = 2.35, p = 0.018, d = 0.52) and error interference (z = 2.27, p = 0.022, d = 0.61) and FAS (z = 2.65, p = 0.007, d = 0.54).

G2 showed no statistically significant changes compared to the baseline scores.

- between-group analysis:

there were significant differences between the groups in favor of G1 at MOCA (z = 4.27, p = 0.00001), Rey's 15-word test immediate recall (z = 3.32, p = 0.0008), Logical Memory Test immediate recall (z = 2.66, p = 0.007), RM47 (z = 2.49, p = 0.012), Weigl's Test (z = 2.66, p = 0.007), FAB (z = 2.17 , p = 0.029), TMTA (z = 3.17, p = 0.001), Stroop Test time interference (z = 3.11 , p = 0.001) and error interference (z = 2.26, p = 0.023) and FAS (z = 2.33, p = 0.019) between G1 and G2.

Table 4 shows these results.

Table 4. *z-value differences of T0 and T1. Intra-group comparisons (Wilcoxon signed-rank test (W) and Cohen's d effect sizes (d)) as well as inter-group comparisons using the Wilcoxon signed-rank test (W) are shown.*

	Interventions Group (G1)			***Control Group (G2)***			***Inter-g***	
	Z	***(W)p Intra-g***	***d***	***Z***	***(W)p Intra-g***	***d***	***Z***	***(W)p***
NpsTests (T0 vs T1)								
MMSE	0.43	0.661		0.21	0.836		0.40	0.684
MOCA	3.47	**0.0005***	*0.87*	0.22	0.821		4.27	**0.00001***
DIGIT SPAN	1.13	0.258		0.19	0.850		1.29	0.196
CBTT	1.41	0.158		0.26	0.792		1.33	0.181
VERBAL SPAN	1.37	0.169		1.19	0.234		0	1.00
REY-ir	3.42	**0.0006***	*0.68*	1.18	0.237		3.32	**0.0008***
REY- dr	1.43	0.151		0.96	0.332		1.65	0.098
LOGICAL MEM- ir	2.57	**0.010***	*0.55*	0.35	0.724		2.66	**0.007***
LOGICAL MEM- dr	1.54	0.123		1.13	0.255		0.59	0.550
RFC-dr	1.80	0.071		1.71	0.087		0.52	0.6
RM47	2.30	**0.021***	*0.44*	1.21	0.225		2.49	**0.012***
WEIGL'S TEST	2.93	**0.003***	*1.07*	0.98	0.325		2.66	**0.007***
FAB	2.17	**0.029***	*0.61*	0.52	0.601		2.17	**0.029***
TMT A	2.32	**0.020***	*0.59*	0.56	0.569		3.17	**0.001***
TMT B	1.55	0.120		0.18	0.856		0.87	0.379
ATTENTIVE MATRICES	1.25	0.208		0.59	0.553		0.52	0.596
STROOP TIME interf.	2.35	**0.018***	*0.52*	1.67	0.0936		3.11	**0.001***
STROOP ERROR interf.	2.27	**0.022***	*0.61*	1.33	0.182		2.26	**0.023***
FAS	2.65	**0.007***	*0.54*	0.65	0.516		2.33	**0.019***
SEMANTIC FLUENCY	0.09	0.923		1.05	0.293		0.64	0.516
RCF copy	0.62	0.53		0.44	0.660		0.21	0.829

Abbreviation: Nps= neuropsychological; ir = immediate recall; dr= delayed recall;
z = z-value differences between T0 and T1 intra-groups and inter groups; d = Cohen's d effect size intra-groups with d = .2 small effect, d = .5 moderate effect, d = .8 large effect; (W) p intra-g = Wilcoxon signed-rank test for intra-group comparisons; (W) p inter-g = Wilcoxon signed-rank test for inter-group comparisons ; * significance $p < 0.05$.

Between T1 and T2

- within-group analysis:

G1 showed significant worsening at MOCA (z = 2.40, p = 0.016, d = -0.32), RM47 (z = 2.38, p = 0.017, d = -0.40) and FAS (z = 2.63, p = 0.008, d = -0.49).
G2 showed significant worsening at MOCA (z = 3.22, p = 0.001, d = -0.40) and FAS (z = 2.42, p = 0.015, d = -0.19) as G1, but also in MMSE (z = 3.62, p = 0.0002, d = -0.42), Logical Memory Test delayed recall (z = 2.15, p = 0.031, d = -0.32), Weigl's Test (z = 2.33, p = 0.019, d = -0.22), FAB (z = 2.82, p = 0.004, d = -0.79), TMTA (z = 2.09, p = 0.036, d = -0.30).

- between-group analysis:

there were no significant differences in the test scores variations between the groups.
Table 5 shows these results.

Table 5. *z-value differences of T1 and T2. Intra-group comparisons (Wilcoxon signed-rank test (W) and Cohen's d effect sizes(d)) as well as inter-group comparisons using the Wilcoxon signed-rank test are shown.*

	Interventions Group (G1)			***Control Group (G2)***			***Inter-g***	
	Z	***(W)p Intra-g***	***d***	***Z***	***(W)p Intra-g***	***d***	***Z***	***(W)p***
NpsTests (T1 vs T2)								
MMSE	0.53	0.596		3.62	**0.0002***	*-0.42*	1.83	0.066
MOCA	2.40	**0.016***	*-0.32*	3.22	**0.001***	*-0.40*	1.09	0.274
DIGIT SPAN	1.51	0.129		1.92	0.054		00.14	0.887
CBTT	0.83	0.40		1.33	0.182		0.22	0.821
VERBAL SPAN	0.93	0.350		1.33	0.182		0	1.0
REY-ir	1.72	0.084		1.33	0.182		0.54	0.582
REY- dr	0.35	0.721		0.51	0.608		0.84	0.398
LOGICAL MEM- ir	1.73	0.083		0.99	0.319		0.79	0.427
LOGICAL MEM- dr	0.99	0.319		2.15	**0.031***	*-0.32*	0.76	0.447
RFC-dr	1.61	0.106		1.23	0.217		0.21	0.829
RM47	2.38	**0.017***	*-0.40*	0.94	0.346		0.86	0.386
WEIGL'S TEST	1.58	0.113		2.33	**0.019***	*-0.22*	0.03	0.972
FAB	1.06	0.287		2.82	**0.004***	*-0.79*	1.31	0.189
TMT A	1.32	0.187		2.09	**0.036***	*-0.30*	0	1.0
TMT B	0.97	0.328		0.85	0.394		1.74	0.081
ATTENTIVE MATRICES	0.39	0.697		1.68	0.092		0.64	0.518
STROOP TIME interf.	1.78	0.074		1.71	0.087		0.22	0.822
STROOP ERROR interf.	1.66	0.096		1.87	0.0612		0.29	0.768
FAS	2.63	**0.008***	*-0.49*	2.42	**0.015***	*-0.19*	1.61	0.107
SEMANTIC FLUENCY	0.54	0.588		0.43	0.666		0.629	0.529
RCF copy	1.03	0.299		1.37	0.168		0	1.0

Abbreviation: Nps= neuropsychological; ir = immediate recall; dr= delayed recall;
z = z-value differences between T0 and T1 intra-groups and inter groups; d = Cohen's d effect size intra-groups with d = .2 small effect, d = .5 moderate effect, d = .8 large effect; (W) p intra-g = Wilcoxon signed-rank test for intra-group comparisons; (W) p inter-g = Wilcoxon signed-rank test for inter-group comparisons ; * significance $p < 0.05$.

Between T0 and T2

- within-group analysis:

G1 showed statistically significant improvement at MOCA (z = 2.38, p = 0.017, d = 0.71), Rey's 15-word test immediate (z = 2.70, p = 0.006, d = 0.47) and delayed (z = 2.40, p = 0.016, d = 0.69) recall, Weigl's Test (z = 2.96, p = 0.003, d = 0.79) and TMTA (z = 2.17, p = 0.029, d = 0.40).
G2 showed significant worsening at MMSE (z = 2.33, p = 0.019, d = -0.35), MOCA (z = 3.22, p = 0.001, d = -0.41), Digit Span (z = 2.15, p = 0.031, d = -0.37), RM47 (z = 1.97, p = 0.048, d = -0.32), FAB (z = 3.14, p = 0.001, d = -0.82), TMTA (z = 2.20, p = 0.027, d = -0.35) and Stroop Test time interference (z = 2.35, p = 0.018, d = -0.61) and error interference (z = 2.55, p = 0.010, d = -0.30).

- between-group analysis:

there were significant differences between the groups in favor of G1 at MOCA (z = 3.69, p = 0.0002), Digit Span (z = 2.13, p = 0.032), Rey's 15-word test immediate (z = 2.70, p = 0.006) and delayed (z = 2.79, p = 0.005) recall, Weigl's Test (z = 3.15, p = 0.001), FAB (z = 3.38, p = 0.0007), TMTA (z = 2.96, p = 0.003) and Stroop Test time interference (z = 3.11, p = 0.001) and error interference (z = 2.66, p = 0.007).
Table 6 shows these results.

Table 6. *z-value differences of T0 and T2. Intra-group comparisons (Wilcoxon signed-rank test (W) and Cohen's d effect sizes (d)) as well as Inter-group comparisons using the Wilcoxon signed-rank test (W) are shown.*

	Interventions Group (G1)			***Control Group (G2)***			***Inter-g***	
	Z	***(W)p Intra-g***	***d***	***Z***	***(W)p Intra-g***	***d***	***Z***	***(W)p***
NpsTests (T0 vs T2)								
MMSE	0	1.0		2.33	**0.019***	*-0.35*	1.87	0.060
MOCA	2.38	**0.017***	*0.71*	3.22	**0.001***	*-0.41*	3.69	**0.0002***
DIGIT SPAN	0	1.0		2.15	**0.031***	*-0.37*	2.13	**0.032***
CBTT	1.18	0.236		1.42	0.154		1.60	0.107
VERBAL SPAN	0.44	0.656		0.18	0.850		0.72	0.468
REY-ir	2.70	**0.006***	*0.47*	0.97	0.329		2.70	**0.006***
REY- dr	2.40	**0.016***	*0.69*	1.64	0.099		2.79	**0.005***
LOGICAL MEM- ir	1.18	0.236		1.18	0.234		1.45	0.145
LOGICAL MEM- dr	1.18	0.234		0.31	0.756		1.24	0.214
RFC-dr	1.37	0.170		0.65	0.513		0.41	0.679
RM47	0.49	0.623		1.97	**0.048***	*-0.32*	1.75	0.078
WEIGL'S TEST	2.96	**0.003***	*0.79*	0.40	0.684		3.15	**0.001***
FAB	1.82	0.068		3.14	**0.001***	*-0.82*	3.38	**0.0007***
TMT A	2.17	**0.029***	*0.40*	2.20	**0.027***	*-0.35*	2.96	**0.003***
TMT B	1.26	0.205		1.62	0.105		0.03	0.972
ATTENTIVE MATRICES	0.65	0.513		0.76	0.447		0.57	0.562
STROOP TIME interf.	0.90	0.365		2.35	**0.018***	*-0.61*	3.11	**0.001***
STROOP ERROR interf.	0.56	0.573		2.55	**0.010***	*-0.30*	2.66	**0.007***
FAS	0.94	0.343		0.88	0.378		1.38	0.164
SEMANTIC FLUENCY	0.85	0.390		0.55	0.582		0.23	0.816
RCF copy	0.85	0.393		0.64	0.522		0.16	0.868

Abbreviation: Nps= neuropsychological; ir = immediate recall; dr= delayed recall;
z = z-value differences between T0 and T2 intra-groups and inter groups; d = Cohen's d effect size intra-groups with d = .2 small effect, d = .5 moderate effect, d = .8 large effect; (W) p intra-g = Wilcoxon signed-rank test for intra-group comparisons; (W) p inter-g = Wilcoxon signed-rank test for inter-group comparisons ; * significance $p < 0.05$.

Mean percentage change scores between T0 and T1 and between T0 and T2 were calculated for G1 and G2 both for MMSE and MOCA (Tab. 7a and 7b).
G1 improved its performance at MOCA, respectively of 17.18% (±12.09) between T0 and T1 and 9.69% (±13.57) between T0 and T2, while mean percentage change scores observed at MMSE were lower (T0 vs T1: 1.02% ±6.12; T0 vs T2: 1.96% ±11.19).
G2 showed worsening at MOCA respectively of -0.036% (±4.67) between T0 and T1 and
-8.78% (±8.5) between T0 and T2; while mean percentage change scores observed
at MMSE slightly improved between T0 and T1 (0.54% ±6.63) and worsened between T0 and T2 (-3.02% ±5.16). In particular, between T0 and T1, there was no significant difference in the mean percentage change scores at MMSE between the groups ($p = 0.5$), while there was significant difference between groups in favor of G1 at MOCA ($p < 0.0001$, $d = 1.87$). Similarly, between T0 and T2, the difference in the mean percentage scores at MMSE was not significant (although at the limit of significance: p 0.058), while there was significant difference between groups in favor of G1 at MOCA ($p < 0.0001$, $d = 1.63$).

Table 7a. *Mean percentage change scores at MMSE and MOCA for G1 and G2 between T0 and T1*

T0 vs T1

Test	Intervention Group (G1)	Control Group (G2)	p-value
MMSE *M (DS)*	1.02 (6.12)	0.54 (6.63)	0.5 (n.s.)
MOCA *M (DS)*	17.18 (12.09)	- 0.036 (4.67)	< 0.0001

Table 7b. *Mean percentage change scores at MMSE and MOCA for G1 and G2 between T0 and T2*

T0 vs T2

Test	Intervention Group (G1)	Control Group (G2)	p-value
MMSE *M (DS)*	1.96 (11.19)	- 3.02 (5.16)	0.058 (n.s.)
MOCA *M (DS)*	9.69 (13.57)	- 8.78 (8.5)	< 0.0001

Abbreviation: n.s.= not significant; M = mean; SD = standard deviation

Contingency tables (Tab. 8a and 8b) display for each groups the number and percentage of patients that improved, remained stable or worsened respectively in MOCA and MMSE between the baseline and the next evaluations; the Fisher's Exact test p-values show whether there is a significant association between groups (G1 and G2) and performance (improved, stable and worsened).

Table 8a. *Performance at MMSE in G1 and G2 between T0 and T1 and between T0 and T2*

	MMSE (T0 vs T1)		
	Improved	**Stable**	**worsened**
G1	7 (41.2%)	5 (29.4%)	5 (29.4%)
G2	6 (33.3%)	6 (33.3%)	6 (33.3%)
F p-values: not significant (0.838)			

	MMSE (T0 vs T2)		
	Improved	**Stable**	**Worsened**
G1	6 (35.3%)	7 (41.2%)	4 (23.5%)
G2	2 (11.1%)	4 (22.2%)	12 (66.7%)
F p-values: = 0.043			

Table 8b. *Performance at MOCA in G1 and G2 between T0 and T1 and between T0 and T2*

	MOCA (T0 vs T1)		
	Improved	**Stable**	**Worsened**
G1	16 (94.1%)	0	1 (5.9%)
G2	3 (16.7.%)	10 (55.5%)	5 (27.8%)
F p-values: <0.0001			

	MOCA (T0 vs T2)		
	Improved	**Stable**	**Worsened**
G1	13 (76.5%)	0	4 (23.5%)
G2	1 (5.5%)	3 (16.7%)	14 (77.8%)
F p-values: <0.0001			

Between T0 and T1:

- MMSE score

In G1 seven patients improved (41.2%), five patients remained stable (29.4%) and five patients worsened (29.4%).
In G2 six patients improved (33.3%), six patients remained stable (33.35) and six patients worsened (33%).
In this interval, there were no significant differences between the performance of the two groups (F p-values 0.838).

- MOCA score

In G1 sixteen patients improved (94.1%), no patients remained stable and one patients worsened (5.9%).
In G2 three patients improved (16.7%), ten patients remained stable (55.5%) and five patients worsened (27.8%).
In this interval, there were significant differences between the performance of the two groups (F p-value <0.0001).

Between T0 and T2:

- MMSE score

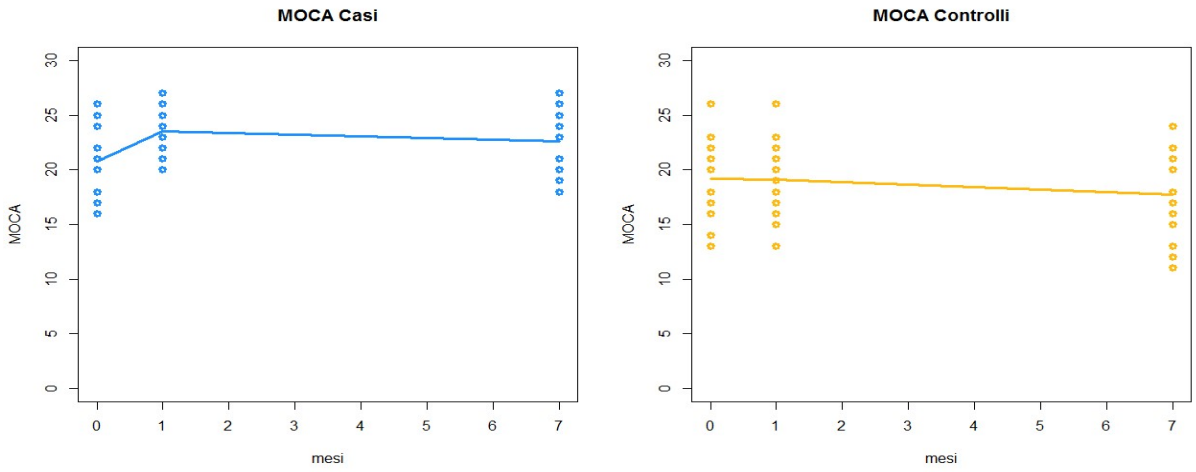
In G1 six patients improved (35.3%), seven patients remained stable (41.2%) and four patients worsened (23.5%).
In G2 two patients improved (11.1%), four patients remained stable (22.2%) and twelve patients worsened (66.7%).
In this interval, there were significant differences between the performance of the two groups (F p-values 0.043).

- MOCA score

In G1 thirteen patients improved (76.5%), no patients remained stable and four patients worsened (23.5%).
In G2 one patients improved (5.5%), three patients remained stable (16.7%) and fourteen patients worsened (77.8%).
In this interval, there were significant differences between the performance of the two groups (F p-value <0.0001).

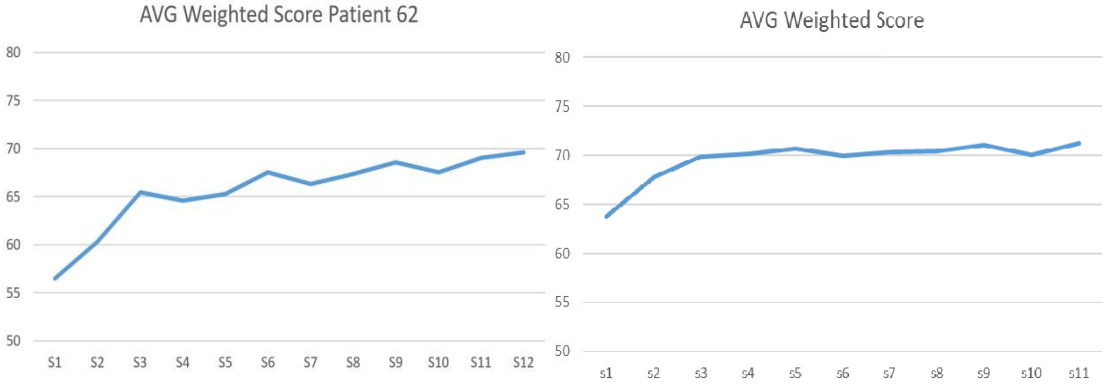
As an example, we report in the Figure 5 the results at MOCA test, which was one of the two primary outcome measures; the picture shows that during the first month G1 performed much better than G2 while between T1 and T2 both groups presented a slight worsening; however, G1 performance after seven month was higher than the baseline.

Figure 5. *MOCA assessment performance in T0, T1 and T2 for case (G1) and control (G2) group*



The weighted score, described in Section 6.3.4, has been calculated, as a qualitative performance indicator, for each sitting and for each patient. In Figure 6, the temporal trend is shown for an exemplar patient and for the whole group (average). The trend clearly shows that the global score of the sitting improves during the rehabilitation treatment.

Figure 6. *Individual (left) and average weighted (right) scores in the different sittings.*



8. Discussion and conclusion

This single-blind study aimed to evaluate the effectiveness of a computerized tool (CoRe system) dedicated to the training of logical-executive functions in PD-MCI patients, in which the logical-executive disorders are most common. Before performing the clinical study, CoRe system has undergone some preliminary tests conducted on healthy volunteers and on a small patients sample to verify its overall functionality as well as to assess its usability (Alloni et al., 2015; 2017). The feedback obtained confirmed general appreciation and positive reaction to the system and allowed the identification of specific problems, consequently new strategy and solutions have been introduced to make CoRe as compliant to the patients' need as possible. In our clinical study, intra-group and inter-group analysis made it possible to statistically compare the two population samples and draw several considerations.

The first point concerns the presence of a significant training effect. Summing up, between T0 e T1, patients undergoing computerized cognitive training showed significant improvement in the overall cognitive performance score (primary outcome measure), in many executive tests (secondary outcome measure) and also in some memory tests; these training gains were consistent and coincided with medium/large effect size improvement. The same cannot be said for control group that tended to remain stable in its performance. In particular, G1 showed significant improvement in general cognitive index measured by MOCA, while non-verbal/abstract reasoning, frontal functionality, simple speed processing and susceptibility to interference are the executive functions that better responded to training; an improvement in immediate recall memory tests has also been observed. Furthermore, comparing the two groups, this improvement of G1 was statistically different from trend of G2 in all above mentioned tests. These inter-group differences suggested a positive effect of cognitive training. Since training tasks differed from the tests applied in the neuropsychological examination and parallel test versions were used on postassessment, these results may reflect learning of appropriate strategies rather than simple practice effects.

To check whether the improvement observed immediately after treatment are maintained over time, it is necessary to observe the groups' values between T1 and T2. In this interval, intra-group analysis showed significant worsening in both groups. G2 worsened in global cognitive functioning (MMSE and MOCA) and in both executive and memory tests, suggesting an evolution of cognitive disorder. In G1, worsened in three logical-executive tests only (MOCA, RM47 and FAS) that improved between T0 and T1. Therefore, on the basis of this result, G1 seemed to maintain the gain obtained from cognitive training in all tests with the exception of three that worsened even in G2. However, comparing the two groups between T1 and T2, the trend in the above mentioned tests was similar and no significant difference was observed in the trajectory of the two groups in this interval. So, G1 behaved as G2 despite treatment and no post-training improvement was maintained after the discharge six months later. We can conclude that the benefits of the training are evident immediately afterward but not at the follow-up check six month later.

Finally, between T0 and T2, G1 showed a medium/large effect size improvement on several tests. Moreover inter-group comparison revealed significant differences in favor of G1 in global cognitive functioning (MOCA) and in both logical-executive

and mnemonic domains. These data should be considered in the light of the fact that we are facing with a neurodegenerative disease, thus the worsening observed in G2 can be interpreted as a cognitive profile modification due to natural disease evolution, while G1 showed a better evolution of cognitive decline compared to G2, probably as a result of cognitive training intervention with CoRe system.

With regard to overall cognitive functions, it is necessary to make some clarifications. In our study, we used two different global cognitive screening tests: MMSE and MOCA. The first, despite being the most commonly used, is less susceptible to executive deficit, while the latter is more sensitive and adequate to investigate logical-executive dysfunctions in PD patients (Dalrymple-Alford et al., 2010). As indicator of response to cognitive training on overall cognitive functions, the mean percentage change scores of MOCA and MMSE were used: our results indicate significant improvement in G1 of overall cognitive functions measured by MOCA between the baseline and the next post-training assessments (with a large effect size) as opposed to decline in the control group. This improvement was more consistent immediately after the end of training and decreases over time, but even after seven months the performance was higher than the baseline.

Furthermore, we distinguished for each groups the number and percentage of patients that improved, remained stable or worsened in MOCA and MMSE between the baseline and the next evaluations. Regarding MMSE, no significant group differences was observed between T0 and T1, whilst the rate of patients who worsened in G2 was significantly greater than G1 between T0 and T2 (G1: 23.5% vs G2: 66.7, with a rate almost three times higher in G2). Instead, regarding MOCA, the rate of patients who improved in G1 was significantly greater than G2 both between T0 and T1 (G1: 94.1% vs G2:16.7%, with a rate almost six times higher in G1) and between T0 and T2 (G1:76.5% vs G2:5.5%, with a rate almost fourteen times higher in G1). In G2, most patients maintained their performance stable (55.5%) between T0 and T1 and worsened (77.8%) between T0 and T2; these data confirmed that untreated patients were more likely to get worse over time.

Therefore, this cognitive training with CoRe system seems to be a complementary treatment for patients with PD in the attempt of briefly stabilizing cognitive decline, delaying the downward trajectory. However, in this study, post-training improvement was not maintained over time, the reason why this happens is an important matter to be investigated. Literature suggests the importance of the duration of a training program; the length of time needed is absolutely crucial, since executive functions are strongly influenced by the effects of the training (Rapp et al., 2002). The executive functions need to be continuously stimulated over time since training has a strong impact in the short term but not always enough of an effect to maintain efficient functioning in the long term (Moro et al., 2015). A possible solution would be to increase the number of weekly sittings during the period of hospitalization and then encourage the patient to continue treatment at home. In fact, computerized cognitive training interventions entails many advantages including the opportunity to offer a number of remote rehabilitation services through telecommunications technologies. Walton and colleague (2017) highlighted the possible role of boosters or additional cognitive training after completion; these may act to extend any observed changes for a longer period of time. Cognitive training has to be regarded as a permanent treatment option, which should at best regularly accompany medication.

Another consideration is the following. This cognitive training focuses on executive functions in patients affected by PD-MCI, but improvements observed in our patients seem to transfer even to untrained domain, such as memory functions. Probably benefits recorded in our patients in some memory tests do not reflect a specific improvement in memory, but rather a more efficient and strategic use of memory abilities which has been learned during the training. Indeed, a training concerning cognitive strategies (e.g. task planning, inhibition of interference, divided attention) may have some impact on the organization of the information that the patient has to remember, with a positive secondary effect on memory. In our sample, the memory test that improves after training corresponds to a task in which the quality of the performance is influenced by the encoding and recall strategies efficiency (in immediate recall memory tests - Rey's 15-word test and Logical Memory Test) .

Lastly, there are some limitations that need to be addressed. First, the study sample was too small to draw definitive conclusion; one major issue is the need for studies that use larger samples of participants and randomized controlled designs. Secondly, the follow-up interval was only 6 month; however to date few RCTs have published follow-up data of CT intervention in PD (Leung et al., 2015) and only one with follow-up interval of 12 month (Petrelli et al., 2015). Third, the identification of proper outcome measures will be critical. Most non-pharmacological studies on MCI have used cognitive symptoms as their endpoint, as in our study. Yet, conversion to dementia may be viewed as a more appropriate endpoint, but long longitudinal studies with numerous follow-up are needed to investigate the conversion process. The question of functional outcomes is another unresolved issue raised in treatment studies. Functional measures are important both because they are key in the definition of dementia and because their sensitivity to treatment provides valid observable endings (functional outcome as a generalization index of the effect of the training). Yet, we need to measure functional effects of treatment on measures that are sensitive to MCI, in which functional abilities are expected to be intact, and sensitive to the training provided.

Concluding, despite these limitations, data suggested that cognitive training with CoRe systems has an effect on cognitive global functioning measured with MOCA and in both logical-executive and mnemonic domains immediately after the end of training, but these benefits are not always maintained over time. Moreover, patients undergoing cognitive training showed better evolution of cognitive decline, in the sense of a brief stabilization of cognitive decline, compared to the control group in the same time interval. Besides, data about high percentage of completed sessions can be considered an indicator of the system quality, in particular of good usability and confidence of use by patients. Thanks to these features, the caregiver can be trained easily in order to facilitate the proper use of the software at home and even non-deteriorated patients can easily learn to use it autonomously. Therefore the software could be incorporated into clinical routine and after discharge this tool could be recommended as a non-pharmacological therapy to be implemented also at home in order to maintain its benefits over time.

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