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# Cognitive Rehabilitation in Parkinson's Disease Using Neuropsychological Training, Transfer Training and Sports Therapy

I. Reuter<sup>1</sup>, S. Mehnert<sup>1</sup>, M. Oechsner<sup>2</sup> and M. Engelhardt<sup>3</sup>

<sup>1</sup>*Dept. of Neurology, Justus-Liebig University, Giessen, Germany*

<sup>2</sup>*Neurologisches Rehabilitationszentrum, HELIOS Klinik Zihlschlacht AG,*

<sup>3</sup>*Dept. of Orthopedic Surgery, Klinikum Osnabrück,*

<sup>1,3</sup>*Germany*

<sup>2</sup>*Swiss*

## 1. Introduction

### 1.1 Cognitive impairment in Parkinson's disease

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder characterized by basal ganglia dysfunction frequently being associated with frontostriatal dysfunction and cognitive impairment. The prevalence of PD increases with age and is estimated at 100-200/100000 people (Chen et al., 2001; Schrag et al., 2000) worldwide. The clinical hallmarks of PD are akinesia, rigidity and tremor (Douglas et al., 1999; Hughes et al., 1992). In the past PD has been considered as a pure movement disorder, but in recent years the presence of non-motor symptoms in PD has been recognized. Non-motor symptoms include a variety of autonomic dysfunctions such as orthostatic hypotension, postural tachycardia, bladder dysfunction, sleep disturbances, psychiatric symptoms, i.e. depression, hallucinations or psychosis and cognitive impairment. Non-motor symptoms such as pain, depression or sleep disturbances might precede the onset of motor symptoms in PD and are sometimes even more disabling than motor deficits. For many years cognitive impairment and the occurrence of dementia have been considered as not typical for IPD. James Parkinson (Parkinson, 1817) wrote in his essay on the shaking palsy "the senses are not disturbed". However, there is now enough evidence in the literature that dementia might occur in up to 40% of PD-patients (Emre et al., 2004). PD dementia is the third most common reason for dementia. Dementia in PD has been associated with reduced quality of life, greater sensitivity to medication, higher risk of developing psychosis, shortened survival (Levy, 2002), increased caregivers stress and frequent transfer to nursing homes (Aarsland et al., 2000) compared to PD-patients without dementia. In contrast to dementia mild cognitive impairment might occur early in the course of the disease. Approximately, a quarter of PD-patients without dementia have mild cognitive impairment (PD-MCI) and 20% might have MCI at the time of diagnosis (Aarsland et al., 2011). The cognitive deficits in PD are specific and include executive dysfunction, attentional and visuospatial deficits. Executive functions include control, manipulation, and cognitive flexibility (Funahashi et al., 2001; Lezak, 1995) and is part of working memory (Carpenter et al., 2000). The executive system is thought to

be involved in handling new situations outside the domain of automatic psychological processes (no reproduction of learned schedules or set behaviours). The theoretic model of the executive system has been modified several times over the years. Crucial contributions to the concept of executive functions came from Norman (1980, 2000), Shallice (1982), Baddeley (1986) and Miller & Cohen (2001). In summary, executive functions involve planning and decision making, influence our handling and the processing of information. Furthermore, they are involved in error corrections or troubleshooting, in situations which require new sequences of actions. Components of the executive systems are attention (focusing on relevant information), selective visual attention, inhibition (inhibition of irrelevant information) (Smith & Jonides, 1999), overcoming of strong habitual responses or resisting temptation (Burgess & Shallice, 1996), task and time management, monitoring and coding of information for processing in the working memory, flexibility, set maintenance and set shifting. The executive system can be viewed as a manager enabling the adaptation of the perceptive, cognitive and motor system to new tasks. Some authors have claimed that cognitive control is the primary function of the prefrontal cortex (Miller & Cohens, 2001). Cognitive control is implemented by increasing gain of sensory or motor neurons that are involved in task or goal relevant actions (Miller & Cohen, 2001).

Patients with impaired executive functions face many difficulties in everyday life. They have a low attention span, difficulties in problem solving and decision making, in dual tasking, in set shifting, in visuoconstructive tasks, in adaptation to new tasks and even in verbal learning and delayed recall. Thus, PD-patients with impairment of executive functions have difficulties in simultaneously driving a car and searching for a street or in preparing a meal for several people. They also have difficulties in keeping appointments. Relatives report that patients avoid difficult tasks and retreat from social life. Executive dysfunctions also affect the social components and the interaction with other people (Smith & Jonides, 1999). Patients are reported of being more irritable and having difficulties in suppressing inadequate behaviour.

It has been proposed that executive dysfunction underlies all manifestations of cognitive impairment in PD (Lewis et al., 2005) as part of the 'frontal-executive brain syndrome' (Godefroy, 2003). In accordance Colman et al. (2009) found that executive dysfunction also underlies the performance of PD-patients on verb production.

Pathophysiologically (Leverenz et al., 2009) cognitive impairment in PD might be either associated with catecholaminergic or indolaminergic neurotransmission or with Alzheimer's disease (AD) related pathology. While the first form manifests mainly with non amnesic features like impaired EF, and might be correlated with Lewy related pathology in limbic and neocortical regions. The second type of CI manifests in amnesic CI and might derive from processes of AD intersecting with PD. 40% of patients develop dementia (Emre et al., 2004).

## **1.2 Pathophysiology of cognitive impairment in PD**

Decline of cognitive performance in PD might result from rupture of nigro-striatum-thalamus cortical circuit interconnecting the striatum to the prefrontal cortex, cholinergic deficits through the differentiation of neurons in the nucleus basalis of Meynert and the pedunculopontine-lateral dorsal tegmental neurons (Calabresi et al., 2006).

In PD the production of dopamine (DA) in the substantia nigra (SN) is decreased. DA is a major neurotransmitter of the basal ganglia, contributing seriously to the development of

frontal-executive dysfunction. Dopaminergic frontal systems play a major role in working memory and executive function (Goldman-Rakic et al., 1992), especially the dorsolateral prefrontal lobe. However, dopaminergic medication has not shown to have a substantial effect on cognitive problems in PD (Fournet et al., 2000; Lewis et al., 2005). So far, medical treatment has not been effective enough to prevent PD dementia and restore executive dysfunction. Acetylcholine esterase inhibitors improve cognitive functioning only in some patients.

Furthermore, there is a large body of studies on animals and humans in the literature showing a positive effect of exercise and sports on cognition (Abbott et al., 2004; Colombe et al., 2003a, 2003b, 2006; Laurin et al., 2001; Rolland et al., 2010). Several studies suggest an enhancement of cortical plasticity by exercise. It is assumed that physical exercise mediates increased expression of neurotrophic factors as glial-derived neurotrophic factor (GDNF), basic fibroblast growth factor (FGF-2), or brain-derived neurotrophic factor (BDNF) (Kleim et al., 2003). BDNF is a member of the neurotrophin family of growth factors vital for trophic support of neurons within both the peripheral and central nervous system. BDNF signals through tyrosine kinase receptor B and through the p75 receptor. Both are expressed by dopamine neurons. Postmortem studies in PD have shown that PD is associated with reduced BDNF levels in the SNC (Howells et al., 2000)

### **1.3 Treatment options for cognitive decline in PD**

Executive functioning was found to be improved by aerobic endurance exercise (Colcombe & Kramer, 2003; Kramer et al., 1999). Motor training was reported to improve cortical plasticity and cortical reorganisation (Nelles 2004; Shepherd 2001). Physical exercise also was found to improve the quality of daily living (Baatile et al., 2000, Reuter et al., 1999) in PD-patients. Furthermore, Hausdorff et al (2005) have shown that higher cognitive functions correlate with gait variability while Ble et al. (2005) reported a close correlation between executive functions and tasks of the lower extremities.

Since patients with mild cognitive impairment have a higher risk to develop dementia, intervention at an early stage of cognitive decline is desirable. Patients who complain of cognitive problems suffer more often from cognitive deficits than patients without complaints (Dujardin et al., 2010). Therefore, these patients should be offered neuropsychological testing and treatment. However, according to our experience, it is difficult to convince patients to participate in cognitive training programmes. PD-patients noting declining cognitive performance are often anxious and ashamed of having cognitive problems. They rather deny their problems and try to avoid situations which make their problems obvious to other people. On the other hand the majority of PD-patients is very interested in exercise- and sport-programmes focusing on improvement of motor skills and mobility. Considering the correlation between cognitive function and motor tasks, it might be possible to improve cognitive function by physical training. Furthermore, achievements in cognitive training performed at a writing desk are often difficult to transfer into daily life. Therefore, we have chosen a comprehensive approach and designed a study using a multimodal cognitive training to improve cognitive functions.

The aim of the present study was to compare the effect of a multimodal cognitive training regime including paper and pencil tasks combined with transfer tasks and a psychomotor training with a cognitive training performed at a writing desk and a cognitive training consisting of various tasks requiring executive functions combined with transfer tasks.

## 2. Methods

### 2.1 Subjects

240 patients with idiopathic Parkinson's disease according to the UK brain bank criteria (Hughes et al., 1991) and complaints about cognitive problems were recruited for the study at the Parkinson clinic Bad Nauheim. Exclusion criteria were severe concomitant diseases, which limit physical performances, and a second neurodegenerative disease. All patients were assessed by a movement disorder specialist. Medical treatment was optimised prior to the study. It was aimed at keeping medication stable during the study. Demographic data included age, body mass index (BMI), duration of disease, weekly sports activity, smoking habits, medication and concomitant diseases (hypertension, chronic obstructive pulmonary disease, thyroid disease, diabetes mellitus, hypercholesterinaemia, osteoarthritis).

### 2.2 Design

The study was divided into two phases, the first part consisted of a 4-week in-patient stay on a rehabilitation unit with a supervised cognitive training conducted by physiotherapists, occupational therapists and two neuropsychologists.

Patients were randomly allocated to one of the three training groups. Randomisation was conducted by using a computer-generated sequence. All groups received a cognitive training regime using paper and pencil material and a multimedial PC-training. Group A received cognitive training only, while group B took part in a transfer training and a cognitive training. Group C conducted a cognitive training, transfer- and psychomotor training. Patients of group A and B had relaxation training in addition to compensate for the additional training times and occupational therapy without translation training. (Fig. 1) The ethical committee of the Justus-Liebig University has approved the study and all patients gave informed consent. At the baseline visit a medical history was taken and all patients underwent a neurological assessment. Severity of disease was assessed by using the Unified Parkinson's Disease rating scale (UPDRS).

Demographic data included information about education, profession, family, onset and severity of disease, medication, history of psychosis and impairments in daily living. Patients kept an activity log one week prior to the training programme and one week prior to the third assessment. Sports activities and time spent sitting, doing light, moderate, heavy work were recorded.

#### 2.2.1 Scales used for neurological and neuropsychological assessment of PD

##### 2.2.1.1 UPDRS

For the assessment of the longitudinal course of the disease the Unified Parkinson's disease rating scale (UPDRS) was applied. The UPDRS is the most frequently used outcome measure in clinical trials in Parkinson's disease (Fahn et al., 1987). The UPDRS has four subscales: part 1, which has 4 questions on mentation, behaviour and mood (range 0-16 points), part 2, which has 13 questions on activities of daily living (ADL) (range 0-52 points); part 3, which has 14 questions on motor functions (range 0-108 points); and part 4, which has 11 questions on motor and other complications of advanced disease (0-23 points). The UPDRS-Sum score ranges from 0 to 199 points, with a higher score indicating greater problems.

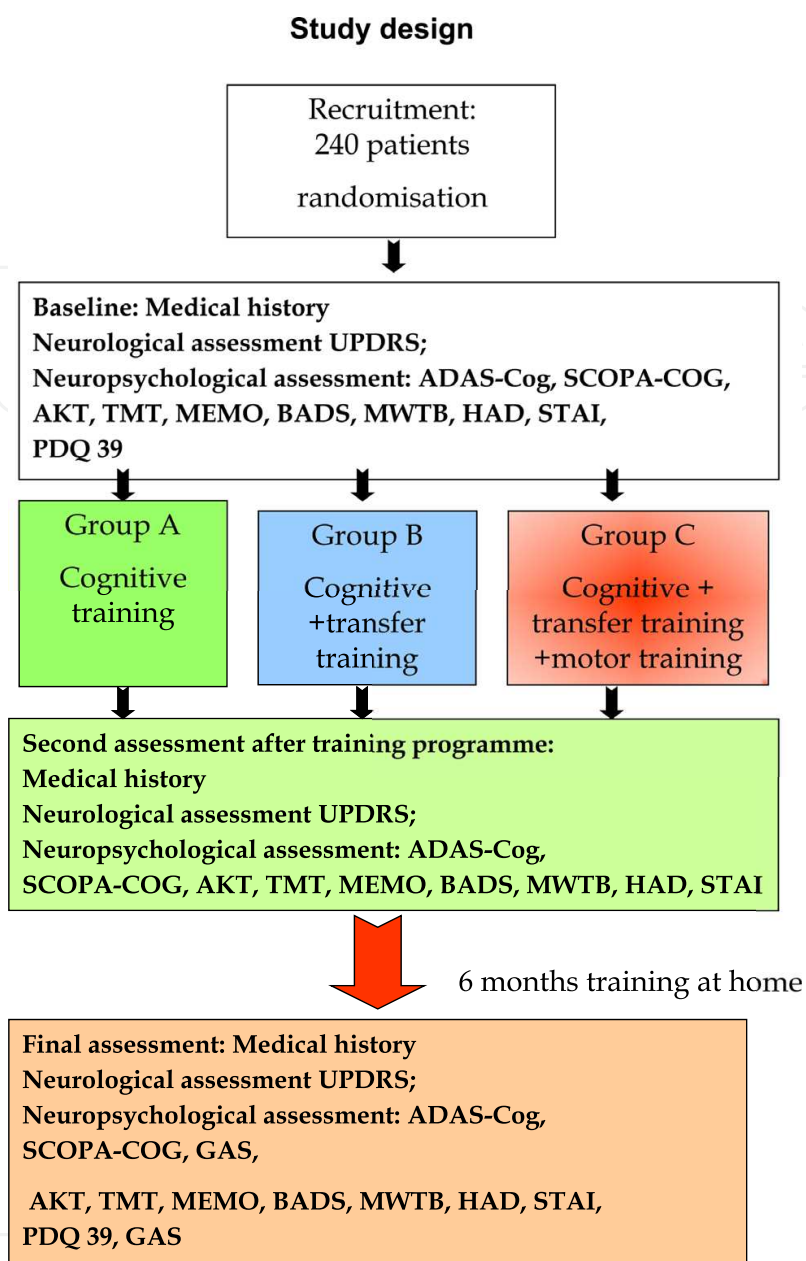


Fig. 1. Study design: First phase of the study: randomisation into three treatment arms, in-patient treatment; second phase of the study: training at home

Posture, postural stability, alternating movements and leg agility were assessed by using the single items of the UPDRS motor scale. The score of each item ranges between 0 to 4 points.

### 2.2.1.2 Goal attainment scale

The Goal Attainment Scaling (GAS) allows individualisation of realistic and feasible goals according to patient needs and expectations. All patients identified a task they want to improve by the training programme. In this study, GAS was measured using a 6-point scale, where -3 represented function that is worse than at the start of treatment, -2 was no change, -1 represented some improvement but did not meet the expected goal, 0 represented goal achievement and +1 or +2 represented over-achievement or exceeding the defined therapeutic goal (Royal College of Physicians, 2008).

### 2.2.1.3 Neuropsychological tests:

For neuropsychological assessment all patients underwent a detailed cognitive test battery at the beginning of the study including the ADAS-Cog subscale and the SCOPA-COG as outcome measures.

*A: ADAS-Cog (Alzheimer Disease Assessment Scale-Cognition)*

Although the ADAS-Cog is not a specific test for cognitive impairment in Parkinson's Disease the scale was chosen as primary outcome measure in the current study, because it was the primary outcome measure in earlier trials assessing effects of medication on cognitive function in PD (Tab.1).

No	. Task	Characteristics	Score
1	Word recall	The recall task of frequent, easily to imagine words	0-10p
2	Naming	Naming of 12 presented objects and fingers on a hand	0-5p
3	Commands	Task of understanding and fulfilling	0-5p
4	Constructional	Drawing 4 geometric forms using praxis a pattern	0-5p
5	Ideational	The task of ability to perform praxis a familiar but complex sequence of actions	0-5p
6	Orientation	Assessment of time and space orientation	0-8 p
7	Word recognition	The task of discriminating new words from the already presented ones	0-12p
8	Instructions	Ability to remember instructions from remembering the previous recognition task	0-5p
9	Spoken language	Assessment of the quality of patient.s age ability speech	0-5p
10	Word finding	Assessment of patients ability to difficulty communicate verbally	0-5p
11	Comprehension	The patients ability to understand the spoken speech	0-5p

Table 1. Structure of ADAS-Cog scale.

The ADAS-Cog scale was the primary outcome measure in many clinical trials (Rosen WG et al., 1984). The conceptual framework underlying the ADAS-Cog identifies three reproducible factors: memory, language, praxis (Talwalker et al., 1996). The ADAS-Cog score ranges in total from 0 to 70 points with higher scores indicating greater impairment. Language ability is tested by naming objects and fingers, observer rated comprehension of spoken language, expressive language and word finding (range 0-25 points; memory is tested by recall of instructions, word list recall and recognition (range 0-27 points), test of praxis (range 0-10 points) consists of constructional praxis (copying geometric figures) and ideational praxis (preparing envelope to send to oneself), orientation is assessed for time and space orientation (range 0-8points).

*B: SCOPA-COG(Scales for Outcome of Parkinson`s disease-Cognition)*

The SCOPA-COG is an instrument which was designed to assess the specific cognitive deficits found in Parkinson's disease (Marinus et al., 2003). The scale consisting of 10 items covers the domains: memory and recall (verbal recall, digit span backward, indicate cubes), attention (counting backward, months backward), executive function (fist-edge-palm, semantic fluency, dice), visual-spatial functions (assembly pattern) and memory (delayed recall). The score ranges from 0 to 43 points with higher scores reflecting better performance.

Further tests requiring executive and memory functions for assessment of cognitive performance of the PD-patients at baseline, second and final assessment were conducted.

*C: Mini Mental test (MMSE)*

The Mini mental state examination (Folstein et al., 1975) was used as screening tool for dementia. The test assesses orientation, registration, attention, calculation, recall, language, writing and copying. The maximum score is 30 points; high scores indicate good performance. The cut off criteria for an abnormal result are 24 points and below. Dementia was assumed for less than 20 points.

*D: Alters-Konzentrationstest*

For assessment of attention the Alters-Konzentrationstest (Gatterer et al., 1989) was applied. Patients are asked to mark specific figures out of other figures alike the target. Time to complete the test, number of correctly marked figures, number and type of mistakes are recorded.

*E: Paced auditory serial addition test (PASAT)*

The Paced Auditory Serial Addition Test (Gronwall et al., 1977) assesses auditory information processing speed and flexibility and ability to calculate. Single digits are presented either every 3 seconds (trial 1) or every 2 seconds (trial 2). The patient has to add each new digit to the one immediately prior to it. The maximal possible score adds up to 60, the individual test score is equal to the total number of correct sums in each trial. In the current study the slower speed was used.

*F: Trail making test*

The trail making test (Reitan, 1958) assesses visual attention and task switching. Numbers from 1 to 30 are spread over a sheet, the patient is asked to connect the numbers in ascending order. Time and errors are recorded.

*G: MEMO-Test*

The MEMO-Test (Schaaf et al., 1994) assesses short-term verbal memory. Ten words are read to the patient. Five trials are performed. Patients are asked to repeat the words immediately, after each trial the words left out are read again. The following assessments are performed: UR: all words produced by short-term memory, ALZS: all words recalled from long term memory, UR + ALZS: all words recalled; KALZS: all words permanently recalled from long term memory; NKALZS: all words inconsistently recalled from long term memory; LZS: all words recalled from long term memory; delayed recall after 15 min..

*H: Behavioural assessment of the dysexecutive syndrome (BADs)*

The BADs (Wilson et al., 1998) is a battery of tests assessing executive function and comprises several subtests. In this study the Rule Shift Card test was applied to identify perseverative tendencies and mental flexibility, the Zoo Map test assessing was used the ability to plan and the Modified Six Element test, a test of planning, task scheduling and performance monitoring, were applied.

*I: Mehrfach-Wortschatz-Test (MWT-B) Multiple choice word test*

The MWT-B (Lehrl, 1989) serves as a control factor. A list consisting of 37 rows with 5 words is shown to the patient. Only one of the five words has a real meaning the others are fantasy words. The patients should mark the word with the meaning. The correct answers are added up to the sum-score. Each score is related to a standard score (z) which estimates the IQ of the patient.



*K: Hospital anxiety and depression scale*

The Hospital anxiety and depression scale (Zigmond & Snaith, 1983) was applied for exclusion of significant depression and anxiety. The scale consists of two subscales, an anxiety scale and a depression scale ranging from 0 to 21 points respectively. Patients are asked to choose one response from the four given for each question. Patients were strongly encouraged to respond promptly. Questions related to anxiety are marked with A and to depression with D. Depression and anxiety are scored separately. On each scale 0 to 7 points indicate a normal, 8 to 10 points a borderline abnormal and 11 or more points an abnormal result.

*L: State Trait anxiety inventory (STAI)*

The STAI scales (Spielberger et al., 1970) assess the trait anxiety (X2) and the anxiety in a specific situation (X1). Each scale consists of 20 items. Both scales present the answers on a 4 point Likert scale. Both scales range from 20 to 80 points with high scores indicating a high anxiety level.

*M: Parkinson's disease Questionnaire 39 (PDQ 39)*

For assessment of health related quality of life patients filled in the PDQ 39 (Jenkinson et al., 1997, Peto et al., 1995). It consists of 8 subscales: subscale 1 mobility (max. 40 points); subscale 2 activities of daily living (max. 24 points), subscale 3 emotional well being (max. 24 points), subscale 4 stigma (max 16 points), subscale 5 social support (max 12 points), subscale 6 cognition (max.16 points), subscale 7 communication (max.12 points), subscale 8 bodily discomfort (max. 12 points) . The sum score of raw data ranges from 0 to 156 points, with high scores indicating lower health related quality of life. For better comparison of the results raw data were transformed and expressed in percentages of maximal possible sum score.

**2.2.2 Training programmes***A: Cognitive training*

The cognitive training content was individually tailored to patients' requirements based on the results of the baseline tests. Four individual (one to one) lessons took place each week each lasting 60 min. All patients received at least 14 cognitive training sessions.

The training included training of attention, concentration, biographical work, reasoning, memory, working memory, social rules, anticipation, cognitive information speed, prospective memory, cognitive estimation, problem solving, sequencing and planning, associations and coping with disease.

For the training programme a set of tasks requiring executive and memory functions were chosen from a variety of specific tests. Executive tasks of the BADS, which were not used for baseline tests were included in the training. Simple patterns of the "Raven's Progressive Matrices" were used to establish problem solving strategies in the patients. Picture arrangement tasks, picture completion tasks, block design, and object assembly were adapted from the "Wechsler Intelligence test for children". For improvement of verbal fluency patients were encouraged to tell short stories or discuss short text-passages. Photos were used for training of working memory. Tasks including visual search, rule finding were practised by using a PC-based programme. The training methods were designed to improve the various cognitive deficits, diagnosed at baseline and focused on the executive functions. Task difficulty was adapted to the individual performance level of the patients.

### *B: Transfer tasks*

The aim of the training was to support patients to manage better their daily life and to become more self-confident. Therefore, patients were asked to practise competence in tasks of daily routines. The transfer training programme was composed according to the baseline test results. Special preferences of the patients were considered. The transfer training included a training of concentration, use of mnemonics, strategy (planning), navigational skills, impulse control, decision processes, listening training and memory, behaviour, calculating, handling of money, summarising of articles read or heard and decision making. Typical tasks were to find the way to the supermarket or to prepare a meal, to go to the bank, pay a bill and to use mnemonics. For better evaluation of the training tasks were allocated to different categories: concentration, strategy, improvement of orientation, planning, use of mnemonic devices. The training took place 3 times a week each lasted 90 min. Patients received at least 10 sessions of transfer training.

### *C: Motor training*

Group C performed a motor training resembling psychomotor training lessons applied in children. Psychomotor training (Golubović et al., 2011; Oswald et al., 1996) reflects a relationship between cognitive functions and physical movements. It includes training of coordination, strength, speed, perception and orientation. Patients should discover their body and their feelings. The therapeutic approach is multidimensional and based on individual capabilities and needs. The aim of the training was to practise motor sequences, dual tasking (walking and bouncing or throwing a ball, orientation in a space, walking through a parcours to improve anticipation. In summer the training was conducted partly outdoors with inclusion of Nordic walking. Thus, the training combines aerobic and psychomotor components. The training included at least 10, maximal 12 sessions each lasting 60 minutes.

## **2.2.3 Education of caregivers**

A long lasting training effect depends on continuing training. Thus, cognitive training and exercises need to be adapted to the home environment. Consequently, the caregivers most often the patients' family were included in the programme. The education for the caregivers consisted of 5 modules (information about Parkinson's disease, psychological aspects and the role of a caregiver, information about help aids, information on care instructions, assessment of individual problems, support in cognitive (all groups) and transfer training (group A and B), NW and psychomotor training). Course instructors were a specialist nurse, physiotherapist and a psychologist.

### **2.2.3.1 Phase II Continuing training**

Corresponding to the allocation to the training groups patients got lessons for the cognitive training, transfer training and physical exercises for the training at home. Caregivers were advised how to organise the training but the hospital staff did not organise the training at home.

### **2.2.3.2 Evaluation of the training**

All patients were tested using a neuropsychological test battery: prior to the training and prior to discharge to assess the short term effect and 3 months after the training to assess the long-term effect.

Caregivers were asked regarding their own well being and regarding the cognitive competence of the patients in daily living. Patients and caregivers kept a diary to record training lesions. The diaries were collected and analysed at the 3<sup>rd</sup>. assessment.

### 2.3 Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics 18.0 (IBM, Somers, USA) statistical software. Formal power analysis was performed prior to the study. The power analysis was based on an improvement of the ADAS-Cog by 3 points. The results indicated that a sample size of 60 subjects per group was sufficient. Since comprehensive training programmes including several assessments imply drop outs, a drop out rate of 20% was taken into account. Demographic data on ordinal level were analysed by using a non-parametric test (Kruskall-Wallis). The Kruskal-Wallis test was also applied for the analysis of depression and the BADS subscales. Continuous data were analysed by using a One - way-ANOVA. The repeated measure analysis provides information about “between and within subjects” effects. Within subject effects give information about training effects over the assessment period. Linear trends were extracted by orthogonal polynomials and analysed for days and for trials (Memo test). Linear trends showed if there was a systematic change of training effects over time. The interaction between groups and the linear trend of days yielded information about difference in the rate of improvement between groups. The between subject factor compared the overall treatment effect between the groups. Post hoc analysis was done using Bonferroni tests. Parametric data were tested for normal distribution by using the Kolmogorov-Smirnov test. Significance level was set at 0.05.

		Group A (N = 71)		Group B (N = 75)		Group C (N = 76)	
gender		F=35	M = 36	F = 36	M = 39	F = 36	M = 40
Duration of PD (months)		98± 8		95 ± 9		100 ± 6	
Stage (Hoehn & Yahr)	II	8		6		10	
	III	55		59		58	
	IV	9		10		8	
Medication	L-Dopa	Yes = 68		Yes = 64		Yes = 59	
	Dopamine agonist	Yes = 53		Yes = 56		Yes = 59	
	MAO inhibitor	N = 43		N = 38		N = 43	
	COMT inhibitor	N = 33		N = 31		N = 34	
	Antidepressants	N = 7		N = 8		N = 8	
	Neuroleptic drugs	N = 5		N = 8		N = 7	
Formal education (years)		10 ± 1.2		11 ± 0.6		11 ± 1.0	
Marital status m = married, s = single, c = partner		m = 58	s = 9	p = 5	m = 61	s = 11	p = 3
Home (own home, renting)		Own = 40	Renting = 32	Own = 43	Renting = 32	Own = 40	Renting= 36
BMI		27.5 ± 4		26.8 ± 7		27.2 ± 3	
Smoking		Yes = 7	No = 65	Yes = 10	No = 65	Yes = 9	No = 67
Sports activities (min)		Ø 155 ± 17		Ø 163 ± 25		Ø 147 ± 17	
Comorbidity	Coronary Heart disease	N = 7		N = 6		N = 8	
	Hypertension	N = 32		N = 33		N = 36	
	Diabetes mellitus	N = 7		N = 10		N = 8	
	COPD	N = 5		N = 6		N = 9	
	Thyroid disease	N = 12		N = 10		N = 11	
	Hypercholesteriaemia	N = 36		N = 32		N = 27	
	Osteoarthritis	N = 27		N = 31		N = 34	

Table 2. Demographic data

### 3. Results

#### 3.1 General results, demographic data and accomplishment of the training

In total 222 patients (97.1%) completed the programme, 71 patients in group A, 75 patients in group B and 76 patients in group C.

The patients were on average  $64 \pm 4$  years old and c. 8 years diagnosed with PD. The patients did not differ significantly in demographic data (Tab. 2). There was no difference in PD specific impairment and in the progress of PD between the groups.

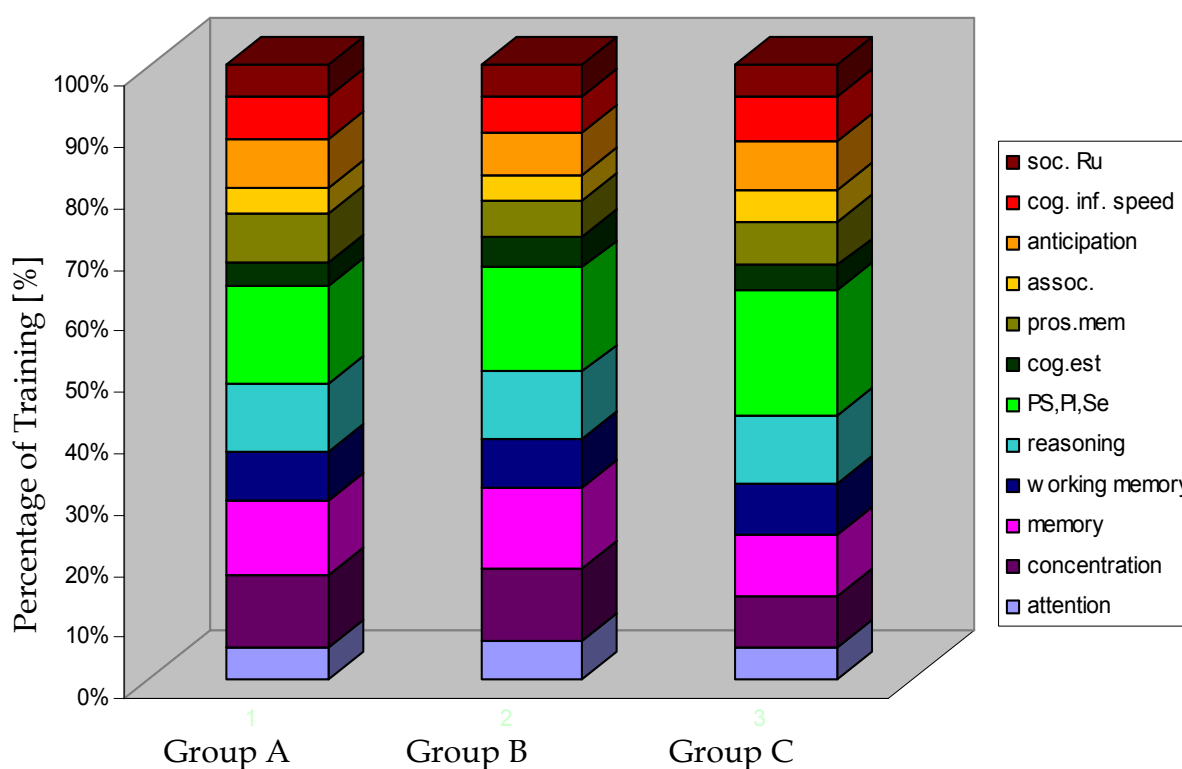
The physical activity of the patients did not differ significantly either.

Patients of group A reported to perform  $8.5 \pm 2.6$  hours very hard work per week, while patients of group B and C reported of  $9.2 \pm 2.8$  and  $9.8 \pm 2.1$  hours very hard work respectively. Group A managed  $15.2 \pm 4.5$ , Group B  $14.9 \pm 5$  and Group C  $15.1 \pm 5.5$  hard work.

The neuropsychological baseline assessment did not reveal any differences between the groups. The multiple choice word test (MWT-B) was conducted as a measure for premorbid intelligence, the groups did not differ significantly, either. Thus the randomisation process was successful.

#### A: Cognitive Training:

The groups differed in time of practising concentration tasks and sequencing and planning tasks ( $F = 3.60$ ;  $df = 2$ ;  $p < 0.03$ ). Group A and B spent 12% respectively 15% of the training with concentration training, group c only 8%. In contrast group C spent 22% of the training time with sequencing and planning tasks while group A 16% and group B 17%. The other training areas did not differ significantly between the groups (Fig. 2).



Soc.Ru= social rules; cog.inf.speed= cognitive information speed, assoc.=association; pros.mem= prospective memory

Fig. 2. Group C spent more time of the training with sequencing and planning tasks, while group A spent more time with concentration tasks.

### B: Transfer training

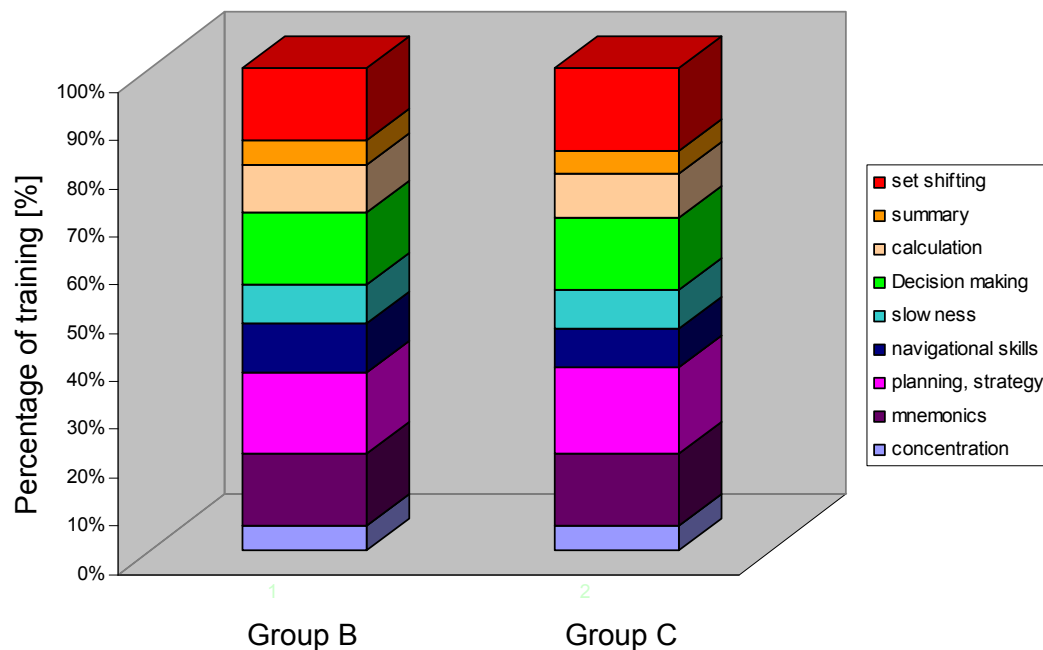


Fig. 3. There was no difference in the quantity and quality of transfer training between group B and C.

### C: Motor training

Patients had many difficulties to cope with the tasks. They struggled to find strategies to solve the tasks on their own. The type of tasks and exercises were new to the majority of patients. The character of the tasks challenged the patients since PD-patients have both, deficits in proprioception and in perception of stimuli. The lessons were conducted as individual lessons. It was not possible to conduct group lessons. About 40% of the training took place outdoors, 60% in the gym.

### D: Training at home

60% of patients of group A continued practising cognitive tasks 3 times a week, while 40% conducted the training only once or twice per week. All patients of group B tried to continue the transfer tasks learnt during the rehabilitation but further assessment showed that only 60% performed transfer tasks following a regular schedule. 90% of the patients practised cognitive tasks 3 times a week. Patients of Group C spent more time practising cognitive and transfer tasks than the other both groups. Patients conducted the physical training programme most often together with their spouses and very regularly.

### E: Assessment of the training by the patients

Patients were asked to evaluate the training programme. Patients of group A felt that the cognitive training was arduous at times. Some patients perceived the training as stressful. Patients of group B and C were asked to compare the training programmes. Patients of group C preferred the motor training to transfer training and cognitive pencil and paper tasks. 80% of patients judged the training as strenuous and felt sometimes exhausted. 30% of patients reported of being frustrated at times but did not ask for help or further explanations.

*F: Assessment of the training programme by the caregivers*

Caregivers felt more relaxed and competent to handle difficult situation, while patients accepted the guidance of their care, felt more confident and thought that the caregivers were more understanding. Both, patients and caregivers felt competent to continue the training at home.

**3.2 Neuropsychological results**

Test	Baseline	T1	T2	Significance between groups
MMST				
Group A	27.36 ± 1.76	n.d.	26.4 ± 1.8	n.s.
Group B	27.6 ± 1.89	n.d.	27.1 ± 1.7	
Group C	28.14 ± 1.81	n.d.	28.5 ± 1.8	
ADAS-Cog				
Group A	21.51 ± 2.27	20.81 ± 2.77	20.5 ± 3.6	p < 0.001
Group B	21.37 ± 4.11	18.33 ± 3.67	18.5 ± 4.2	
Group C	22.92 ± 4.02	17.98 ± 2.76	17.4 ± 2.5	
SCOPA-COG				
Group A	29.07 ± 3.8	27.21 ± 3.6	26.86 ± 3.32	p < 0.001
Group B	29.68 ± 2.87	31.32 ± 3.24	30.71 ± 2.9	
Group C	31.83 ± 3.21	39.15 ± 2.9	39.29 ± 2.72	
TMT				
Group A	34.23 ± 16.87	31.7 ± 13.79	32.6 ± 14.5	p < 0.001
Group B	34.19 ± 15.6	32.0 ± 14.5	31.4 ± 13.5	
Group C	33.98 ± 15.8	26.2 ± 13.4	23.12 ± 9.8	
AKT (time)				
Group A	40.76 ± 15.2	42.85 ± 15.2	42.3 ± 14.2	n.s.
Group B	44.96 ± 16.5	41.67 ± 16.4	42.5 ± 15.3	
Group C	41.36 ± 15.23	40.98 ± 16.3	41.3 ± 16.3	
BADS Zoo (profile)				
Group A	2.5 ± 0.95	3.0 ± 1.2	2.4 ± 1.2	T1: Chi-square: 49.31; p < 0.001 T2: Chi-square: 14.421; p > 0.001
Group B	2.4 ± 0.9	2.8 ± 1.1	2.6 ± 1.1	
Group C	2.6 ± 0.98	3.54 ± 0.82	3.43 ± 1.0	
BADS instruction				
Group A	2.8 ± 1.3	3.3 ± 1.1	2.9 ± 0.8	T1: Chi-square: 7.1; p < 0.03 T2: Chi-square: 9.1 p > 0.01
Group B	2.6 ± 1.3	2.9 ± 1.2	3.2 ± 1.1	
Group C	2.7 ± 1.1	3.5 ± 1.1	3.8 ± 0.9	

BADS 6 elements				
Group A	2.8 ± 1.2	3.14 ± 0.89	3.1 ± 0.9	T1: Chi-square: 39.4; p < 0.001 T2: Chi-square: 25.3 p > 0.01
Group B	2.9 ± 1.2	3.0 ± 1.2	2.9 ± 1.1	
Group C	3.0 ± 0.7	3.55 ± 0.8	3.6 ± 0.9	
PASAT				
Group A	29.94 ± 14.32	32.8 ± 14.83	32.5 ± 13.87	p < 0.001
Group B	31.00 ± 13.32	37.43 ± 12.72	39.57 ± 13.65	
Group C	30.4 ± 12.98	46.5 ± 11.5	49.2 ± 13.4	
TKS (points)				
Group A	10.1 ± 2.4	11.2 ± 2.2	11.2 ± 2.1	p < 0.01
Group B	10.7 ± 2.5	11.2 ± 2.1	11.24 ± 2	
Group C	11.0 ± 2.5	12.5 ± 2.2	12.8 ± 1.9	
STAI X1				
Group A	44.8 ± 10.9	39.62 ± 10.56	38.98 ± 10.4	n.s.
Group B	44.42 ± 11.43	42.43 ± 11.2	38.65 ± 9.87	
Group C	43.53 ± 9.8	38.76 ± 9.8	36.87 ± 10.0	
STAI X2				
Group A	42.68 ± 10.42	40.03 ± 10.2	41.2 ± 10.1	n.s.
Group B	41.84 ± 10.44	39.8 ± 9.8	40.2 ± 9.8	
Group C	40.72 ± 9.98	38.8 ± 9.6	38.2 ± 10.2	

Table 3. Summary of neuropsychological test results

### 3.2.1 Primary outcome measure

#### A: ADAS-Cog

All groups improved on the ADAS-Cog significantly shown by a significant linear trend ( $F_{lin}[1, 220] = 150; p < 0.001$ ). Group C improved most indicated by a significant interaction between groups and days ( $F_{groups \times days}[1, 220] = 27.26; p < 0.001$ ) and a significant group difference ( $F[2, 220] = 7.7, p < 0.001$ ). Further analysis showed that 78% of the patients showed some improvement at the second assessment, 51% of patients of group A, 85% of patients of group B and 96% of patients of group C. 50% of the patients reached a reduction of the ADAS-Cog score of 3 or more points, 18% of group A, 54% of group B and 76% of group C. Six months after discharge of the rehabilitation unit 35% of patients (50% of patients of group A, 31% of patients of group B and 28% of group C) showed a deterioration compared to the assessment at the end of the in-patient training programme. Further improvement was observed in 21% patients of Group A, 37% patients of group B and 50% patients of group C.

#### B: SCOPA-COG

In accordance the SCOPA-COG test showed a significant difference between the groups (Fig. 4). All groups improved, indicated by the linear trend of days ( $F_{lin}[1, 220] = 46.09; p <$

0.001). Group C improved most resulting in a significant difference between the groups ( $F[2, 220] = 31.4$ ,  $df = 2$ ;  $p < 0.001$ ). Since the slopes of the improvements differed between the groups, a significant interaction between days and groups occurred ( $F [2, 220] = 65.63$ ;  $p < 0.001$ ). Post hoc tests revealed a significant difference between all groups ( $p < 0.001$ ). Patients of Group A reached  $28.8 \pm 3.7$  points, Group B  $30.3 \pm 2.7$  points and group C  $37.6 \pm 3.4$  points. After completion of the in-patient training programme 31% of group A, 64% of group B and 88% of group C had shown a significant improvement on the SCOPA-COG, six months later at the final assessment 70% of patients of group A, 80% of patients of group B and 94% of patients of group C had been able to keep their level of performance.

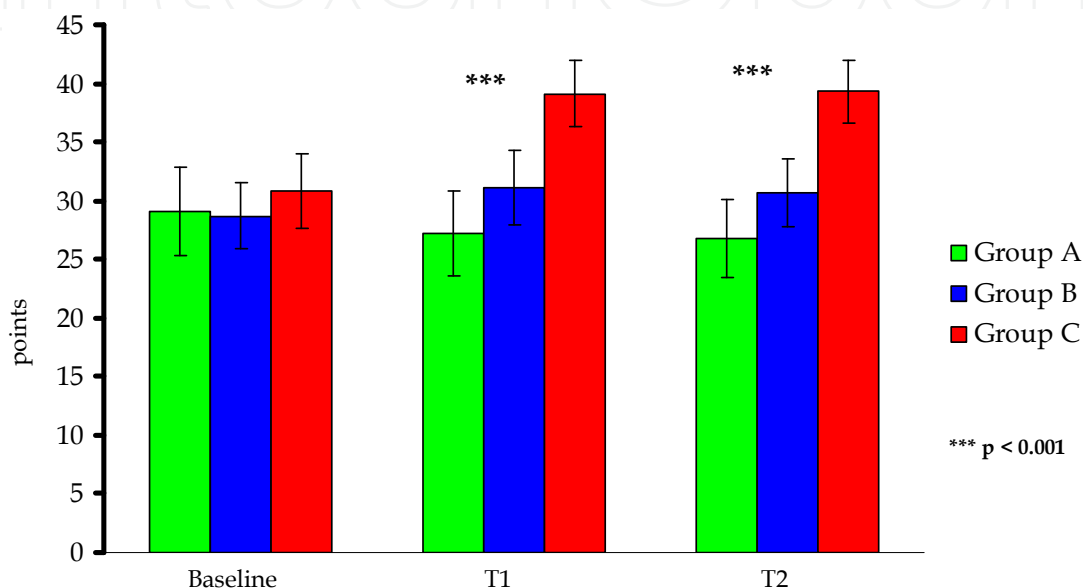


Fig. 4. Group C improved significantly more than group A and B

#### C: GAS

The GAS was performed on the final assessment. Group C reached more often the main goal than the other groups (Chi-square: 57.1;  $p < 0.001$ ). The detailed analysis of the results is shown in table 4 and 5.

The main cognitive impairments reported by the patients could be attributed to the following domains: dual tasking, planning of complex and sequential tasks, decision making, rule recognition and rule shifting problems with delayed recall, difficulties in finding misplaced items. The patients based the selection of the goals on their individual main impairment. Table 4 shows the goals patients had chosen and if they were obtained.

More patients of group A compared to group B and C did not obtain the chosen goal or deteriorated compared to baseline while 27.6% of patients of group C obtained the goal and 39.4% exceeded the expectations mildly and 7.6% substantially.

#### D: Concentration

In the Alterskonzentrationstest (AKT) no difference between the groups was detected. Patients did not differ in attention span neither at baseline nor at the final assessment.

#### E: Information processing

In the ZVT no difference between the groups was detected at baseline assessment. The time to complete the test decreased in all groups after the training ( $F_{lin} [2,220] = 17.71$ ;  $p < 0.001$ ).



Groups	Goal	Goals chosen		Goals obtained	
		Total number	Percentage [%]	Total number	Percentage [%]
A N = 71	Dual tasking	15	21.1	3	20
B N = 75		14	18.7	9	6.4
C N = 76		15	20	10	67
A N = 71	Planning of complex tasks	15	21.2	3	20
B N = 75		16	21.3	9	56.3
C N = 76		17	22.4	10	58.9
A N = 71	Decision making	10	14.1	4	40
B N = 75		11	14.7	6	54.5
C N = 76		14	18.4	10	71.4
A N = 71	Rule recognition and rule shifting	13	18.3	4	30.8
B N = 75		16	21.3	7	43.8
C N = 76		14	18.4	10	71.4
A N = 71	Delayed recall	12	16.9	3	25
B N = 75		12	16	7	58.3
C N = 76		11	14.5	9	82
A N = 71	Search strategies	6	8.5	4	67
B N = 75		6	8	5	83.3
C N = 76		5	6.6	4	80

Table 4. Goals chosen by the patients

Group C was superior to group A and B ( $p < 0.003$ ) while group A and B did not differ resulting in a significant group difference ( $F[2,220] = 7.81; p < 0.001$ ).

In the PASAT test the groups produced on average 50% correct answers at the baseline assessment, group A improved only marginally. Group B and C benefitted from the training programme shown in a significant linear trend for days ( $F_{lin} [1, 154] = 63.71; p < 0.001$ ). Since

GAS	Group A N = 71		Group B N = 75		Group C N = 76		Total	
	Total	Percent	Total	Percent	Total	Percent	Total	Percent
-3	12	16.7	6	8	2	2.6	20	8.9
-2	10	13.8	5	6.7	3	3.9	18	23.7
-1	28	40.3	21	28	18	23.6	67	30
0	13	18.1	19	25.3	23	30.2	55	24.7
1	8	11.1	24	32	24	26.3	56	25.112
2	0	0	0	0	6	7.9	6	2.7
	71		75		76		223	

Table 5. Results of the GAS

the improvement of the groups differed there was also a significant interaction between days and groups ( $F [2, 154] = 18.99; p < 0.001$ ). Group C improved significantly more than group B ( $p < 0.03$ ) and A ( $p < 0.001$ ) ( $F [2, 154] = 15.46; p < 0.001$ ).

Only 157 patients (Group A: 50, Group B: 53, Group C: 54) managed the PASAT test on the first assessment and were included in the statistical model. The other patients did not succeed in finding a strategy to cope with the task. On the second and third assessment 56 patients of group A, 64 of group B and 71 of group C scored on the test.

*F: Memory*

In the MEMO-Test the recall of words improved in all groups over the trials as well as over the assessment days. The subscales of all words permanently stored in the long-term store ( $F[2,220] = 2.95; p < 0.05$ ).and the total number of words in the long-term store ( $F[2,220] = 3.27; p < 0.05$ ) differed between the groups (Fig 4).

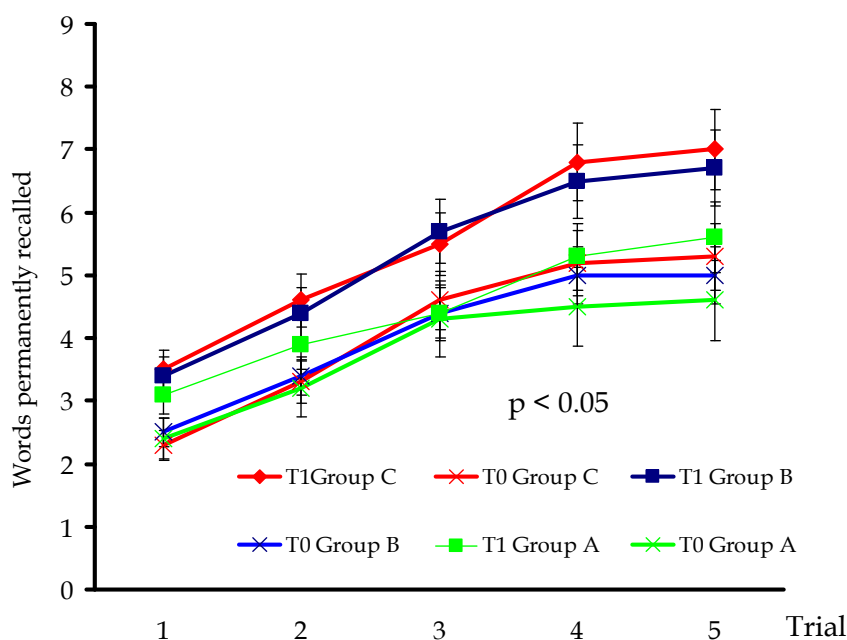


Fig. 5. Group B and C kept more words permanently in memory than group A.

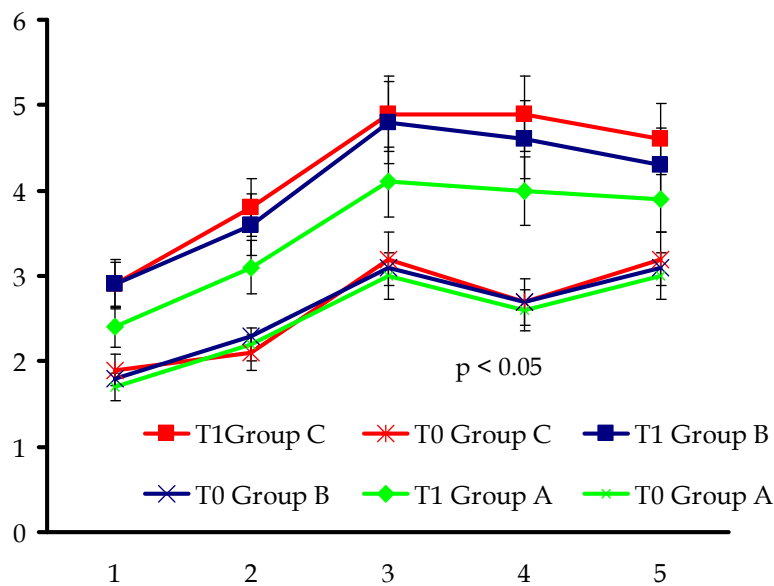


Fig. 6. Group B and C recalled more words than group A.

#### G: Executive function

The subtests of the BADS (rule shift cards, zoo map, modified 6 elements test) showed the following results:

The baseline scores of the rule shift cards did not differ between the groups. There was a mild but significant difference between the groups at the second assessment (Chi-square = 7.1;  $p < 0.03$ ) and final assessment (Chi-square = 9.1;  $p < 0.01$ ).

At baseline assessment Group C showed a tendency to better performance on the BADS Zoo Test. The mean profile scores of all groups were higher at the second assessment, but significantly more patients of group C improved compared to group A and B. There was a clear group difference at the second (Chi-square = 49.31;  $p < 0.03$ ) and third assessment (Chi-square = 14.42; 0.001)

There was no difference in the performance in the 6 elements test or set shifting test. All groups showed an increase of the average profile scores leading to significant group differences at the second (Chi-square = 39.3;  $p < 0.001$ ) and third assessments (Chi-square = 25.3;  $p < 0.001$ ).

#### H: TKS

The competence in cognitive estimation did not improve in Group A but in group B and C resulting in a significant difference between groups (T1: Chi square = 11.98;  $df = 2$ ;  $p < 0.03$ ; T2: Chi square = 22.153;  $df = 2$ ;  $p < 0.002$ ).

### 3.2.2 Assessment of mental state

15% of the patients in group A, 20% of group B and 18% of patients of group C reported to suffer from depression and received medication. The results on the HADS depression scale indicated in 20% of patients of group A and group C respectively and in 25% of patients of Group B the presence of a mild to moderate depression. The anxiety level was assessed by using the Hamilton anxiety scale and did not differ between the groups. The additional assessments of the current anxiety level at the time of assessment (STAI X1) and of the personality trait anxiety (STAI X2) did not reveal differences between the groups. The anxiety at the time of the assessments decreased mildly from baseline to the final assessment.

### 3.2.3 PD specific impairment

The PDQ39 shows that patients of group C rated their health related quality of life higher than the other groups. 13.8% of patients of group A, 38% of patients of group B and 52% of patients of group C reported less impairment due to PD. (Fig. 7)

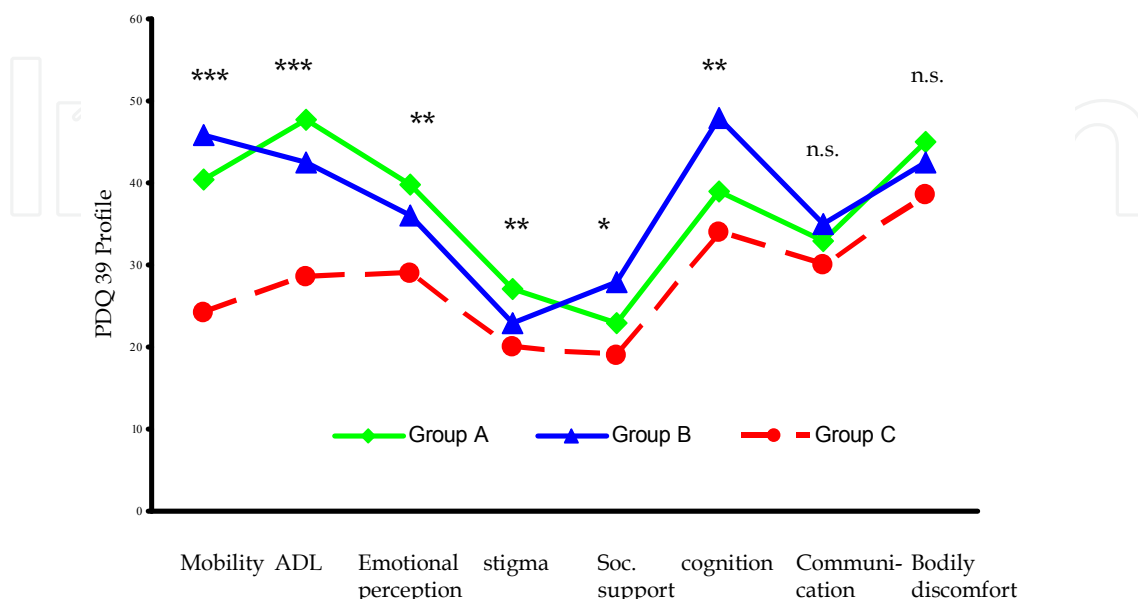


Fig. 7. PD-patients of group C reported less PD-specific impairment at the final assessment. \*\*\* p < 0.001; \*\* p < 0.01; \* p < 0.05

The UPDRS score showed a mild improvement in all groups at the final assessment but there was no significant difference between the groups indicating that cognitive improvement was not an unspecific effect resulting from general physical improvement. (Tab. 5)

	Group A N=71	Group B N = 75	Group C N = 76
Baseline			
UPDRS Motor scale	38.56 ± 12.44	37.53 ± 10.76	38.4 ± 11.78
UPDRS Sum-Score	59.20 ± 12.4	60.3 ± 12.4	61.5 ± 12.8
Final assessment			
UPDRS Motor scale	34.1 ± 11.4	34.2 ± 11.2	35.2 ± 12.4
UPDRS Sum-Score	55.4 ± 12.4	56.3 ± 11.5	57.2 ± 11.4

Table 5. UPDRS

### 3.2.4 Performance in daily living

The patients of Group C reported that they had adapted a more active life style, felt more confident in activities of daily living and had taken over some more chores. They perceived their partners and caregivers as being helpful. They enjoyed the participation of their partners in conjoint sports activities.

Patients of Group B also regarded the training programme as helpful but reported of having still problems with activities of daily living. Patients of group A had more difficulties with transfer of skills into daily life and the carry over effect was smaller than in the other groups.

Sports activities were with 300min/week higher in Group C than in group B (196min/week) and A (176 min/ week).

Patients of group A reported to perform  $7.4 \pm 3.1$  hours very hard work per week, while patients of group B and C reported of  $10.4 \pm 2.2$  and  $11.5 \pm 2.7$  hours very hard work respectively. Group A managed  $14.2 \pm 3.9$ , Group B  $16.1 \pm 4.3$  and Group C  $17.9 \pm 4.1$  hard work

In accordance with the patients' reports 65% of the caregivers of patients in Group C found competence and cognition of the patients improved. In group B 54% of caregivers and in group A 49% of caregivers confirmed an improvement. A deterioration of the performance in daily living was reported in 11% of group C, 17% of group B and 25% of group A. In summary patients who conducted a multimodal cognitive rehabilitation programme improved most and continued coping with daily tasks. Patients of group C were more active in daily living and took more often part in sports activities.

#### 4. Discussion

In summary 90 % of patients of group A, 93.8% of patients of group B and 95% of patients of group C completed the training. Data of patients who did not continue with the programme were not included into the statistical analysis. Although patients complained of a lack of concentration, they performed well on the AKT. The second and third assessment did not reveal further improvement. The lack of improvement might be due to a ceiling effect since the performance on this test at baseline was good in all groups. The same might apply for the MMST which did not differ significantly between baseline and follow-up assessments. The training programme did not affect the mood of the patients.

At the baseline assessment patients of all three groups had shown deficits mainly in tests addressing executive functions. Consecutively, the performance of the patients was worse on the subtests of the SCOPA-COG semantic fluency, LURIA, dice and assembly pattern of the SCOPA-COG, Zoo test of the BADS, PASAT and cognitive estimation. The memory tasks such as immediate and delayed word recall were only mildly disturbed. All groups showed some improvements at the assessment immediately after completion of the training programme in the following tests: TMT, BADS Rule shift cards, zoo map, modified 6 elements test, PASAT and TKS. The mean scores of the ADAS-Cog and SCOPA-COG test in group A were not significantly better compared to the baseline assessment although 18% of the patients reached an improvement of 3 or more points on the ADAS-Cog. The findings were similar for the SCOPA-COG test. 31% of the patients showed an improvement on the SCOPA-COG test. Clear differences between the groups were found for the following tests: TMT, BADS zoo map, BADS rule shift cards, BADS 6 elements, PASAT, TKS, 2 subtests of the Memo Test.

At the second outcome assessment, 6 months after completion of the training programme, 21% of the patients of group A showed a further improvement on the ADAS-Cog, on the other hand 50% of patients of group A deteriorated, 31% of patients of group B and 28% of patients of group C within the 6 months after discharge from the rehabilitation unit. Most of the patients of group B and C were able to keep their performance level between the second and third assessment on the SCOPA-COG, while group A deteriorated. Further improvements between the second and the final assessment were obtained in group B and C on the TKS, PASAT and MEMO test.

The BADS subscales especially the zoo map is a very demanding task requiring excellent planning skills. Even patients of group A and B with previously shown improvement on the BADS subscales lost most of that. Only patients of group C managed to keep their level of performance. The performance of group B and A dropped nearly to baseline level. Thus, Group C has been superior to group B and A immediately after completing the training programme and at the second assessment six months later.

The difficulties patients experienced while solving the tasks have been in accordance with the results of other studies (Lewis et al., 2003, 2005). Most improvement has been observed in the LURIA, dice, assembly pattern, MOSAIC test of the SCOPA-COG. Mild improvement has been observed in the ZOO map and the PASAT-test. The pattern of improvement did not differ between the groups but the percentage of subjects showing an improvement differed significantly as well as the speed of recovery. The UPDRS - score improved in all groups slightly. There were no significant differences between the groups and no significant change of medication. Accordingly, the improvement in the neuropsychological tests cannot be referred to a better physical condition of one group and can be attributed to the training programme.

90% of patients of group C pursued the training at home with the same quantity and intensity while only 75% of group B and 50% of group A did so. Patients of group C conducted a motor training programme three times/week and practised cognitive tasks twice a week for 45 min. Patients of group B and C continued with some tasks resembling the transfer tasks they had performed during the training programme. The partners of the patients of group B and C managed to support the patients in practising transfer tasks, they asked them to prepare a meal or to do the shopping. The majority of the spouses of patients of group C joined their partners in the sports programme. The support of the spouses alleviated the home training significantly. As known from a questionnaire sent to the patients social aspects are very important for PD- patients. It is difficult to decide whether the further improvement of cognitive performance which occurred in some tests was due to the quantity of training or the content of the training. However, group C was already superior to the other groups at the second assessment. Since patients were compliant with the programme during the in-patient stay and received the same quantity of training, the different performance might rather be due to the content of the training than to the quantity. The performance of the patients differed between the tasks suggesting that the different training schedules between the groups affect the training outcome. For example the BADS zoo map a very challenging test as mentioned above requires various training approaches to achieve an improvement. As a result only patients of group C obtained an improvement on this test. Depression might also influence the performance in neuropsychological tests. Klepac et al. (2009) had found that depression preceding PD motor signs might favour poorer cognitive abilities. However, there was no significant difference between the groups regarding the percentage of patients being depressed and the onset of depression. Thus, an influence of depression and anxiety on cognitive performance could be ruled out.

Assessment bias in favour for one treatment can be excluded because the movement disorder specialists conducting the tests were blinded to the treatment arms.

Thus, the findings of the study suggest that PD patients benefit from a specific cognitive training and that a multimodal training might be most suitable for improving cognitive performance in PD. As already shown in a previous study (Hullmann et al., 2004) the cognitive training needs to be specific. Therefore, we had chosen an individual approach based on the Patients` results in the neuropsychological test battery. The specificity of the

training for executive functions is also shown in the fact that an other functional domain such as attention was not influenced by the training. Home based cognitive exercises were sufficient to keep the performance of the second assessment in patients of group C. However, patients of group B and C were able to keep some improvements as well. Home based cognitive training without transfer and physical training as performed by group A was less attractive for the patients. However, the poorer results of group A were not due to fewer training lessons since the performance of group A was already poorer on the second assessment. During the in-patient stay the quantity of training lessons were similar in all groups, only the percentage of specific training differed. Thus, the content of the training might be responsible for the different performance of the groups. The superiority of group B compared to group A suggests the efficacy of the transfer tasks. The psychomotor training helps the group C to improve further, especially in the challenging executive tasks regarding rule cognition, set shifting and decision making. However, it is not clear whether patients of group B and C could also cope better with completely new situations.

In contrast to a study by Paris et al. (2011), the present study suggested a translation of improved cognitive performance on the neuropsychological tests into daily living. Group C scored much higher on the PDQ 39 than the other groups. Thus, health related quality of life was improved markedly in these patients. The patients' caregivers also reported an improved competence in real life. In addition the goal attainment scale had been used in the present study. The patients picked the goals according to the cognitive problems they experienced in daily living. Most often the cognitive problem, they suffered most of, was chosen as goal. Half of the patients managed to obtain the goals agreed on prior to the training programme. Patients of group C reached significantly more often the goal than the patients of group B or A.

The cognitive training performed in the study of Paris et al. (2011) resembled the training of group A in the current study. Only 29% of patients of group A obtained the goal compared to 69.8% of group C.

Some goals seemed to be more difficult to achieve (see Table 4). Patients faced more difficulties in attaining goals regarding rule generation and rule shifting while goals like dual tasking and memory improvement were easier to obtain. Group C was more successful to achieve an improvement in planning of complex tasks, rule generation and decision finding than group B and C.

Goebel et al. (2010) compared the ability of PD-patients to internally initiate a strategy with their ability to utilize an externally provided strategy in a simple Numerosity judgement task. The data of the study showed a general slowdown after strategy instruction. Furthermore, some patients reported difficulties in applying the strategies. The authors referred the findings to a failure in metacognition. Inferior utilization of metacognitive memory strategies seems to induce problems of PD-patients in real-life situations (Johnson et al., 2005, Shimamura, 2000). External instruction might activate metacognitive control processes and slow down the system. However, when PD-patients had sufficient time to solve the tasks there was no general deficit in the ability to internally generate a cognitive strategy in PD. Patients of group C had sufficient time during the psychomotor training to work out strategies to solve tasks and had time to initiate internal strategies. The combination of the psychomotor training with the transfer training provided the patients with some guidance and instructions to solve the tasks. However, the guidance was not too restrictive, there was enough time to find individual solutions. Additionally, the training was less standardised and strongly tailored to the patients' needs.

Our results are in accordance with the authors' conclusions (Goebel et al., 2008): "Adding training time and scheduling repetitive, cue-initiated learning trials may further improve training effects. Such a procedure may lead to more automated, implicit strategy application that demands less executive control (e.g., Baddeley, 1998; Norman & Shallice, 1986; Sammer et al., 2006) whereas instruction alone bears the risk of increasing working memory load".

This is in accord with a work of Sinforiani et al (2004) who showed a significant improvement at verbal fluency, logic memory and Raven's matrices tests after a 6-week cognitive rehabilitation training including cognitive and physical training. After the completion of the training a carry-over effect has been observed and the authors referred the effects to the combination of a cognitive and physical training. The authors suggested that the cognitive rehabilitation training exerts its positive effects by reinforcing cognitive strategies with improvement of frontal lobe functions.

Therefore, emphasis should be placed on the reduction of cognitive load in psychological training programmes. The combination of cognitive training at the writing table with transfer tasks and a physical training is recommended.

Research over the last decade has shown that cognitive deficits affect motor performance. Patients with cognitive deficits had more difficulties in motor tests than patients without cognitive deficits (Goldmann, 1998). Hausdorff et al (2005) have found a close correlation between walking and executive functions. Yogeve et al. (2005) have shown that gait variability in dual tasking is closely associated with the performance in neuropsychological tests of executive tasks.

Therefore, one might speculate that motor functions might affect cognitive performance as well. There is a huge body of literature suggesting a prevention of cognitive decline by life long exercise or even an improvement of cognitive deficits by physical activity. Executive functions may be selectively maintained or improved in people with better physical condition provided by physical training (Churchill et al., 2002). The importance of aerobic physical exercise on cognitive functions, especially on executive functions has been shown (Kramer 1999, Colcombe et al., 2003, 2004, 2006). The studies have been mainly conducted in healthy elderly or patients with dementia. Tanaka et al. (2008) have shown that older people with PD can benefit their executive functions in the same way, as do their peers without PD. The results of some studies have shown that brain areas undergoing biological aging benefit most from endurance sports. Even structural changes have been observed (Colcombe et al., 2006). Exercise is thought to enhance brain plasticity. Neuroplasticity might be supported by BDNF release, which is exercise regulated. Physical exercise increases the release of growth hormone (GH) which represents the main stimulus for the release of insulin growth factor (IGF-1). IGF-1 is involved in processes regulating learning, memory, neurogenesis and amyloid degradation (Holzenberger et al., 2003, Carter & Ramsey, 2002). The release of IGF-1 is closely related to the release of BDNF. Several responses of the brain to exercise have been described. In animal studies comparing young and old animals a difference was shown in the location of the BDNF mRNA upregulation in the hippocampus. Young animal showed an increase of BDNF mRNA in dentate gyrus, hilus and Ca3 region, old animals in the Ca1 and Ca2 region. Long term potentiation which is relevant for memory and learning was also found. LTP was correlated with increased expression of mRNA of the NR2B receptor unit of the NMDA (N-methyl-D-aspartate) receptor. Increase of cerebral blood flow and reduction of cardiovascular risk factors might also contribute to the positive effects of sport on cognition. The reduction of cardiovascular risk factors does not play a role in the present study because of the short observation time. The release of dopamine by exercise might also



play a role. An increase in the activity of antioxidant enzymes, and thus increases the capacity to defend against the stress of oxidation in the central nervous system (Rodák et al., 2001) might also support neuroplasticity.

It is not specified so far which type of exercise might be most promising for improving cognitive performance. The role of endurance training has been shown, whether a combination of aerobic training with a cognitive challenging physical training is of advantage needs further research. The physical training in the present study provided both, a training of strategies to solve tasks and an aerobic training. Since intermittent training schedules have been shown to be as effective as daily training, the frequency of training sessions should have been sufficient as well.

It is not clear so far how cognitive training at the writing table might improve cognitive performance. The destruction of the nigrostriatal dopaminergic pathways is often about 75% and involves the ventral tegmental area, which innervates the prefrontal cortex. Therefore, it is unlikely that cognitive training reconstructs the dopaminergic system.

The multimodal training of cognitive functions is time- consuming and put demands on resources. Due to the quantity and quality of the trainings sessions it will also be costly. On the other hand dementia is a risk factor for falls and transfer to nursing -homes, which increases the costs for the patients' care substantially and jeopardizes the patients' quality of life. Considering the sequelae of dementia such as increased dependence on care givers, high morbidity and increased mortality it is justified to spend more time and effort into prevention of dementia. Therefore, provision of adequate financing is also required.

## 5. Limitations of the study

One might criticise that we compared three different treatment arms and did not include a control group without cognitive training in this study. Patients were enrolled into the study during their stay in a rehabilitation unit and complained of a deterioration of their cognitive performance. For this reason it was not possible to withhold treatment. Further, we had shown in a previous study (Hullmann et al., 2004) the superiority of a cognitive training compared to standard treatment in control subjects. Therefore, we compared three different treatment arms with increasing stimulus modality.

Another limitation is that there are no evidence based data for the transfer training. Further research is necessary to evaluate and validate which transfer exercises are useful tools. The psychomotor training has been used for many years in children and has been used in patients with dementia (Oswald WP, 1996). However, it has not been validated in PD-patients so far. The selection of tasks had been based on the clinical experience of the therapists and medical staff and the published data based on the work with children.

One might also argue which improvement might be clinically relevant. However, the scales we used are all validated and had been often applied in clinical studies. The clinical relevance of the improvements is also shown by the observed translation into real life. One might criticize that the patients were not tested regarding their performance in completely new situations. Patients, caregivers and the neurologist supervising the treatment agreed on certain goals at the beginning of the study. Hence, situations resembling the agreed goals were trained during the study.

Furthermore, due to the short follow up period of 6 months we cannot report on long-term results. However, studies assessing long-term results are very difficult to conduct since it is very difficult to keep the medication stable. A change in dopaminergic (Fournet et al., 2000)

or antidepressant medication might influence cognitive performance. In order to correct for these confounders a larger sample of patients will be needed.

## 6. Strengths of the study

To our knowledge, the results of the current study show for the first time, that a multidisciplinary cognitive training in patients with Parkinson's disease can lead to improvements of cognitive function which translate into everyday life and are not only shown by improvements on neuropsychological scales. We want to emphasize that a blinded randomised design and a standardised neuropsychological test battery were employed. Furthermore, the cohort of patients undergoing the study protocol was big and the dropout rate was low for this type of study. In addition the training of the caregivers guaranteed a supporting environment in all groups. We were able to keep the medication stable avoiding confounding effects by the change of medication.

## 7. Conclusion

In conclusion, we have shown that PD-patients with cognitive deficits benefit from a multidisciplinary cognitive training. A multimodal training is superior to a paper and pencil based cognitive treatment. We have shown a translation of improvements in cognitive tests into performance in real life. Although the multimodal training is time consuming and requires high motivation, it is worth to pursue the training considering the secondary diseases, loss of quality of life and the costs following the diagnosis of dementia. The role of the caregivers has also to be emphasized, the involvement of the family improves the compliance with the training at home.

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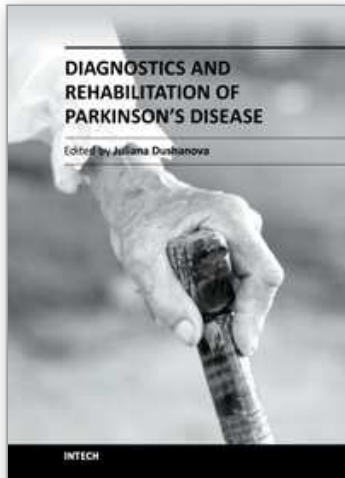
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## **Diagnostics and Rehabilitation of Parkinson's Disease**

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Diagnostics and Rehabilitation of Parkinson's Disease presents the most current information pertaining to news-making topics relating to this disease, including etiology, early biomarkers for the diagnostics, novel methods to evaluate symptoms, research, multidisciplinary rehabilitation, new applications of brain imaging and invasive methods to the study of Parkinson's disease. Researchers have only recently begun to focus on the non-motor symptoms of Parkinson's disease, which are poorly recognized and inadequately treated by clinicians. The non-motor symptoms of Parkinson's disease have a significant impact on patient quality of life and mortality and include cognitive impairments, autonomic, gastrointestinal, and sensory symptoms. In-depth discussion of the use of imaging tools to study disease mechanisms is also provided, with emphasis on the abnormal network organization in parkinsonism. Deep brain stimulation management is a paradigm-shifting therapy for Parkinson's disease, essential tremor, and dystonia. In the recent years, new approaches of early diagnostics, training programmes and treatments have vastly improved the lives of people with Parkinson's disease, substantially reducing symptoms and significantly delaying disability. Written by leading scientists on movement and neurological disorders, this comprehensive book should appeal to a multidisciplinary audience and help people cope with medical, emotional, and practical challenges.

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Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
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