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Effects of cognitive training in Parkinson's disease: A randomized controlled trial

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ABSTRACT

Background: In Parkinson's Disease (PD), cognitive dysfunctions which can reduce patients' quality of life occur frequently. Data on non-pharmacological intervention effects on cognitive functions in patients with PD are rare. The aim of this study was to examine the effects of different cognitive group trainings (structured vs. unstructured) on cognition, depression, and quality of life in non-demented PD patients.
Methods: In this randomized controlled trial, 65 non-demented patients with PD according to UK Brain Bank criteria (Hoehn & Yahr I-III) were allocated to one of two cognitive multi-component treatments ("NEUROvitalis", a structured training, or the unstructured training "Mentally fit" with randomly assembled cognitive tasks, each including 12 group-sessions à 90 min over 6 weeks) or a waiting list control group (CG). A neuropsychological test battery was performed before and after the training.
Results: Compared to the CG, patients from the "NEUROvitalis" group improved in short-term memory (word list learning "Memo": $p < .01$) and working memory (digit span reverse from "DemTect": $p < .05$), whereas depression scores where reduced in the "Mentally fit" group (Beck Depression Inventory-II: $p < .05$). The "NEUROvitalis" group improved significantly more in working memory than the "Mentally fit" group (DemTect: $p < .05$).
Discussion: Cognitive and affective functions can be improved by cognitive trainings in PD patients. Specific effects (e.g. on memory and working memory versus depression) seem to be dependent on the type of training. Further research is needed to define long-term effects and the efficacy in PD patients with different extent of cognitive and neuropsychiatric symptoms.

1. Introduction

1.1. Background

Cognitive dysfunctions are frequent symptoms of Parkinson's disease (PD) [1–4] and can limit the patients' quality of life and their ability to organize their lives independently [5]. Since PD represents a high risk for the development of Mild Cognitive Impairment (MCI) and dementia [6] and since there is no prevention strategy for cognitive decline and no approved pharmacological approach to treat PD-MCI yet, non-pharmacological approaches have attracted increasing interest. Remarkably, there is evidence for the effectiveness of cognitive training programs in healthy subjects and (non-PD) MCI patients [4,7].

A recent review demonstrates that cognitive training (CT) and exercise training are the most frequently used non-pharmacological approaches to enhance cognitive functions in non-demented PD patients [8]. Another systematic review on the effects of exercise on cognition in PD patients shows that various types of exercise can improve cognitive function [9].

Although these studies indicate positive effects, data appeared limited. Only three CT studies were randomized controlled trials (RCTs) [10–12], and studies showed heterogeneous designs (treatment, patient characteristics, outcome measures etc.).

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1.2. Objectives

The aim of this study was to conduct an RCT to investigate a) whether non-demented PD patients who receive a six-week cognitive group training can improve their cognitive functions (especially attention, memory, and executive functions, which are often impaired in PD patients [3]), depression scores and quality of life ratings compared to PD patients without training, and b) whether there is a difference in the effects depending on the kind of training (structured training with sessions targeting specific cognitive functions and psychoeducational elements pronouncing metacognitive knowledge versus an unstructured brain training program - similar to "brain jogging", as it is frequently offered in "memory groups" and many books and in which cognitive tasks are randomly put together.).

We hypothesized that PD patients benefit from CT (hypothesis I) and that benefits are more pronounced when taking part in a structured rather than an unstructured training (hypothesis II).

2. Methods

2.1. Trial design

In this RCT with two intervention groups (the structured "NEUROvitalis" [NV] [13] and the unstructured "Mentally fit" [MF]) and one waiting group (CG) PD patients were recruited from the outpatient clinic at the Movement Disorders Unit of the Department of Neurology, University Hospital of Cologne, Germany ($n = 40$), or from regional PD support groups ($n = 30$). After recruitment, all patients were randomly allocated with a computer program (http://www.randomizer.org); support groups: NV/MF/CG: $n = 7/7/16$; University Hospital: NV/MF/CG: $n = 18/17/5$). Ten training groups were built with comparable group sizes (5 NV-groups [University Hospital: $n = 4 + 5 + 8$; support groups: $n = 3 + 4$], 5 MF-groups [University Hospital: $n = 3 + 6 + 8$; support groups: $n = 3 + 4$]. Due to the informed consent, only patients in the treatment groups were blinded for the kind of treatment. The examinators were blinded for the condition, trainers were not.

2.2. Study setting

The study took place between May 2010 and June 2012. It was conducted in accordance with the Helsinki Declaration of 1964 (2008 revision), was approved of by the local Ethics Committee of the University of Cologne (11–061) and is registered in the German Clinical Trials Register (#DRKS00004978). Written informed consent was obtained from each patient.

2.3. Inclusion and exclusion criteria and clinical examinations

70 patients with idiopathic PD according to UK Brain Bank Criteria [14] were recruited. Exclusion criteria were suspected dementia (Mini Mental State Examination, MMSE<25), other neurological or psychiatric diseases (except for depression), impaired hearing or sight, and treatment with DBS. Only patients who completed at least 75% (>9 sessions) of the training were included in the analysis. Change of medication from pre- to posttest served as a post-hoc exclusion criterion.

2.4. Clinical examination

The Hoehn and Yahr (H&Y) staging of PD [15] was defined at baseline. The motor score of the Unified Parkinson's Disease Rating Scale [16] (UPDRS part III) was videotaped and rated by an MDS-certified physician (MTB) blinded for the treatment condition. The scales were rated during the "on"-phase; pre- and posttest examinations were usually conducted at the same time of the day after the neuropsychological examination.

2.5. Interventions

Our aim was to conduct interventions which are easily administrable by clinicians and caring employees working with patients and therefore can be made available to a large number of patients. A group setting was selected, because (i) social activity is known to have a positive impact on cognition and the risk of dementia [17], (ii) non-demented PD patients – as compared to other patient groups typically receiving cognitive training such as patients with stroke or head traumas – are relatively comparable with regard to their cognitive profile typically with first impairments in memory and executive functions, and (iii) from an economic point of view, group trainings are more cost-effective. However, where available in the trainings' material, levels of difficulty corresponding to the group's cognitive level were used. The CG did not receive any training between test sessions (Fig. 1).

Both treatment programs were equal with regard to the duration and the frequency of training sessions (12 sessions à 90 min, 6 weeks). However, they differed in structure and partly also in content. Until now, there is little PD specific training available. Thus, our aim was to compare a structured training program (NV) which targets domains that are frequently impaired in PD (attention, memory, executive functions) with an unstructured, not domain-specific "brain jogging" program as it is frequently offered. The structured program NV includes individual tasks, group tasks and group games each focusing on specific cognitive functions (attention, memory, executive functions). In NV each session focuses on one specific cognitive domain or topic and starts with a corresponding psychoeducational part (e.g. cognitive functions, training possibilities, compensation strategies; see also Supplementary material). In MF, domains were not addressed in focused sessions. Individual and group tasks which trained attention, memory and less specific functions (language in general, creative thinking) were combined randomly over the course of the entire program. Instead of psychoeducation, sessions contained group conversations about topics proposed by the trainer or by the patients themselves (e.g. dealing with the disease). The exercises of MF were composed from a representative choice of tasks of eight frequently used German brain trainings in addition to one group game (see Supplementary material).

To guarantee that all patients were involved in the training, patients were trained in small groups with high levels of interaction. Group tasks and games always involved all participants, and individual tasks were supervised by the trainer. Supplementary material with further information on the structure and contents of the trainings is available online.

2.6. Neuropsychological test battery and outcome measures

An elaborate neuropsychological test battery was conducted with each patient (Table 1, for references please see Supplementary material). Attention, memory (verbal short- and long-term, visual long-term), and executive functions (working memory [meaning a multi-component system that holds and manipulates information in short-term memory] and verbal fluency) which are frequently impaired in non-demented PD patients [3] and which are domains trained in both training programs were defined as primary outcome measures. Visuo-construction, depression and quality of life were defined as secondary outcomes. Patients were examined within ten days before (pre-test) and ten days after the training (post-test). In the CG, pre- and posttests were administered in a parallel time interval without training. When available, parallel test versions were applied (for DemTect [a cognitive screening tool to detect MCI and dementia with five subtests assessing verbal short- and long-term memory, working memory, semantic verbal fluency, and number transcoding], Memo, and complex figure test).

2.7. Statistical analysis

A power analysis was performed with G*Power (http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/download-and-register/index_html) to determine the needed sample size for medium to large effects (*partial eta-squared* [$part\eta^2$] = .06). Alpha Level was defined .05, power .80. The calculated sample size when comparing two groups was a minimum of 17 patients for each group. To compare the patients' characteristics at baseline, two-tailed *t*-tests for independent samples (age, education in years, MMSE, DemTect, BDI-II) were used. Additionally, patients who dropped out were compared to the group of all analyzed patients regarding these characteristics. According to our two hypotheses and as suggested by the Cochrane collaboration for studies which compare alternative interventions, we treated the study statistically as three separate trials and performed "head-to-head comparisons": Trial 1 "NV versus CG", Trial 2 "MF versus CG" (both hypothesis I, CT can enhance cognition), and Trial 3 "NV versus MF" (hypothesis II, structured training is more effective than unstructured training). Repeated measurement analyses of variance were performed for each trial. The repeated measurement factor in the ANOVAs was pre- versus posttest. The covariates age, education and duration of disease were included. An adjustment of *p*-values (.05) using Bonferroni correction was applied. Partial eta-squared was calculated as a measure of effect sizes to compare the magnitude of treatment effects (0.01 = small, 0.06 = medium, 0.14 = large effects).

2.8. Patient characteristics

70 PD patients were included, 5 were excluded from analyses (NV/MF/CG: $n = 3/2/0$) because they participated in less than 75% of the training sessions (reasons [NV/MF/CG]: hospital stay [$n = 2/2/0$], changed medication [$n = 1/0/0$]). 65 patients were included in the final analyses. Neither the three groups significantly differed in age, education, overall cognitive, affective state at baseline (Table 1), nor did the group of dropped out patients from the group of analyzed patients.

At baseline, we classified all patients according to the MDS task force Level I guidelines for defining PD-MCI [3]. 50 patients were classified as cognitively unimpaired, 15 patients fulfilled criteria for PD-MCI (NV/MF/CG: $n = 5/6/4$).

Relevant (at least mild) depression scores (BDI-II>13) were found for 13 patients (NV/MF/CG: n[raw scores] = 5[14,15,18,19,27]/4[15,15,20,20]/4[15,16,21,45]). H&Y