● PERSPECTIVE

Efficacy of cognitive rehabilitation in Parkinson's disease

Cognitive rehabilitation is a potential and promising treatment for cognitive impairment in Parkinson's disease (PD) that has shown efficacy in diverse studies. In addition, some few studies have found brain changes after cognitive rehabilitation in PD, which supports the existence of brain plasticity associated to cognitive training in a degenerative disease. In this perspective article authors will discuss current knowledge regarding the efficacy of cognitive interventions in PD and highlight some of the following steps that should be carried out to obtain a complete picture of the efficacy of cognitive rehabilitation in PD.

Cognitive impairment is sometimes a common non-motor symptom in PD from the early stages of the disease. These deficits are present in a wide range of cognitive domains, including working memory, executive functions, visual and verbal memory, visuospatial ability and semantic fluency (Aarsland et al., 2010). The importance of cognitive deficits in PD patients lies in its association with reduced quality of life and functional disability in PD, which lead to a social and economic burden. In most cases, these cognitive deficits deteriorate as the disease progresses, and are generally accompanied by structural and functional brain alterations, until dementia occurs. Dementia in PD patients is diagnosed when these three criteria at met: 1) cognitive deficits are present in more than one cognitive domains; 2) presence of cognitive decline from premorbid intelligence; 3) these cognitive deficits have a negative impact in daily life of the patient (Emre et al., 2007). The pattern of cognitive impairment is similar between PD patients and patients with dementia with Lewy body. However, differential diagnosis can be established following the 1-year rule, that is, when cognitive deficits affecting daily life appear before 1 year from PD diagnosis, the patient should be diagnosed with dementia with Lewy body (Emre et al., 2007). Biomarkers of cognitive impairment and predictors of PD dementia evolution have been investigated, such as structural and functional brain alterations, and altered levels of proteins in cerebrospinal fluid, but further research is needed to confirm their biomarker utility.

Due to the relevance of cognitive dysfunctions in PD, and its evolution to dementia, therapeutic strategies are needed. However, to date no pharmacological treatments have demonstrated efficacy on the reduction of cognitive dysfunctions (Petersen et al., 2014). On the other hand, non-pharmacological therapies, such as cognitive rehabilitation, have demonstrated some efficacy against cognitive decline (Petersen et al., 2014), hence the importance of research focused on cognitive rehabilitation in PD.

Cognitive rehabilitation can be defined as a neuropsychological treatment for cognitive impairment based on the theoretical models of restoration, compensation and optimization of the cognitive functions that target cognitive skills. During the training, the participants have to perform repetitive cognitive exercises that vary depending on the cognitive domain trained and the difficulty of the task. "Restoration" of a cognitive function is based on exercising the specific domain with the final objective of reaching a preserved level. For example, a common task for "sustained attention" based on a restoration strategy is to present rows of random letters in an exercise sheet, all with the same size and type, and the patient has to cross the "A" letters. With this exercise, the patient has to identify the "A" letters among all the rest, which makes the patient focus its attention and train the selective attention. The "compensation" model is focused on learning strategies and enhancing other cognitive domains or actions that could compensate the deficit in the specific cognitive domain. When training learning deficits, a compensation strategy could be to train on mnemonic rules which help improving learning ability. Another example of compensation strategy to enhance memory deficits is to write a personal daily diary at nights. The "optimization" model is based on maximizing the correct performance in the specific domain. An optimization strategy for enhancing memory performance is to gradually increase the list of words that the patient has to learn and later recall. With this type of exercises, the patient will improve its ability to learn and retrieve greater quantity of words.

To date, the cognitive rehabilitation studies that have been published on PD used programs with diverse characteristics. Specifically, all these cognitive interventions differed in the format (applied in group *vs.* individually), the duration of the whole program, the frequency and duration of the sessions, the modality (paper/pencil or computer-based exercises), standardized *vs.* tailored, and the qualification and training of the therapists. Despite these differences, all of them revealed benefits in PD patients' cognition. A meta-analysis showed a significant effect on overall cognition after rehabilitation, and found that executive functions, working memory and processing speed were the cognitive domains with greater improvements after training in PD. However, these changes showed small effect sizes (ranging from Hedges $g = 0.30$ to $g = 0.62$) that could possibly be related to the reduced sample size in the studies and the small number of studies in the field (Leung et al., 2015).

Most of the cognitive rehabilitation programs in PD have been focused on training few cognitive functions and literature on clinical trials with cognitive programs that trained a wide range of cognitive domains is scarce. This is contradictory to the fact that most PD patients with cognitive impairment show deficits in multiple cognitive functions (Aarsland et al., 2010). Therefore, our group aimed to investigate the efficacy of an integrative cognitive rehabilitation program in PD. The rehabilitation program used was a group-based structured program (REHACOP), and during the intervention, PD patients trained diverse cognitive domains, including attention, processing speed, verbal and visual memory, language, executive functions and theory of mind. After 3 months of intervention, PD patients showed improvements in processing speed, visual memory and theory of mind. These changes were also accompanied by reductions in functional disability (Peña et al., 2014).

One promising finding is that cognitive rehabilitation programs in PD not only improve cognitive functions but could also have an impact on quality of life aspects. Another study evaluated the change in quality of life, but found negative results, and authors attributed the absence of change to the short duration of the treatment (1 month) (París et al., 2011). Therefore, the duration of treatment could be a relevant aspect to consider in future randomized controlled trials, in order to evaluate the impact of cognitive rehabilitation on PD patients' quality of life. Additionally, depressive symptomatology is one of the clinical variables that has usually been evaluated in rehabilitation studies, and the overall results point to an absence of efficacy in reducing depression symptomatology after treatment (Leung et al., 2015). However, the absence of significant results could be related to the exclusion of patients with depression diagnosis or with severe symptoms of depression prior to participation.

Moreover, little is known about the neurobiological effects of cognitive rehabilitation programs on PD. To date, few studies have investigated cerebral changes in PD patients after an intervention (Nombela et al., 2011; Cerasa et al., 2014; Díez-Cirarda et al., 2017). These studies found the existence of cognitive improvements and brain plasticity in patients with this pathology despite the neurodegenerative process, which supports the idea of neurofunctional basis related to the cognitive changes obtained. In the first published study, PD patients trained individually with Sudoku exercises at home for 6 months (Nombela et al., 2011). After the training, PD patients showed significantly increased perfomance in the Stroop test, and these changes were accompanied by brain activation changes (Nombela et al., 2011). However, there was no active control group and no randomization, and patients in this study only trained one type of exercise. A second study assessed functional brain changes during a resting-state fMRI acquisition after an attention rehabilitation program in PD patients (Cerasa et al., 2014). This study was a blind-randomized controlled trial, and patients showed increased brain activation in the left dorsolateral prefrontal cortex and in the superior parietal cortex after attending attention rehabilitation compared to the active control group (Cerasa et al., 2014). Cerasa et al., (2014) only selected patients with attention deficit, excluding PD patients with deficits in other cognitive domains; therefore, the sample is not completely representative of the cognitive impairment that usually present patients with PD. But at the same time, the specificity of the sample makes the study a perfect illustration of the effectiveness of a cognitive rehabilitation focused on a specific domain, on the improvement in the same specific cognitive domain and whether exists or not transfer effects to other cognitive domains. In this study, authors did not found transfer effects to other congitive domains. These two studies were pioneer in the evaluation of brain changes after training in PD, and added significant findings. However, both studies only included one neuroimaging technique of analysis and trained one cognitive domain. In another randomized controlled study we evaluated the functional brain changes after rehabilitation, measuring brain activity during resting-state and a memory fMRI paradigm inside the scanner, and also aimed to evaluate whether structural brain changes could be found in PD after cognitive training (Díez-Cirarda et al., 2017). PD patients attending cognitive rehabilitation showed increased brain connectivity during resting-state fMRI between frontal and temporal regions and increased brain activation during a memory paradigm in frontal and temporal lobes, but no structural changes were found (Díez-Cirarda et al., 2017). These studies assessed brain changes after rehabilitation in PD and added new information to the literature; however, all of them had small sample sizes, and PD patients were at the early Hoehn and Yahr stages of the disease. Future studies should also include patients at more advanced stages of the disease.

Furthermore, the ultimate goal of cognitive rehabilitation programs is the longitudinal maintenance of the changes, but few studies have been performed in the field. Previous studies in PD that evaluated the long-term effects of cognitive intervention showed that the cognitive improvements were still present after 6 and 12 months (Biundo et al., 2017), which suggests that cognitive rehabilitation programs could prevent cognitive decline at least for a period of time. A recent study evaluated the long-term effects of a cognitive rehabilitation program on cognition, functionality and brain, and found that cognitive, functional and brain changes were still present 18 months after completing treatment (Díez-Cirarda et al., 2018). These findings are relevant in PD and other neurodegenerative diseases. Despite the progression of the disease (shown in the progression of motor symptoms and brain structural alterations at long-term), and in the absence of maintenance treatment, increased cognition and brain activity were maintained over time in the PD group (Díez-Cirarda et al., 2018). Future studies should include longitudinal follow-up periods in order to replicate these findings. Furthermore, the effects of booster sessions to maintain improvements should be assessed and the cognitive domains that are more likely to require this boost to preserve the improvements should be identified.

Furthermore, combining cognitive rehabilitation treatment with other interventions (*i.e.*, physical intervention, motor training), has demonstrated significant benefits in cognition and quality of life in patients with PD (Biundo et al., 2017). Additionally, the combination of cognitive intervention in PD patients and psycho-education with caregivers has shown promising results for the quality of life of both patients and caregiver (A'Campo et al., 2010). The benefits of cognitive treatments could be enhanced by combining cognitive remediation with other training or interventions, which should be addressed in future trials and their interactions should be explored in greater depth.

All in all, great steps have been taken towards evaluating the efficacy of cognitive rehabilitation in PD but some still remain to be evaluated and clarified. Cognitive rehabilitation programs are non-invasive treatments without negative side effects and have shown to benefit patients in their daily lives. The efficacy of cognitive rehabilitation on improving cognition has been found in several studies in PD, but future studies with larger sample sizes are needed in order to reach generalized conclusions and include cognitive rehabilitation as standard treatment for PD patients. Its efficacy on improving behavioral aspects and producing brain functional changes should be further analyzed. Moreover, the longitudinal maintenance of changes should be examined to consider the periodicity with which PD patients should attend cognitive rehabilitation programs. Likewise, literature on the predictors of change after treatment in PD is scarce.

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