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NEW APPLICATIONS OF NEUROFEEDBACK TECHNIQUES FOR COGNITIVE REHABILITATION IN PARKINSON'S DISEASE

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PREFACE

Patients with Parkinson's disease (PD) present a challenge for rehabilitation specialists due to the distinct nature of their cardinal symptoms and to the degenerative process itself. Health care professionals who work with this group of patients require special knowledge of the disease process, its assessment and its treatment. Although medication often alleviates the motor symptoms of PD, it does not fully remediate non motor symptoms that can interfere with a person's ability to engage in daily activities. So, professional neuro-rehabilitation is asked to put more effort in finding new techniques to increase, maintain or even improve cognitive capabilities.

Since Neurofeedback (NF) has been successfully used to treat epilepsy, alcohol abuse, bipolar disturb, anxiety and particularly to treat attention and executive dysfunctions in children with Attention-Deficit/Hyperactivity Disorder (ADHD), as shown in several recent reviews (Holtmann et al., 2014), we thought that these techniques might be helpful in the treatment of attention problems in PD.

During the last year, the number of articles about NF in PD has exponentially grown, mainly investigating the effects on motor performance (Azarpaikan, 2014).

However, we know that PD is characterized not only by motor symptoms such as muscle rigidity, bradykinesia, resting tremor and postural instability but also by a series of non-motor symptoms.

This study focuses on new applications of Neurofeedback techniques for cognitive rehabilitation in PD.

In order to evaluate the feasibility and adherence of patients to the treatment, the study was initially addressed to four neurological diseases characterized by attention disorders: multiple sclerosis, Parkinson's disease, cerebrovascular insult, cerebellar ataxia. Preliminarily, patients performed five sessions of NF training. Patients suffering from Parkinson's disease were those who appeared more motivated and showed a rapid response to treatment. Notice that Parkinson's disease is a condition that shares neurotransmitter circuits similar to those involved in ADHD; therefore, also learning mechanisms making the treatment effective might be similar.

1. INTRODUCTION

1.1 Overview of Parkinson's Disease

Parkinson's disease (PD) is a lifelong chronic progressive neurodegenerative disorder characterized by motor (bradykinesia, rigidity, resting tremors and postural instability) and non-motor symptoms (cognitive impairment, affective and behavioral disturbances, impairment of the autonomic nervous system). Both motor and non-motor symptoms impact significantly on the function and quality of life of PD patients.

PD is primarily caused by loss of dopaminergic neurons in the nigrostriatal pathway as a result of massive neuronal degeneration (over 60% at the onset of motor symptoms) of the substantia nigra pars compacta [Hughes *et al.* 1992; Kish *et al.* 1988]. Neuropathological hallmark of the disease is the accumulation of filamentous, eosinophilic intracytoplasmic inclusions, called Lewy bodies (LBs), mainly consisting of aggregates of a protein (α-synuclein) in an insoluble altered form.

Significant neural loss also occurs in the locus coeruleus, dorsal motor nucleus of the vagus, raphe nuclei and nucleus basalis. LBs may be found in all of these locations as well as numerous other subcortical structures. Neurodegeneration is accompanied by reactive changes including astrogliosis and microglial cell activation.

It is debated whether the finding of such histological alteration represents itself the primary pathology, or it is only an indicator of the process of neurodegeneration [Gibb *et al.* 1988].

The etiology of Parkinson's disease is currently unknown, but it is considerable to think a multifactorial origin, which involves genetic and environmental factors.

The diagnosis of Parkinson's disease is largely clinical and depends on the presence of a specific set of symptoms and signs, the absence of atypical features, a slowly progressive course and a response to drug therapy [Gelb DJ *et al.* 1999].

To date there is no curative treatment that can stop the progression of the disease; treatment strategies are aimed at controlling the symptoms, without any interference on the course of the disease.

Drug efficacy and symptom control are measured by improvements in validated rating scales: the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr scale (H&Y).

The choice of agent depends on a combination of factors including the relative effectiveness and adverse effect profile of the drugs, patient comorbidities, age, patients' employment status.

The treatment of idiopathic PD with dopaminergic therapy, especially in the early stages, is usually associated with significant improvements in disability. The first few years of pharmacotherapy are often referred to as the "honeymoon phase" because patients experience sustained symptomatic relief [Olanow CW *et al.* 2001]. However, within 2-5 years of dopaminergic therapy, nearly all patients report a decline in the duration of symptomatic benefit during the dosing cycle [Stacy M *et al.* 2007].

Levodopa (L-dopa), the precursor of dopamine, is the first drug with a recognized therapeutic efficacy. It represents the gold standard therapy for motor symptoms. It is given with a dopa decarboxylase inhibitor to reduce the peripheral availability of levodopa and the adverse effects associated with treatment [Fahn S *et al.* 2004].

Prolonged therapy with L-dopa may cause several complications: dyskinesia, fluctuation, reduced response to treatment. The reduction of the response to treatment is related to chronic-degenerative nature of the disease that causes a progressive impairment of the dopaminergic system. The daily fluctuation of the response is instead linked to the term life of the drug, in a variation of the response of dopamine receptors or alteration of intestinal absorption of the drug [Ahlskog JE *et al.* 2001].

Dopamine agonists improve the motor symptoms in early disease and reduce frequency in motor complications. They can be used as an initial treatment in newly diagnosed patients with PD or used as a combination therapy with levodopa.

Dopamine agonists may be classified as ergot derived (bromocriptine, pergolide and cabergoline) or non-ergot derived (apomorphine, primipexole, ropinirole and rotigotine).

Ergot derived are no longer indicated because they are associated with a high risk of moderate to severe cardiac valvulopathy and serosal fibrosis (pleural, pericardial and retroperitoneal).

Non ergot derived are associated with an increase risk of impulse control disorders, daytime somnolence, peripheral oedema, nausea, dizziness, hallucinations [Stowe R *et al.* 2008].

Monoamine oxidase B inhibitors increase the availability of dopamine, provide a significant beneficial symptomatic effect (reduction of motor fluctuations), but do not change the progression of the disease (no evidence for neuroprotective benefit) [Turnbull K *et al.* 2012; Rascol O *et al.* 2011].

Catechol-o-methyl transferase inhibitors (COMT) stop central and/or peripheral enzymatic degradation of dopamine and increase the bioavailability of L-dopa; improve fluctuations (wearing off) and motor complications (mainly dyskinesia), reduce the dosage of L-dopa. The use of COMT may be considered for the reduction in "off" time in patients with advance Parkinson's disease who have motor fluctuation [Parkinson's Study Group 1997; Talati R. *et al.* 2009].

Anticholinergics are used for symptomatic treatment (motor function) but at the expense of neuropsychiatric and cognitive adverse events. Anticholinergics should not be given to patients with comorbidities such as cognitive impairment or clinically significant psychiatric illness [Katzenschlager R *et al.* 2002].

Amantadine stimulates dopamine release and inhibits glutamate neurotransmission. It has a mild effect to improve tremor, rigidity and bradykinesia in early stage PD patients. It tends to lose its efficacy over time. However for late stage PD patients, amantadine can again be used to reduce dyskinesia.

1.1.1 Basal ganglia pathophysiology, neurobiological and neurochemical correlates of cognitive deficits in Parkinson's Disease

Voluntary movement is initiated by cerebral cortex and regulated by complex feedback loops that involve the cortex, thalamus, basal ganglia (caudate, putamen, globus pallidus, subthalamic nucleus and substantia nigra) and cerebellum. The cerebral cortex is the command center of the brain and it sends signals to the striatum (putamen and globus pallidus) by two pathways: direct and indirect.

The direct pathway exits from the putamen to the globus pallidus interna (GPi). The indirect pathway exits from the putamen to the globus pallisus externa (GPe), to the subthalamus nucleus (STN) and then reaches GPi. Neurons in putamen, GPi and GPe use gamma-aminobutyric acid (GABA) as the primary neurotransmitter, which is inhibitory over the postsynaptic neurons. Dopamina (DA) in the substantia nigra regulates the putamen by using different DA receptors to enhance the GABA inhibitory effect on the direct pathway and to attenuate the GABA effect on the indirect pathway. Thus, a decreased DA level will cause disinhibition of STN and GPi and subsequently inhibit output from thalamus to the cerebral cortex, leading to various motor manifestations of parkinsonism, including bradykinesia, rigidity and resting tremor [Gibb 1997].

Moreover, the basal ganglia are involved in two major systems associated with the regulation of emotions, mood, executive functions and behavior:

a) the “limbic” structures with widely distributed brainstem, striatal and paralimbic sites, with rich reciprocal connections to the basal ganglia, in particular between the amygdalae and caudate;

b) five frontosubcortical circuits, linking frontal lobe regions to subcortical structures, including the basal ganglia, and back to frontal lobe areas. In addition to motor and eye movement control, the frontosubcortical circuits subserve key behaviors including executive functioning, motivated behavior and integration of emotional information into contextually appropriate behavior. Thus, the basal ganglia are interpositioned as an interface between internal personal drives (mood and motivation) and behavioral responses to external stimuli.

The clinical diagnosis of PD rests on the identification of the characteristics related to dopamine deficiency that are a consequence of degeneration of the substantia nigra pars compacta. However, non-dopaminergic and non-motor symptoms are sometimes present before diagnosis and almost inevitably emerge with disease progression. Indeed, non-motor symptoms dominate the clinical picture of advanced Parkinson's disease and contribute to severe disability, impaired quality of life, and shortened life expectancy. By contrast with the dopaminergic symptoms of the disease, for which treatment is available, non-motor symptoms are often poorly recognized and inadequately treated [Chaudhuri KR *et al.* 2006].

A variety of non-motor symptoms that lessen the patient's quality of life include psychiatric symptoms (depression, anxiety), autonomic dysfunctions, sleep disturbances, sensory disturbances (especially pain), cognitive impairment and dementia.

Cognitive changes have been reported at all stages of the disease process [Bassett SS. 2006]. Although the cognitive decline reported in early stage PD is subtle and does not often interfere with daily functioning, PD patients have been shown to demonstrate cognitive slowing and executive functioning problems at early stages.

PD-related cognitive deficits in language, visuospatial functioning, long-term memory and executive functioning are greater than what would be expected to occur as a result of normal aging.

A consensus has not been reached on how to define the criteria for PD-related mild cognitive changes. Mild Cognitive Impairment (MCI) is recognized as the intermediate classification that occurs between the cognitive statuses of "within normal limits" to "demented". Individuals with MCI are impaired in one cognitive domain but continue to be independent with their daily functioning (Knopman et al. 2003).

Generally, the cognitive impairment in PD is different from cortical dementia, which is found with Alzheimer's disease. The subcortical dementia found in PD patients encompasses the clinical symptoms of cognitive slowing, impaired attention, memory recall and retrieval, and executive deficits, which arise from dysfunction between subcortical areas (thalamus, striatum) and cortical areas. However about 15% to 30% of demented patients with PD may also have coexisting Alzheimer's disease and reveal symptoms of affected language, memory and visuospatial functioning early in the course of the disease, including the presence of aphasia, agnosia and apraxia [Rippon GA *et al.* 2005; Rajput AH *et al.* 1993].

Cognitive dysfunction in PD may be a consequence of disruption not only in the primary motor circuit, but also in a number of interconnected pathways from the basal ganglia to the cortex. Dopamine depletion in the lateral orbitofrontal and the dorsolateral prefrontal circuits has been suggested as a possible mechanism of cognitive impairment in PD.

Two circuits have been mainly investigated and have been related in cognitive deficits of PD patients [Alexander G *et al.* 1986]:

- “dorsolateral” circuit: the dorsolateral prefrontal cortex, the striatum (dorsolateral caudate nucleus), the globus pallidus (dorsomedial) and the thalamus.
- “orbital” circuit: the orbitofrontal cortex, the striatum (ventromedial caudate nucleus), the globus pallidus (dorsomedial) and the thalamus.

Frontostriatal circuits are involved in executive functions, necessary for an appropriate, contextual goal-directed behavior, allowing us to formulate goals with regard to their consequences, to generate multiple response alternatives, to choose and to initiate appropriate actions, to self-monitor the adequacy and correctness of these actions, to correct and modify them when conditions change and finally to persist in the face of distractions [Miyake *et al.* 2012].

Then, the impairment of executive functions that characterizes most of PD patients from early disease stages is not primarily due to a direct neuropathology of prefrontal cortex, but to reduced dopaminergic striatal stimulation, disrupting the physiological functioning of frontostriatal circuits.

There are three component factors underlying executive functions: inhibition and switching, working memory, and sustained and selective attention. In particular, the dorsolateral prefrontal cortex has been linked to a variety of executive functions, including verbal and design fluency, response inhibition, working memory, organizational skills, maintaining and shifting set, planning, reasoning, problem solving, and abstract thinking. Frontostriatal functioning is vital for the execution of more complex tasks such as decision making, problem solving, behavioral adaptation, everyday social interactions, and management of occupational demands (eg, switching from one task to another). Given the frontostriatal pathology implicated in PD, patients with PD have been found to be impaired on a variety of executive function tasks.

A spatiotemporal difference in dopamine depletion is present within the striatum. In the early clinical stages of PD the dopamine depletion is greatest in the foremost dorsolateral extent of the caudate nucleus, an area involved in the “dorsolateral” circuit. Executive functions related to this frontostriatal circuit include functions of attentional control, such as working memory, set-switching and planning, and are usually impaired from the early stages of PD [Sawamoto *et al.* 2008].

On the contrary, in the early clinical stages of PD the "orbital" circuit and the related executive functions, providing a reward-based control of behavior, are mostly preserved.
With the progression of disease, the dopamine depletion impairs also the orbital circuit, probably resulting in an impairment of related executive functions [Poletti *et al.* 2012].

Temporal and spatial asymmetries of dopamine depletion and their relation with cognition during the progression of the PD-related neuropathology, determine the differential cognitive effects of dopaminergic medication on executive functions in PD. The impairment of executive functions represents the core cognitive feature of PD patients and is clearly related to the nigrostriatal degeneration, as suggested by the correlation between the severity of executive dysfunction and the severity of bradykinesia [Domellof *et al.* 2011].
Deficits may involve other cognitive functions at an early stage, such as memory, language and visuospatial functions [Muslimovic *et al.* 2005]: these deficits are probably due not only to the indirect effect of executive dysfunction on them, but also to an early cortical neuropathological involvement of posterior regions. With the neuropathological progression of the disease, the widespread cortical diffusion of Lewy bodies [Braak *et al*. 2003] produces a more severe cognitive impairment, involving several cognitive functions, and often leading to dementia.

Dopaminergic deficit represents the most studied characteristic in PD. Therefore, it was initially proposed that the neurochemical basis of cognitive disorders associated with PD was only related to subcortical dopaminergic deficit. Afterwards, a more detailed analysis of cognitive-motor symptoms showed that cognitive dysfunction can be also associated with the degeneration of non-dopaminergic systems (Pillon et al. 1989) such as the cholinergic, noradrenergic, serotoninergic system. In particular, it has been proposed a model (Fig. 1) in which every single neurotransmitter deficiency is associated with a particular cognitive-behavioral symptom (Emre et al., 2003).

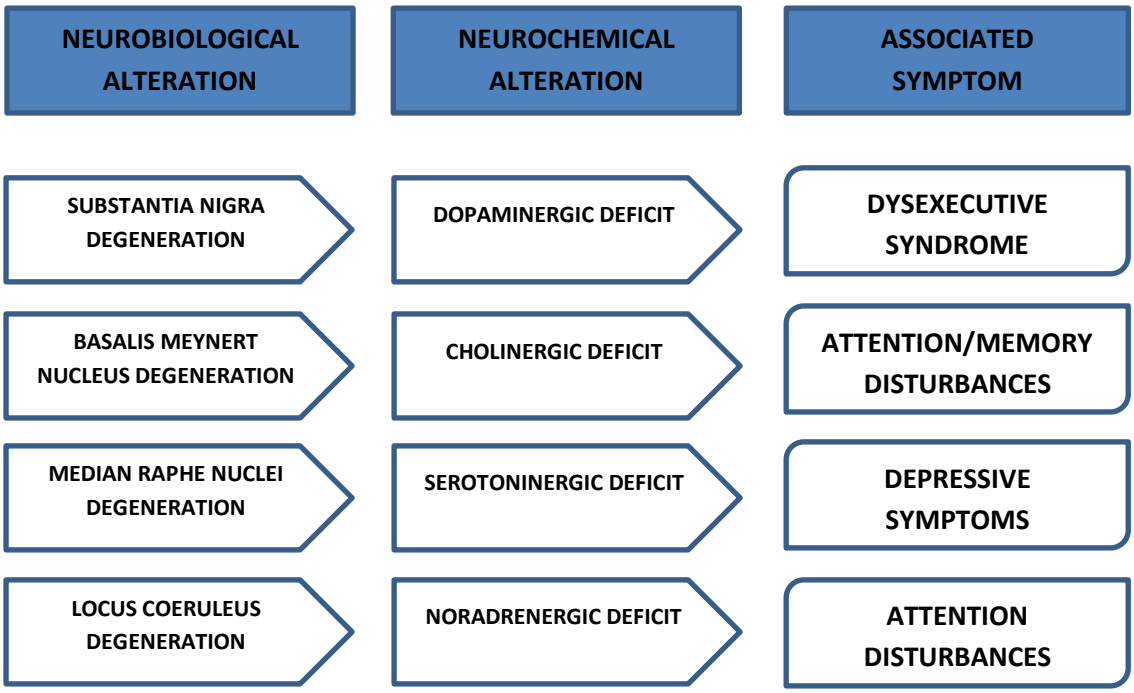

Fig. 1 **The "parallel model".** All the described neurochemical deficits in dopaminergic, cholinergic, noradrenergic and serotonergic systems contribute to the pathogenesis of cognitive disorders associated with PD. In particular, the model assumes that each neurotransmitter deficit is associated with a particular cognitive and behavioral symptom.

1.1.2 Cognitive impairments and EEG changes associated with Parkinson's Disease

The most characteristic and frequent cognitive disorder in PD is bradyphrenia that becomes manifest with loss of concentration and generalized slowing of thought processes. Characteristic of the frontal lobes dysfunction are the alterations in attention functions, very frequent in PD patients. Attention is not a unitary concept. Several more or less independent types (eg, simple, selective, divided, shifting) have been identified.

Attentional deficit can be completely or partially responsible for observed impairment in working memory, learning, retention, perception, and problem solving (Lezak 1995) and most of the cognitive disorders described in the PD seem to be related to an increase in the reaction time.

Several studies demonstrate a robust relationship between cognitive status and brain rhythms in PD (Caviness et al. 2007).

In fact, attentional disorders and bradyphrenia are inferred from the typical electroencephalographic feature of PD which contains abnormally lower frequencies.

Even in the absence of a frank dementia, a slowdown in cerebral signal is observed regardless of disease duration and severity of motor symptoms (Stoffers et al. 2007).

Some studies propose the quantitative EEG (QEEG) as biomarker for cognitive decline since the prevalence of slow-waves and the decrease in rapid-waves would be observed even in presence of initial cognitive disorders (Caviness et al. 2007).

Caviness et al. demonstrate a correlation between longitudinal changes in frequency domain quantitative electroencephalography (QEEG) measures and change in neuropsychological performance testing in PD. In particular, changes in delta bandpower showed the highest and most consistent pattern of correlations with longitudinal changes in neuropsychological testing. The highest correlation was between delta bandpower increase and decline in the Rey Auditory-Verbal Learning Test. Delta bandpower was also correlated with the incidence of dementia. These results constitute preliminary evidence that delta bandpower may be a suitable biomarker for evaluating PD cognitive deterioration longitudinally (Caviness et al. 2015).

In patients with PD, a low background rhythm (characterized by the predominance of slow rhythms, <8.5 Hz) points to a risk of developing dementia 13 times higher than a faster background rhythm (Klassen et al. 2011).

In addition, the incidence of dementia seems to be significantly correlated with the presence of an increased power of theta waves (Klassen et al. 2011).

PD patients have an excess of theta waves associated with internal focus and drowsiness and not enough beta activity associated with external focus, alertness and concentration.

During a cognitive activity, a sudden manifestation of slow waves may indicate that the individual is diverting attention from the task, as frequently happens in the PD patient who tends to be easily attracted by irrelevant aspects of the environment.

There are multiple possible physiological explanations for EEG changes that correlate with the cognitive status in PD, but the precise circuitry defects responsible for these changes are unknown. The different frequency bands have had various normal functions and anatomical correlates proposed. Alpha rhythm is a normal EEG activity generated by thalamocortical

and local corticocortical circuits. However, those systems may in turn be affected by other connections with other neuronal circuits. Beta rhythms, whether diffuse or focal, are thought to represent primarily neocortical activity. From a functional point of view, evidence shows that beta activity reflects cognitive processes and correlates with regional cerebral blood flow. Thus, the normal alpha and beta rhythms both depend on intact neocortical function and associated circuits. An increase in theta and delta activity is believed to represent dysfunction in diffuse gray matter areas in both cortical and subcortical areas as well as partial deafferentation of cerebral cortex. In PD, abnormalities in both diffusely projecting systems and intrinsic cortical circuits have been implicated to cause cognitive decline. (Caviness et al. 2007).

Neurofeedback protocol in PD patients would involve training to reduce the excess in theta/lower alpha waves during attention task, responsible of mind-wandering, enhancing beta activities.

1.1.3 Implications of pharmacological and rehabilitation therapies on cognitive functions

Pharmacological therapy

The gold standard in drug therapy of Parkinson's disease is the administration of levodopa and/or dopamine agonists. Motor symptoms show a good response to the therapy. Non-motor symptoms, especially the cognitive ones, do not seem to adequately respond to drug treatment.

Specifically, a review of last year on the cognitive acute and chronic effects of levodopa and dopamine agonists' administration reports an improvement of executive functions in the first 6 months of therapy. Such effects are gradually reduced until a return to the baseline of test scores after the first year of therapy (Poletti et al. 2013).

Although the depletion of dopamine is the key neurochemical impairment in PD and anticholinergic medications are used for symptomatic treatment, significant deficits in cholinergic transmission are also present and have been associated with cognitive decline and gait dysfunction. Therefore, use of a cholinesterase inhibitor (ChI) might improve

cognitive function and reduce the risk of falls in patients with PD, although it could plausibly worsen motor features.

A recent systematic review (Pagano et al. 2014) reports that ChIs are effective in the treatment of cognitive impairment in patients with PD, but do not affect the risk of falling and suggests that the choice of treatment has to be balanced considering the increased tremor and adverse drug reactions.

Cognitive rehabilitation

The interest in training programs designed to improve cognitive abilities in adults neurological patients is exponentially growing. Ample evidence now suggests cognitive training interventions can improve cognitive performance (Ball et al. 2002).

Cognitive rehabilitation is a behavioral treatment approach for individuals with cognitive dysfunction, designed to reduce functional impairment and increase engagement in daily adaptive activities. Originally developed to improve cognitive functioning after traumatic brain injury (TBI), cognitive rehabilitation programs have recently been adapted for other neurological conditions. However, there are no standardized guidelines that would guide application in PD regarding the types of strategies that offer the most beneficial outcomes, or the types of cognitive impairments or stages of cognitive decline for which treatment is most beneficial.

Although there is variation across programs, the essential elements of cognitive rehabilitation consist of basic skills training related to performance of vocational, social, and adaptive daily living skills. Subsets of cognitive training programs target improvements in specific cognitive domains, including visual-spatial awareness, attention, working memory or executive functioning, which are the essential cognitive skills to complete daily living tasks. Cognitive rehabilitation strategies consist of restorative or compensatory techniques. Restorative techniques focus on strategies to improve cognitive functioning, getting closer the patient to his level before the decline. Specific restorative skills include techniques to improve recall of information over increasing periods of time (spaced retrieval) or using less intense cues (vanishing cues), computerized drills and repeated prompting to improve memory and attention and recall of remote memories (reminiscence therapy).

Compensatory techniques provide strategies that organize information to improve recall and learning and provide instruction in self-management strategies. Compensatory techniques also include using multiple senses to improve learning and retrieval, procedural training to learn increasingly more complex behaviors, and external cues such as memory notebooks or calendars to improve recall. Programs may also teach, in-person or with the aid of computerized devices and software, strategies to improve self-management, such as problem solving, time management, and compensation for impaired memory (Schutz et al. 2007).

According to a review (Calleo et al. 2012) on the effectiveness of cognitive rehabilitation in Parkinson's disease, this behavioural approach improves and maintains cognitive skills and increases the quality of life. Because PD involves progressive heterogeneous physical, neurological, and affective difficulties, the review underlines the need of further cognitive rehabilitation programs, which aim at flexibility and individualization, according to each patient's strengths and deficits.

1.2 Overview of Neurofeedback

Biofeedback (BF) is a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance. Precise instruments measure physiological activity such as heart function, breathing, muscle activity, skin temperature. These instruments rapidly and accurately "feed back" information to the user. The presentation of this information — often in conjunction with changes in thinking, emotions, and behavior — supports desired physiological changes. Over time, these changes can endure without continued use of an instrument.

The term 'bio-signal' is defined as any signal measured and monitored from a biological being, although it is commonly used to refer to a bio-electrical signals, a current generated by electrical potential differences across a tissue, organ or cell system.

Typical bio-electrical signals are ECG (Electrocardiogram), EMG (Electromyogram) and EOG (Electroculogram).

‘Neuro-signal’ refers to a signal related to the brain. The Electroencephalograph (EEG) is a common approach to obtain, measure and record neuro-signals information using electrodes placed on the scalp.

EEG-biofeedback, so called Neurofeedback (NF), like other forms of BF, uses monitoring devices to provide moment-to-moment information to an individual on the state of his physiological functioning, with a focus on the central nervous system and the brain. Neurofeedback training (NFT) has its foundations in basic and applied neuroscience as well as data-based clinical practice. It takes into account behavioral, cognitive, and subjective aspects as well as brain activity.

NFT is preceded by an objective assessment of brain activity and/or psychological-cognitive status. During training, sensors are placed on the scalp and then connected to sensitive electronics and computer software that detects, amplifies, and records specific brain activity. Resulting information is fed back to the patient virtually instantaneously with the conceptual understanding that changes in the feedback signal indicate whether or not the patient's brain activity is within the designated range. Based on this feedback, various principles of learning, and therapist guidance, changes in brain patterns occur which are associated with positive changes in physical, emotional and cognitive states. Often the patient is not consciously aware of the mechanisms by which such changes are accomplished although people routinely acquire a "felt sense" of these positive changes and often are able to access these states outside the feedback session.

NFT does not involve either surgery or medication and is neither painful nor embarassing. When provided by a professional with appropriate training, generally patients do not experience negative side-effects. Typically patients find NFT to be an interesting experience. Neurofeedback operates at a brain functional level and transcends the need to classify using existing diagnostic categories. It modulates the brain activity at the level of the neuronal dynamics of excitation and inhibition which underly the characteristic effects that are reported.

Neurofeedback addresses several problems of brain disregulation. Research demonstrates that Neurofeedback is an effective intervention for ADHD (Holtmann et al. 2014) and epilepsy (Nagai, 2014). Ongoing research is investigating the effectiveness of neurofeedback

for other disorders such as anxiety-depression spectrum, attention deficits, behavior disorders, various sleep disorders, headaches and migraines, emotional disturbances and it is promising. It is also useful for organic brain conditions such as the autism spectrum, cerebral palsy, Traumatic Brain Injury.

Being a self-regulation method, NFT differs from other accepted research-consistent neuro-modulatory approaches such as audio-visual entrainment (AVE) and repetitive transcranial magnetic stimulation (rTMS) that provoke an automatic brain response by presenting a specific signal. Nor is NFT based on deliberate changes in breathing patterns such as respiratory sinus arrhythmia (RSA) that can result in changes in brain waves. At a neuronal level, NFT teaches the brain to modulate excitatory and inhibitory patterns of specific neuronal assemblies and pathways based upon the details of the sensor placement and the feedback algorithms used thereby increasing flexibility and self-regulation of relaxation and activation patterns. The NF system is able to process and, at the same time, feed back to the user the information on his brain activity, displayed from moment to moment, together with the effectiveness of the mental strategy implemented in order to obtain the required modulation, thus allowing a reinforcement in case of success or a revision in case of failure.

Neurofeedback has a direct impact on a central cognitive-control network that can be remodeled through neuroplasticity. Satisfactory results have already been observed after 15 training sessions however usually 40-60 sessions have to be performed (ISNR guidelines).

1.3 Objective

This study aims to investigate the possible effect of specific Neurofeedback techniques on cognitive performance (particularly attentive) of patients with idiopathic PD and their impact on daily activities, in terms of changes in scores at the neurocognitive assessment. Furthermore, the study aims to make a comparison between the effectiveness of Neurofeedback training and conventional cognitive rehabilitation techniques, evaluating neurocognitive scores changes and degree of satisfaction.

2. MATERIALS AND METHODS

2.1 Subjects

Subjects in the present study were enrolled in the Giovanni Paolo Secondo Rehabilitation Center. The Giovanni Paolo Secondo Rehabilitation Center approved all procedures and written informed consent was obtained by participants.

In order to evaluate the feasibility and adherence of patients to the treatment, the study was initially addressed to eight patients suffering from four neurological diseases (two patients for each disease) characterized by attention disorders: multiple sclerosis, Parkinson's disease, cerebrovascular insult, cerebellar ataxia. Patients were cognitive evaluated before ad after performing five sessions of NF training. Patients suffering from Parkinson's disease were those who appeared more motivated and showed a rapid response to treatment as shown in Fig 2.

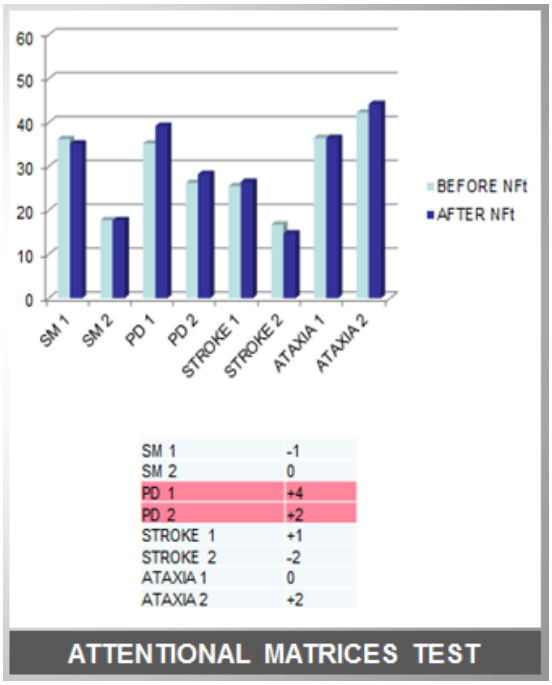

Fig. 2 Variation of Attentional Matrices scores after 5 sessions of NF training. Be noted an increase in the score in both PD patients.

For the study, out of 35 examined patients affected by idiopathic PD (according to the criteria of the Parkinson's Disease Society Brain Bank), parkinsonism excluded, 20 were recruited, staged according to the Hoehn & Yahr (H&Y) scale and previously cognitively evaluated using an assessment protocol that was completed with scales of cognitive-related errors in daily activities.

Patients were selected according to the following inclusion criteria: aged from 55 to 85, intact or correct auditory and visual functions, phase on of dopaminergic therapy, mild cognitive impairment (MMSE>18). Patients with previous cerebrovascular insults, psychosis, severe dyskinesia were excluded from the study. Considered the pharmacological effects on cognitive functions (Poletti et al. 2013 - Pagano et al. 2014), patients taking dopaminergic drugs for less than one year and patients taking ChIs were also excluded.

The sample was divided into two groups of 10 patients homogeneous for age, education level, cognitive impairment and disease severity, randomized to the experimental protocol (NF training) and to the traditional protocol (conventional cognitive training).

Cognitive rehabilitation and Neurofeedback training was provided by an health professional (speech and language therapist specialized in neurocognitive rehabilitation of adult patients).

The experimental protocol consists of 2 weekly sessions of 40 minutes each (30 minutes NF Attention Training/10 minutes muscle relaxation).

The traditional protocol consists of 2 weekly sessions of 40 minutes each (30 minutes conventional cognitive training /10 minutes muscle relaxation).

It is necessary to act on muscular de-tension since it was observed that in PD patients attention training causes an increase in rigidity (Dan A. Mendonca, S. Mandar Jog, 2008).

The rehabilitation program has planned, in both group, 24 sessions of training.

T0 → cognitive assessment (baseline)

NF group: 24 sessions of NF Attention Training

Control group: 24 sessions of Computerized cognitive conventional training

T1 → cognitive re-assessment (after 3 months of training)

T2 → follow-up cognitive assessment (4 months after the end of the training)

2.2 Cognitive assessment

The following tests were used to investigate the cognitive functions before and after the treatment in order to evaluate the effects of rehabilitation.

The *Stroop test* is one of the most widely employed measures of visual selective attention and inhibitory control. The test consists of three sets of stimuli: colour words printed in black ink, colour patches, and colour word printed in incongruous coloured ink. The patient must read the colour words on the first sheet, the colours on the second sheet, and the colour of the ink (not the words) on the third sheet. In the latter task, the normal tendency to read the words, rather than the colour of the ink in which the words are printed, elicits a significant slowing in reaction time called the "Stroop effect" or "interference effect".

The *Trail Making Test* part A was used to evaluate visual attention and visual-spatial exploration. The *Trail Making Test* part B requires the patient to alternate between a series of numbers and letters in order and it was used to evaluate cognitive flexibility and set-shifting. This test requires intact visual tracking and visuomotor integration for optimal performance.

Attentional processes currently are evaluated by a variety of examination procedures, such as cancellation tests in which the patient marks only designated target letters interspersed with other non-target letters or distractor items in lengthy sequences (*Attentional Matrices*).

The *Rey Auditory Verbal Learning Test* (RAVLT) was used to evaluate a wide diversity of functions: short-term auditory-verbal memory, rate of learning, learning strategies, retention of information and differences between learning and retrieval.

Phonemic verbal fluency tests was used to assess the production of words beginning with specific letters. Of these letters, the most frequently used are F, A and S. It is a sensitive test for assessing frontal lobe functions.

The *Frontal Assessment Battery* (*FAB*) is a brief battery of six neuropsychological tasks designed to perform a screening on frontal lobe function. The six FAB tasks explore cognitive and behavioral domains that are thought to be under the control of the frontal lobes, most notably conceptualization and abstract reasoning, lexical verbal fluency and mental

flexibility, motor programming and executive control of action, self-regulation and resistance to interference, inhibitory control, and environmental autonomy.

Raven's coloured progressive matrices PM47 was used to assess intellectual skills that do not depend on verbal skills: logical-deductive abilities and abstract reasoning.

The *Attention-Related Cognitive Errors Scale* (ARCES) is a measure of everyday mistakes that people make as a result of not paying sufficient attention to the task at hand and was used to evaluate the impact of attention disorders on daily activities.

2.3 Neurofeedback training

Most of Brain Computer Interfaces (BCI) are of limited use partly due to their size and complexity. However, a new generation of consumer-oriented BCI has appeared for the video game industry and is exploited for clinical and research purposes.

The Neurosky (NS) headset is a simple device consisting of a single active electrode able to capture faint electrical signals generated by neural activity. The electrical signal across the electrode is measured to determine levels of attention (based on Alpha waveforms) and then translated into binary data. NS headset is useful to define a model of attention. Researches suggest that the NS device provides accurate readings regarding attention, with a positive correlation between measured and self-reported attention levels (Rebolledo-Mendez et al. 2009).

Starting from these remarks, the study planned the use of the NeuroSky MindWave headset and the related software for Neurofeedback training. The device consists of a small single-point dry electrode to be placed on the patient's forehead, in FP1 position, the area underlying the anterior frontal cortex, electively involved in the control of attentional processes and executive functioning. The reference electrode is to be placed on the ipsilateral ear lobe.

Because of volume conduction (the ability to measure electrical potentials at a distance from their source generators), single channels, irrespective of where they are placed on the scalp,

are able to capture a large fraction of the entire brain's dynamics. The forehead is a convenient location for placing a single contact sensor; it avoids the problem of achieving a good connection through hair, and it is over the frontal cortex where cognitive signals linked to higher states of consciousness originate. The headset has noise filters in place in order to ensure any noise (head movements, muscle artifacts etc.) is filtered out of the raw EEG.

In the experimental group, training requires that the patient takes a seat in front of a computer screen, puts on his head the MindWave headset and then starts a NeuroSky software for Neurofeedback training. Through specific graphic visualizations, the program returns to the patient the information on his level of attention, on the basis of EEG activation.
This visualization may be in the form of a video game or simple bars or graphics (fig. 3 - 4) that changes in time and represents the power of the brain waves designed to increase or decrease, depending on the achieved attentional level. The patient is asked to 'make an effort' in increasing the height of a specific bar or in order to complete the video game.

The Neurosky MindWave has the potential not only to record brainwave activity, but also to differentiate between mental states. The system is able to output two custom measures: "Attention" values, which indicate the patient's level of mental focus, and "Relaxation" values, which indicate the level of patient's mental calmness.
During Neurofeedback training, the patient was instructed to generate two different mental states, one in the thirty minutes attention session and the other in the ten minutes relaxation session.
During the "Attention" session, the patient was instructed to engage in concentration exercise (Fig. 3). After this activation, during the "Relaxation" session, the patient was instructed to imagine their breath coming in and out of his chest to promote a relaxed and meditative state of mind (Fig. 4) and a muscle detension.
The difference between the two states is clearly visible.

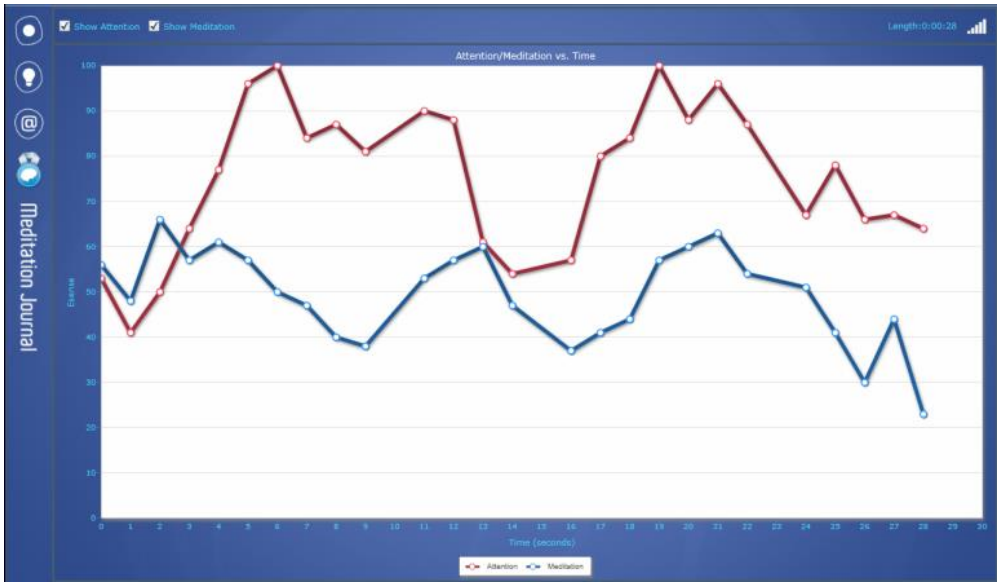

Fig. 3 **Example of Attention session exercise**: to note the increase in attentional levels during training

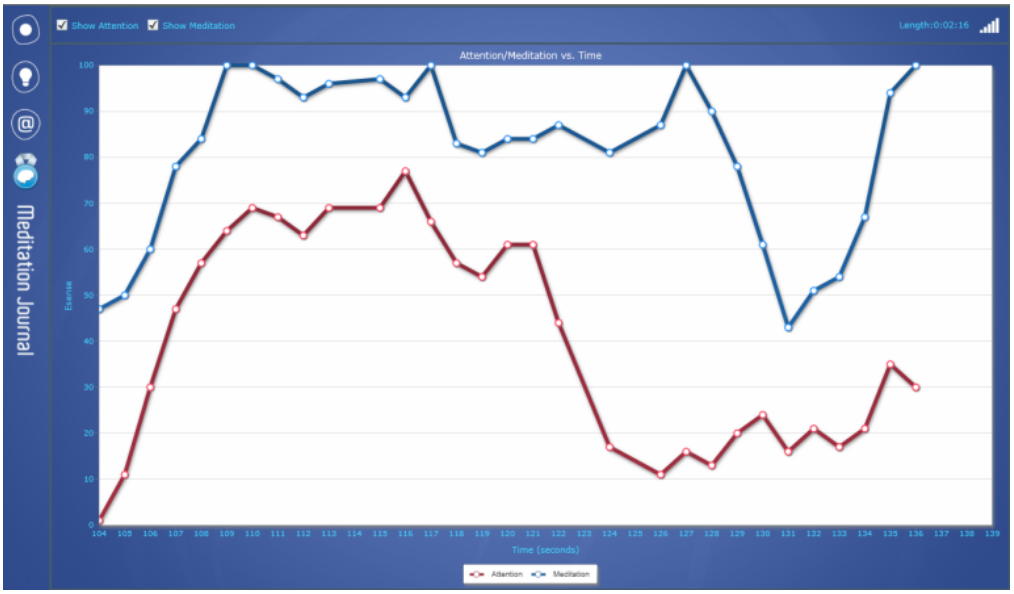

Fig. 4 **Relaxation session exercise**: to note the increase in relaxation levels during training

The headset reads attention levels in an arbitrary scale ranging from 0 to 100. There is an initial delay of between 7 and 10 seconds before the first value reaches the computer. The model of attention not only determines (detects) attention patterns but also provides (reacts) feedback to the patients. When trying to influence their state of mind, patients receive direct feedback whether they are succeeding or not. So, the software enables

patients to train their attention (or relaxation) levels. This is one of the basic principles of Neurofeedback: during different trials patients learn how to train successfully.

2.3 Cognitive training

In order to avoid the influence of the computer itself on the evaluation of Neurofeedback training effectiveness, the control group was not submitted to cognitive paper-pencil exercises but to a computerized cognitive training (e.g., Neurosky neurofeedback-free Applications).

The computerized training targeted a single cognitive domain, the attention, trough classic cognitive training tasks.

Specific aspects of attention was trained such as processing speed (the ability to quickly process information), reaction time (the amount of time needed to process and respond to a stimulus), selective attention (the process by which an individual directs or focuses on specific auditory or visual stimuli in the environment).

In the control group, training requires that the patient takes a seat in front of a computer screen and then performs cognitive exercises for thirty minutes.

After this attention session, patients underwent muscle detension through breathing exercises and relaxation techniques for ten minutes.

2.4 Statistical analysis

Quantitative variables were summarized as mean and standard deviation. As data were normally distributed, comparisons between means have been performed through student t-test for paired or independent data as appropriate. Data non normally distributed has been described using median and interquartile range and analyzed through Wilcoxon test for paired or independent groups as appropriate.

Treatment efficacy have been evaluated through an ANOVA model with a factor between subject (treatment) and a factor within subject (before-after the treatment). The interaction term has also been considered in the analysis.

The ratio between the difference of score before minus score after, divided the score before, has been considered the indicator of patients improvement. To detect which test has the best improvement after treatment, a multivariate analysis of variance has been performed with as dependent variables all tests and independent variable the treatment group. Post-hoc comparison has been made with t-test, and p-value for reject null hypothesis, accounting for multiplicity, have been adjusted according to FDR (False Discovery Rate).

All analysis have been performed with SAS Software V 9.4 for PC. Significance level have been stated as $p<0.05$, except for multiple comparison (FDR correct).

3. RESULTS

Main characteristics of study sample are shown in table 1.

Male were 90% (9/10) in Neurofeedback (NF) group and 80% (8/2) in control group. Mean (SD) age was 68.3 (6.9) in NF group vs 67.4 in control group. The difference for gender and age didn't result statistically significant.

The average time since diagnosis was 6.4 (3) years in NF group and 8.6 (5.4) in control group, the difference did not came out as statistically significant.

Mean MMSE score in NF group resulted 24.3(4) and in control group was 25.5 (3.6), the slight difference did not result significantly different.

The median (Interquartile range) Level of education, assessed as school years, in NF group was 10.5 (5-13) and in controls was 8 (5-13), without statistically significant difference.

The median level of disease severity, assessed through the Hoehn and Yahr scale, resulted in NF group 2 (2-4) and in control group 2.5 (2-2.5).

		Groups			
		Neurofeedback (n=10)		Control (n=10)	
		n	**%**	**n**	**%**
Sex	**M**	9	90%	8	80%
	F	1	10%	2	20%
		mean	sd	mean	sd
Age		68,3	6,9	67,4	6,0
Time since dg		6,4	3,0	8,6	5,4
MMSE		24,3	4	25,5	3,6
		median	interquartile	median	interquartile
Education		10,5	5 - 13	8	5 - 13
H&Y		2	2 - 4	2,5	2 - 2,5

*: chi-square test
§: t-test
@: wilcoxon test

Table 1. Main characteristics of study sample

In the ARCES, mean values decrease significantly (p<0.0001) in both groups (Fig. 1). In NF group falls from 39.5(7.4) before treatment to 30.4 (6.3) after treatment. The same trend was observed in control group: 36.8(7.1) to 29.4(5.9). There was no statistically significant difference between group (p=0.537).

In the TMT_A, mean values decrease significantly (p<0.0001) in both groups (Fig. 2). In NF group falls from 82.5(47.3) before treatment to 51.8(34.1) after treatment. The same trend was observed in control group: 88.1(35.4) to 52.5(34.5). There was no statistically significant difference between group (p=0.8488).

In the TMT_B, mean values decrease significantly (p<0.0001) in both groups (Fig. 3). In NF group falls from 520,5(336.7) before treatment to 341.2(269.5) after treatment. The same trend was observed in control group: 520.5(381.9) to 316,9(287,6). There was no statistically significant difference between group (p= 0,9314).

In the STROOP_E, mean values decrease significantly (p=0,0012) in both groups (Fig. 4). In NF group falls from 3,9(3,2) before treatment to 0,5(1,5) after treatment. The same trend was observed in control group: 4,1(3,5) to 2,2(1,8). There was no statistically significant difference between group (p= 0,3364).

In the STROOP_T, mean values decrease significantly (p<0,0001) in both groups (Fig. 5). In NF group falls from 36,6(17,3) before treatment to 23,7(13,3) after treatment. The same trend was observed in control group: 34,03(12,8) to 25,2(11,2). There was no statistically significant difference between group (p= 0,933).

In the RAVLT_IR, mean values increase significantly (p<0,0001) in both groups (Fig. 6). In NF group raises from 37,1(11,3) before treatment to 44,3(10,7) after treatment. The same trend was observed in control group: 38,3(9,3) to 43,2(8,4). There was no statistically significant difference between group (p= 0,9911).

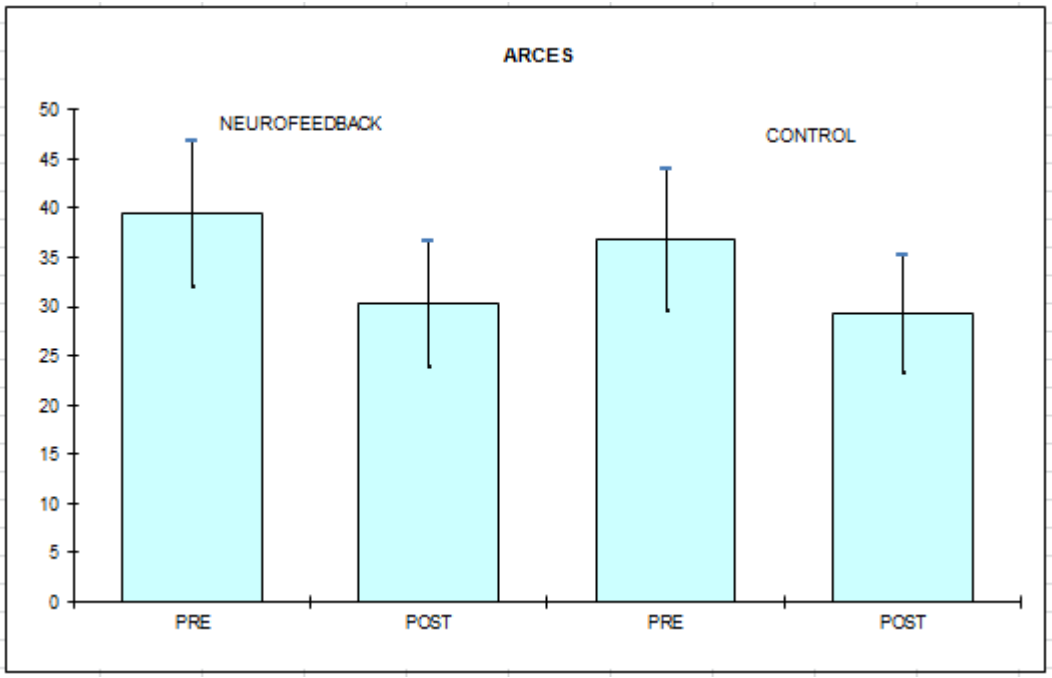

Figure 1: mean and standard deviation of ARCES, before and after treatment, compared between NF and control groups.

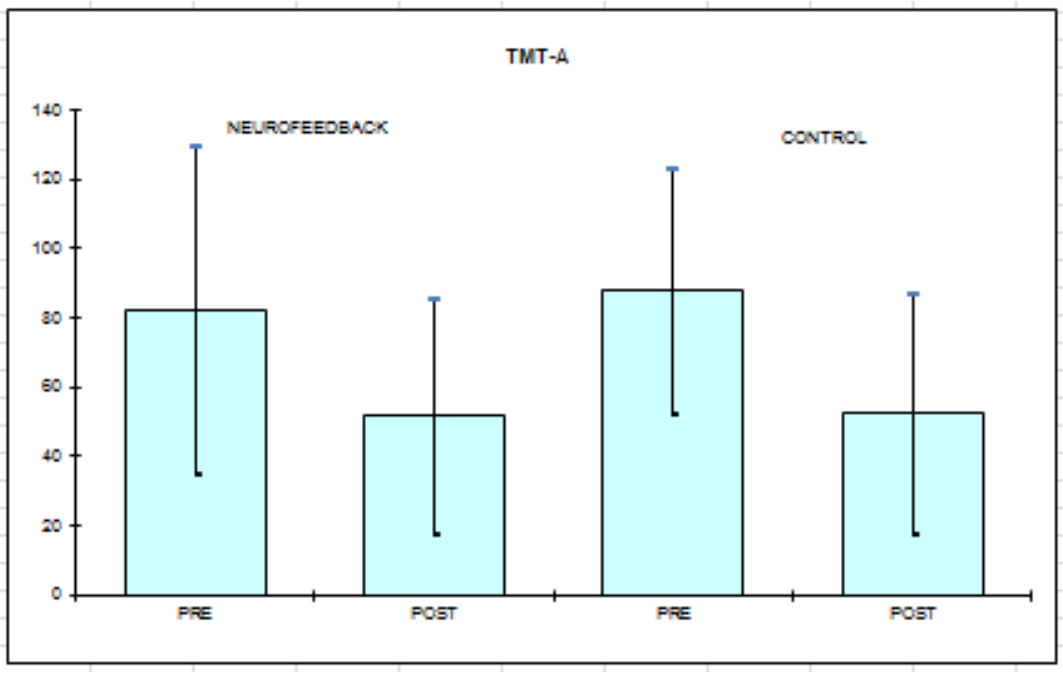

Figure 2: mean and standard deviation of TMT-A, before and after treatment, compared between NF and control groups.

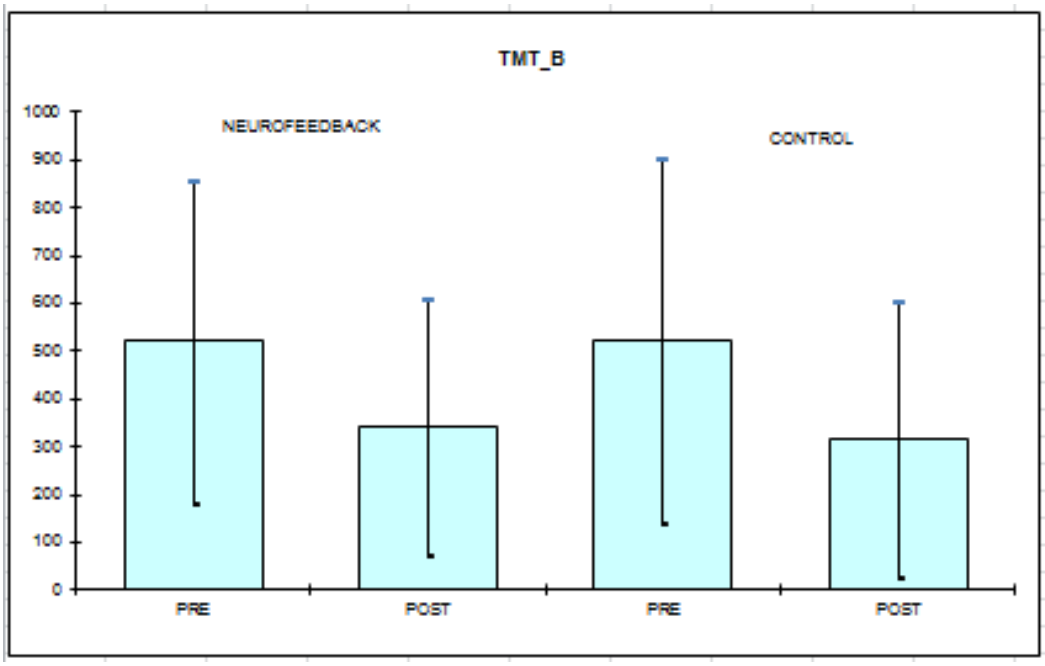

Figure 3: mean and standard deviation of TMT-B, before and after treatment, compared between NF and control groups.

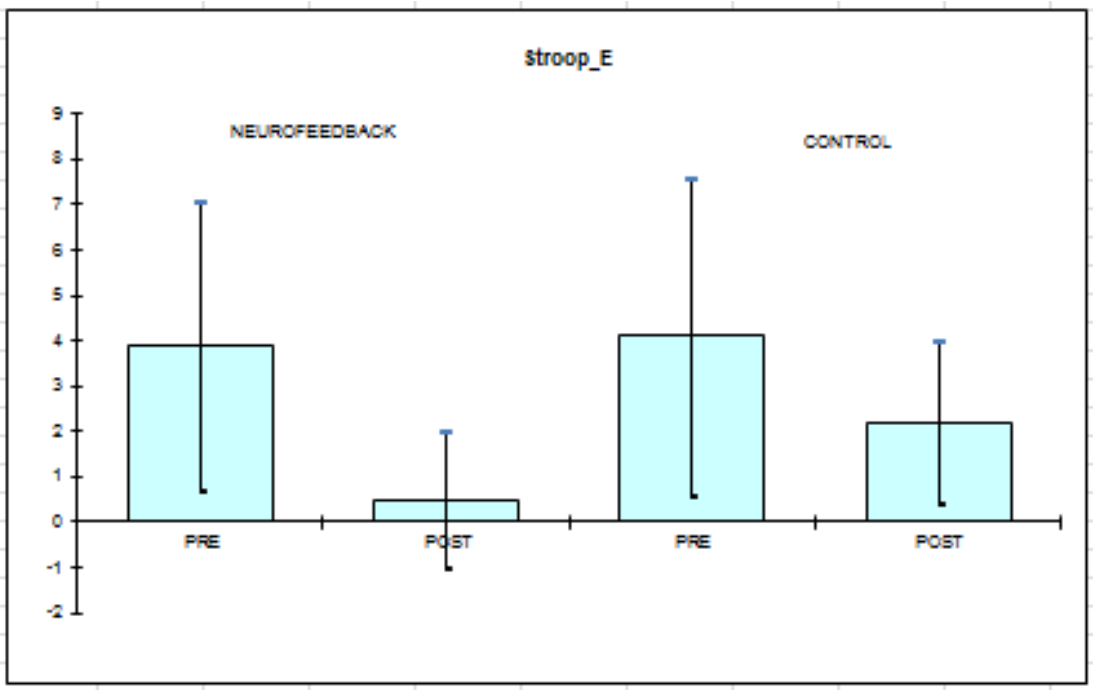

Figure 4: mean and standard deviation of STROOP_E, before and after treatment, compared between NF and control groups.

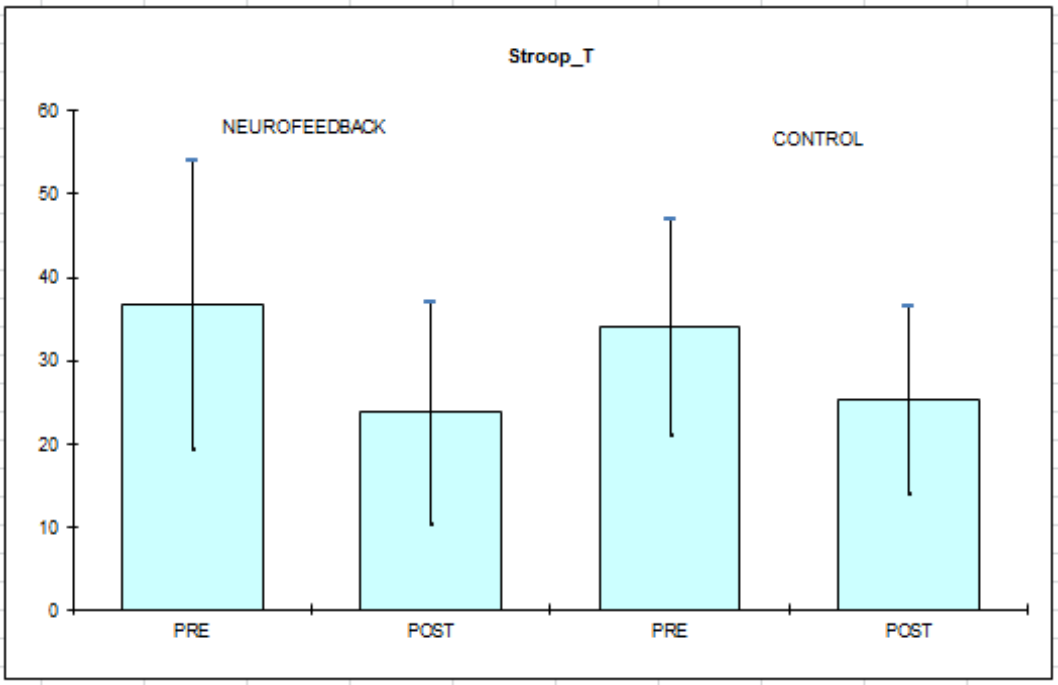

Figure 5: mean and standard deviation of STROOP_T, before and after treatment, compared between NF and control groups.

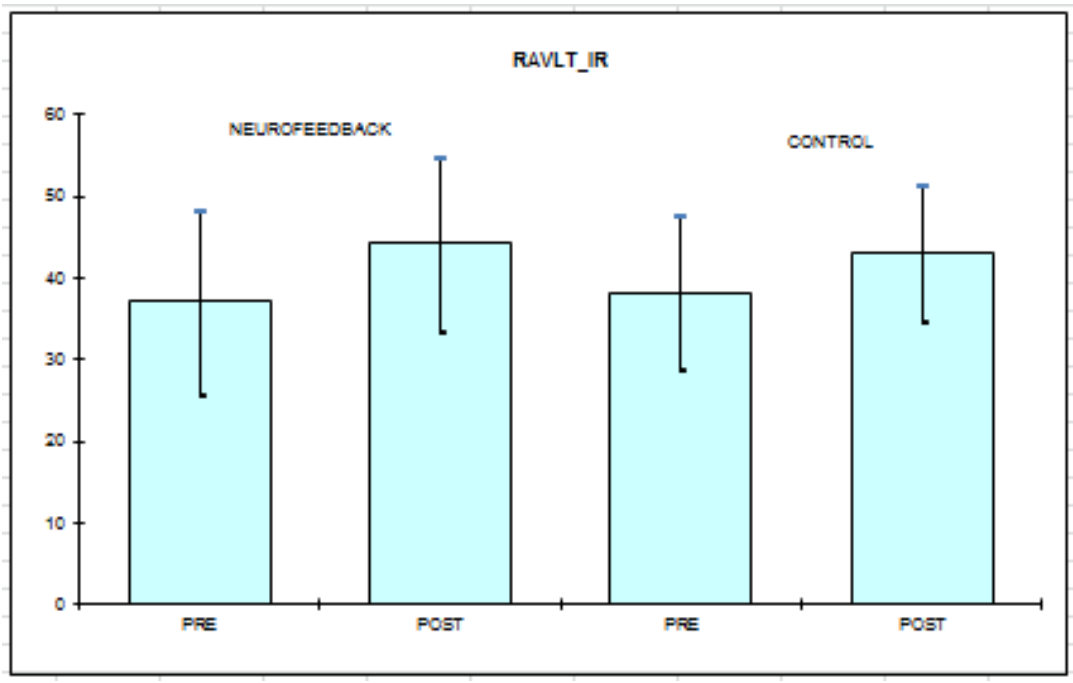

Figure 6: mean and standard deviation of RAVLT_IR, before and after treatment, compared between NF and control groups.

In the RAVLT_DR, mean values increase significantly (p<0,0001) in both groups (Fig. 7). In NF group raises from 8,34(3,5) before treatment to 10,3(3,4) after treatment. The same trend was observed in control group: 7,7(2,9) to 9,8(3,3). There was no statistically significant difference between group (p= 0,6922).

In the FAS, mean values increase significantly (p=0,0009) in both groups (Fig. 8). In NF group raises from 30,2(8,9) before treatment to 32,8(8,1) after treatment. The same trend was observed in control group: 31,4(12,3) to 33,4(12,5). There was no statistically significant difference between group (p= 0,8495).

In the FAB, mean values increase significantly (p=0,0009) in both groups (Fig. 9). In NF group raises from 12,9(3,7) before treatment to 14,5(2,7) after treatment. The same trend was observed in control group: 13,4(3,3) to 15,7(2,8). There was no statistically significant difference between group (p=0,5426).

In the CPM Raven 47, mean values increase significantly (p <0,0001) in both groups (Fig. 10). In NF group raises from 25,9(6,1) before treatment to 29,5(4,1) after treatment. The same trend was observed in control group: 26,9(6,1) to 29,9(5,1). There was no statistically significant difference between group (p= 0,7465).

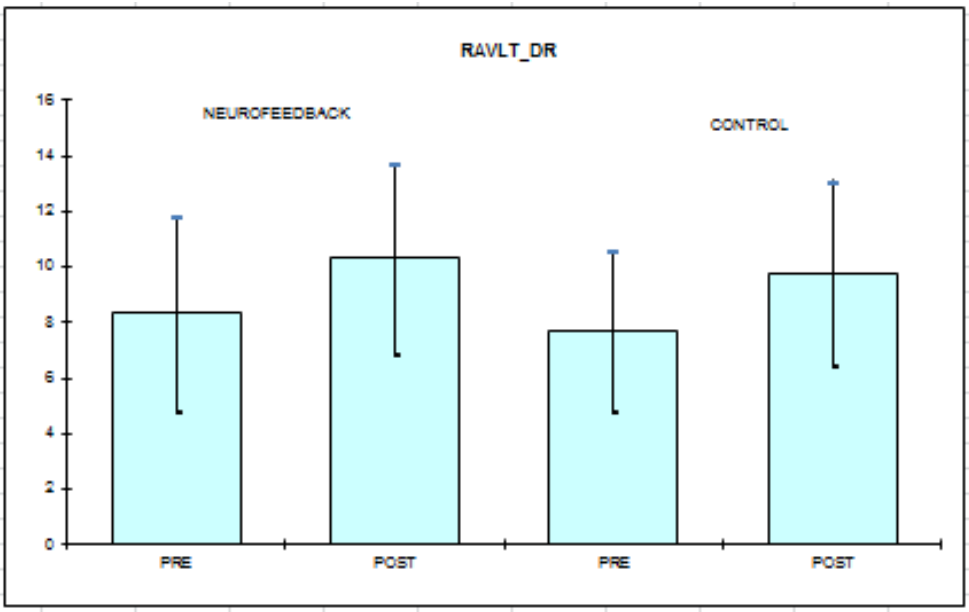

Figure 7: mean and standard deviation of RAVLT_DR, before and after treatment, compared between NF and control groups.

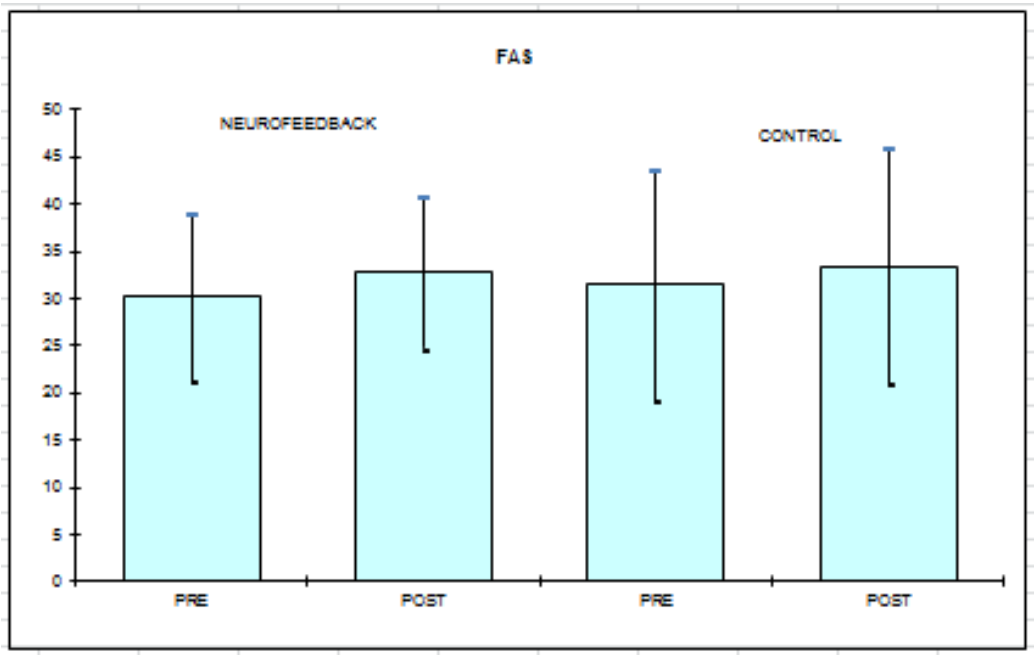

Figure 8: mean and standard deviation of FAS, before and after treatment, compared between NF and control groups.

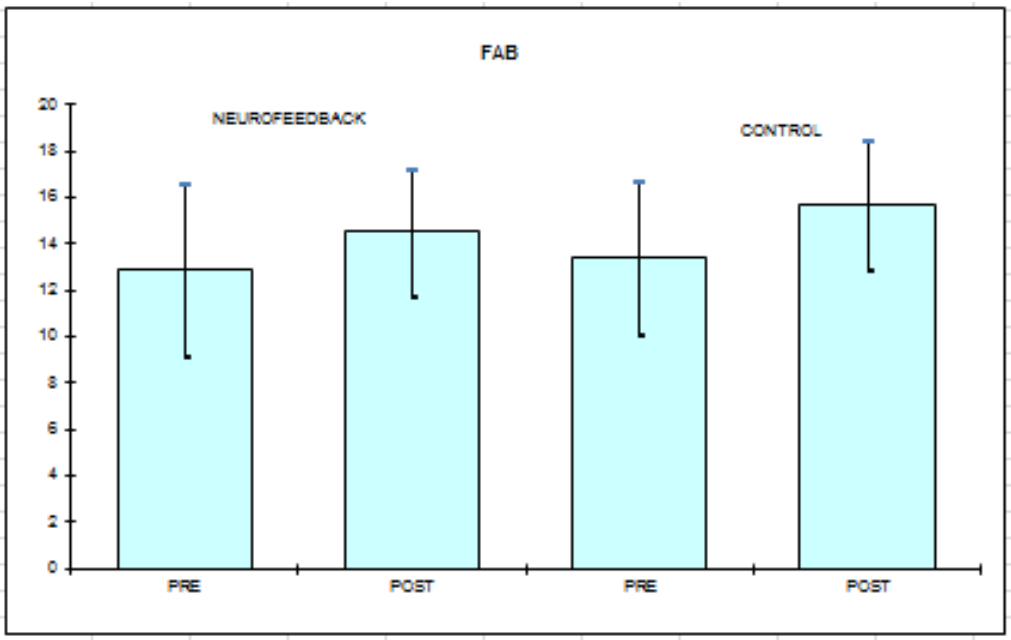

Figure 9: mean and standard deviation of FAB, before and after treatment, compared between NF and control groups.

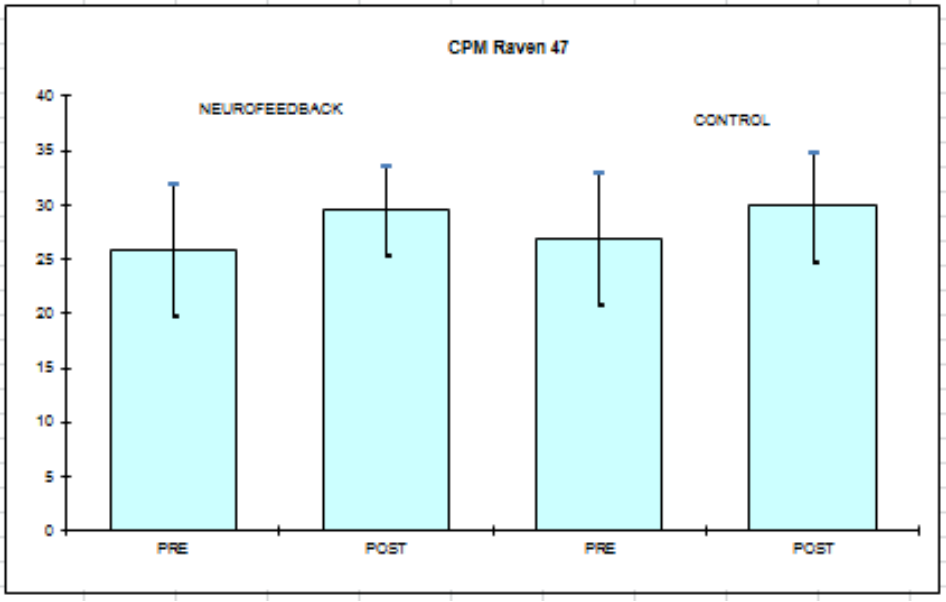

Figure 10: mean and standard deviation of CPM Raven 47, before and after treatment, compared between NF and control groups.

Attentional Matrices have been used to show the changes in cognitive scores before and after treatment and 4 months after its suspension (follow-up). The mean(sd) scores in NF group go from 34,8(12,3) to 45,9(9,7) and then come back to 32,6(13); similarly scores in control group go from 34,8(14,6) to 45,2(10,1) and then come back to 34,9(13,6). The profile resulted statistically significant (p<0,0001): in both groups values increase significantly from pre to post-treatment and then reduced to the baseline values at the follow-up(Fig. 11); there wasn't a statistically significant difference between NF group and control (p=0,9223).

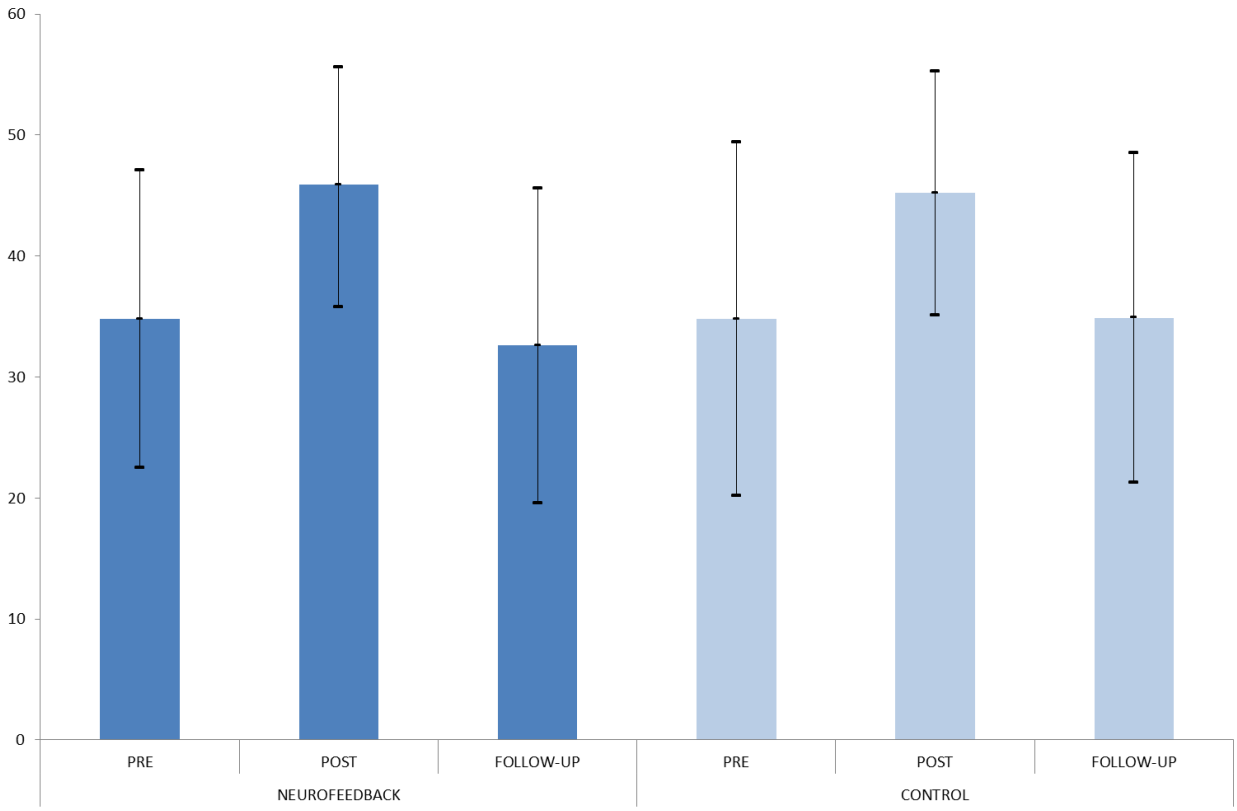

Figure 11. Mean and standard deviation of Attentional Matrices, before and after treatment and at the follow-up, compared between NF and control groups.

Figure 12 shows the improvement percentage, obtained from each test, sorted in increasing order and table 3 shows the adjusted p-values for the comparison of improvement of the scores between all pair of tests. The multivariate analysis of variance pointed out that there is a statistically significant difference improvement detected by each test ($F=54.78$, $p<0.0001$), but there wasn't a statistically significant effect between group ($F=0.08$, $p=0.7838$).

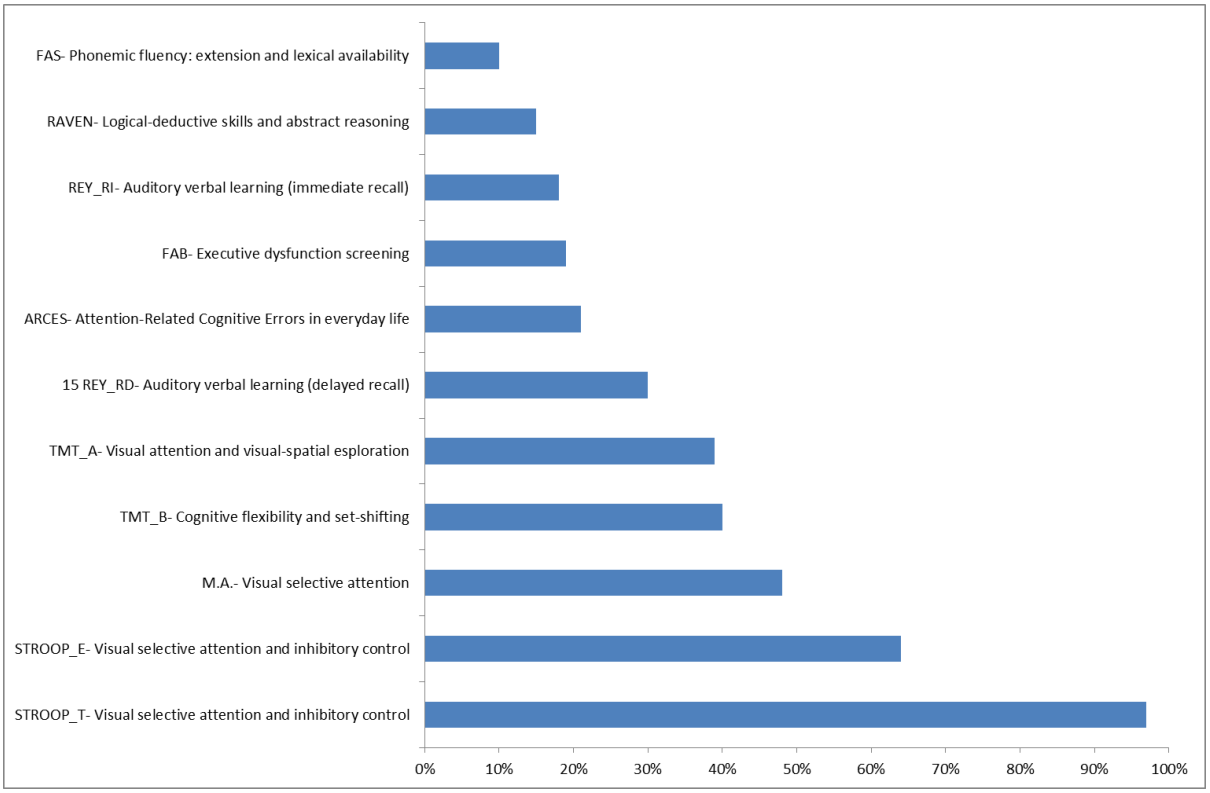

Figure 12. Mean improvement expressed as percentage of pre-treatment score for each test.

	STROOP_T	STROOP_E	M.A.	TMT_B	TMT_A	15 REY_RD	ARCES	FAB	REY_RI	RAVEN	FAS
STROOP_T		0,0117	0,0001	0,0001	0,0001	n.s.	0,0001	0,0001	0,0001	0,0001	0,0001
STROOP_E			0,0001	n.s.	0,0389	n.s.	0,0035	0,0001	0,0001	0,0001	0,0001
M.A.				0,0001	0,0001	n.s.	0,0001	0,0266	0,0314	0,0185	0,0064
TMT_B					n.s.	0,0001	0,0005	0,0001	0,0001	0,0001	0,0001
TMT_A						0,0001	0,0046	0,0001	0,0001	0,0001	0,0001
15 REY_RD							0,0001	n.s.	n.s.	0,0475	0,0016
ARCES								0,0001	0,0001	0,0001	0,0001
FAB									n.s.	n.s.	0,0301
REY_RI										n.s.	0,0071
RAVEN											n.s.
FAS											

Table 3. Comparisons between tests: p-values adjusted according to FDR (highlighted statistically significant comparisons).

Patients satisfaction has been evaluated too by means of PSQ GSat and PSQ Tech (tab 6). Median values of PSQ GSat was 5 in NF group and 4.83 in control group, the difference was slightly significant (p=0.0403). The median of PSQ Tech was 5 in NF group and 4.8 in control group, the difference was statistically significant (p=0.0012).

	Groups				
	Neurofeedback (n=10)		Control (n=10)		
	median	interquartile	median	interquartile	**p-value**
PSQ_GSat	5	5 - 5	4,83	4,5 - 4,8	0,0403°
PSQ_Tech	5	5 - 5	4,8	4,6 - 4,9	0,0012°

°: Wilcoxon test for independent sample
PSQ_GSat: Patient Satisfaction Questionnaire_General Satisfaction subscale
PSQ_Tech: Patient Satisfaction Questionnaire_Technical Quality subscale

Table 6. Comparison between the degree of satisfaction of NF and control group

4. DISCUSSION

At the end of treatment path, cognitive re-evaluation showed a significant increase in scores in both groups; PD patients significantly improved in all investigated cognitive functions (attention, set-shifting, executive functions, verbal fluency, immediate and delayed memory, and visuospatial reasoning) compared with their baseline assessments, with a positive impact on reaction time, processing speed and global cognition.

In particular, the greater improvement was observed in the performance at the attention-related tasks (Stroop Test, TMT, A.M.) and at the self-assessment test ARCES. At the end of treatment, patients report that they commit fewer attention-related errors in daily activities.

A greater improvement in attentional performances was to be expected considering that the training in both groups was selectively focused on the reinforcement of attention functions. The generalization of the improvement to other cognitive functions is probably due to the impact that attention has over all higher cortical functions, impaired in parkinson's disease in consequence of attentional dysregulation.

The comparison between cognitive performances showed no significant differences between the two groups linked to the type of treatment carried out (NF or conventional computerized training).

Several studies report the effectiveness of cognitive rehabilitation in Parkinson's disease (Calleo et al. 2012), therefore, this result does nothing but confirm the literature data.

However, the degree of satisfaction for treatment was significantly greater in the NF group, in term of general satisfaction (PSQ_GSat) and technical quality (PSQ_Tech). This result is probably due to the involvement degree and the established interaction between patient, computer and therapist. Should not be underestimated that training is modulated and adapted moment-to-moment to patient capacity, without creating frustration or discouragement.

To notice that in both groups the 4 months after the end of treatment follow-up control put into evidence a decrease in scores to baseline levels. It’s probably due to the degenerative nature of the disease.

5. CONCLUSIONS

Both approaches to cognitive training, classic computerized cognitive training and neurofeedback training, as long as applied for a long time seems to improve cognitive abilities in PD patients with mild cognitive impairment who have a higher risk of developing dementia. The increase in the satisfactory levels of the experimental group appears to be due to how patients perceive the control they have on their cognitive performance (assumption of NF training), thus increasing the sense of self-efficacy.

Our study shows that Neurofeedback techniques are well accepted: patients have fun, are successful in whatever they do and simultaneously change their brain physiology.
However, this experience so far shows that PD patients periodically need reminder therapy, otherwise recurrence of attention dysfunction is observed.

Based on the results obtained, the study group proposes a time-schedule for cognitive rehabilitation in PD (Tab. 7), to be repeated every year in order to face the decline in progress, since the cognitive training in PD delays the evolution of MCI to dementia.

month	0-3	3-6	6-9	9-12	
NF COGNITIVE TRAINING (with a rehabilitation professional)					
Computerized cognitive training at home (with a caregiver)					
	0		6		12
	COGNITIVE EVALUATION				

Table 7. Cognitive rehabilitation annual schedule.

Many traditional cognitive training programs require face-to-face contact, which entails identifying a convenient meeting location, coordinating schedules, and travel time. Furthermore, traditional face-to-face training programs is expensive, considering the professional costs and the cost of equipment and materials. Given the importance of cognitive training for maintaining cognitive function, cost-effective alternatives are needed.

Neurofeedback-based cognitive interventions are a potentially cost-effective alternative to traditional training programs.

The NF training is usually provided by a trained health professional. Nevertheless, it is possible to train the patient and his caregivers to the self-application of neurofeedback techniques, in order to ensure the care continuity even after the end of treatment "in the presence" of the therapist. This solution would have the goal to reduce the costs of rehabilitation and to facilitate access to the care for patients, also limiting transfers at hospitals. It is a feasible option only if using handy NF tools, like those adopted in this study, which is a proof that a simple device, such as NeuroSky Mindwave, despite the low-cost oriented design (when compared to several thousands of dollars for others EEG systems), can be accurate and reliable in differentiating various states of mind, usable for rehabilitation purpose.

The future of EEG research lies in the mobile recording and real time feedback of emotional and cognitive states. While in the research community there is a focus on developing complex headsets using multiple channels, in the short term, the widespread use of EEG technology by the general public is most likely going to rely on inexpensive, easily usable (mobile, gel-free), single channel acquisition.

Neurofeedback offers an additional treatment option for PD patients. While showing the same cognitive results, training in NF is more motivating, more encouraging, more satisfying than other rehabilitation methods.

The enhancement of fast rhythms (objective of NF in PD) and the resulting increase in the levels of attentional skills have favourable effects both in the performance of cognitive tasks requiring the intervention of attentional processes and in the carrying out of daily activities, in which attention functions are significantly involved.

6. FUTURE PROSPECTS

Since the EEG is sharply slowed down in PD, the study will be expanded by investigating EEG changes in background rhythm and relative power of δ, θ, α and β waves, induced by neuro-rehabilitation, also evaluating the possible difference between NF and control group.

From a healthcare perspective, the expanding number of PD patients, associated with the expanding aging population, highlights the need to identify quick, effective, low-cost solutions to delay severe cognitive decline associated with PD. Developing interventions that can preserve cognitive functions can also help to maintain quality of life and independence (Kueider et al. 2012). With the help of new technology, novel cognitive training platforms and Neurofeedback devices, could be readily disseminated to PD 'population'.

Furthermore, the rapid spread of information and communication technology in healthcare, allows part of the rehabilitation activities may be provided at distance (Telerehabilitation). Although still at their infancy, the techniques of tele-neurofeedback allow the patient to receive cognitive treatment at home while being in constant contact with the therapist via the web. For example, patients who are home bound or live in an assisted living or nursing home facility and have limited access to transportation are difficult to recruit for traditional cognitive training programs. Tele-neurofeedback could offer a more flexible, personalized approach to traditional cognitive training programs, allowing for easier access and dissemination to persons with access to technology. In addition, NF programs provide real-time performance feedback and can adjust to the patient's ability level, keeping the activity engaging and fun. NF software are designed to be fun and exciting and may provide motivation for patients to stick with the training program.

Moreover, given the need to continue with cognitive treatment over time in order to delay the progression of mild cognitive impairment in full-blown dementia, techniques of tele-neurofeedback could be applied once traditional NF or cognitive treatment is stopped.

	Age	DG(y)	H&Y	MMSE	EEG
P1s	65	7	2	26,2	Slow alpha rhythm (8-9 c/sec) of medium-low voltage, symmetrical, reagent, unstable, interrupted by discrete low voltage beta activity.
					Occasional modest theta activity in bilateral frontotemporal regions.
					Photic stimulation did not significantly alter the background rhythm.
					Hyperpnea not performed.
					Conclusion: minimal slow activity in bilateral fronto temporal regions
P2s	59	3	2	26,97	Background rhythm widely slowed with prevalence of theta rhythm (7 c/sec), medium voltage, discretely modulated, symmetrical and slightly reagent.
					SLI not change the background rhythm.
					Conclusion: diffuse slow anomalies.
P3s	63	9	2	27,49	Background activity well modulated and reagent.
					Rare and short trains of theta activity in left temporo-parietal region.
P4s	64	5	2	24,73	Alpha rhythm to 10-11 c/sec, medium voltage, discretely modulated, symmetrical, reagent.
					Drowsiness lasting several minutes (sleep stages 1-2 NREM).
					Conclusions: normal brain activity. Excessive sleepiness.
P5s	66	1	4	18,4	Discretely modulated background activity with prevalence of slow alpha rhythm bi-occipital (9 c/sec), medium voltage, reagent to eyes opening, symmetrical.
					Slow waves on right posterior region, showing no tendency to spread.
					Physiological response to SLI and hyperpnea.
					Conclusion: non-specific focal abnormalities on a normal background activity.
P10s	68	6	1,5	18,2	Diffuse slow anomalies.
P8c	66	12	3	26,2	Slow alpha rhythm (8-9 c/sec) medium voltage, unstable, symmetrical, reagent, interrupted by discrete activity microfused organized in anterior regions.
					Minimal theta activity prevalent in bilateral fronto temporal regions.
					SLI and hyperpnea not change the background rhythm.
					Conclusion: minimal slow activity in bilateral fronto temporal regions.
P9c	65	6	2	25,9	Background rhythm characterized by predominance of NREM sleep stages 1-2. Alpha rhythm to 10-11 c/sec, low voltage, symmetrical.
					Photic stimulation did not significantly alter the background rhythm.
					Conclusions: electrical activity of sleep (expression of hypersomnia). Short stretches of wakefulness show normal brain electrical activity.
P4ex	77	10	4	<18	Background rhythm widely slowed with prevalence of theta rhythm to 7 c/sec, slightly reagent, medium voltage.
					Little slow alpha activity to 8 c/sec.
					Symmetrical and slow irregular theta and delta activities in right fronto-temporal region.
					Conclusions: diffuse slow anomalies prevalent in right fronto-temporal region.

QUALITATIVE EEG DATA recorded from 10 examined PD patients

P = patients; s = experimental group; c = control group; ex = excluded

DG(y) = year from diagnosis; H&Y = Hoehn & Yahr Scale; MMSE = Mini Mental State Examination

EEG = Electroencephalographic report

BIBLIOGRAFIA

- Ahlskog JE, Muenter MD 2001. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord; 16:448-58.
- Alexander G., Delong M. and Strick P. 1986; Parallel organisation of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neuroscience; 9: 357–381.
- Azarpaikan A, Torbati HT, Sohrabi M. 2014; Neurofeedback and physical balance in Parkinson's patients. Gait Posture, 177-81.
- Ball K, Berch DB, Helmer KF, Jobe JB, Leveck MD, et al. 2002; Effects of cognitive training interventions with older adults: A randomized controlled trial. JAMA 288(18): 2271–2271–2281.
- Bassett SS 2005; Cognitive impairment in Parkinson's disease. Primary Psychiatry; 12: 50-55.
- Braak, H. Del Tredici K., Rub U., de Vos R., Jansen Steur E., Braak, E. 2003; Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging; 24: 197–211.
- Benjamini, Y. and Y. Hochberg, 1995; Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society, Series B (Methodological), 57(1): p. 289-300.
- Calleo J, Burrows C, Levin H, Marsh L, Lai E, York MK 2012; Cognitive rehabilitation for executive dysfunction in Parkinson's disease: application and current directions. Parkinsons Dis.;2012:512892.
- Caviness JN, Hentz JG, Evidente VG, Driver-Dunckley E, Samanta J, Mahant P, Connor DJ, Sabbagh MN, Shill HA, Adler CH 2007. Both early and late cognitive dysfunction affects the electroencephalogram in Parkinson's disease. Parkinsonism Relat Disord.;13(6):348-54.
- Caviness JN, Hentz JG, Belden CM, Shill HA, Driver-Dunckley ED, Sabbagh MN, Powell JJ, Adler CH 2015; Longitudinal EEG changes correlate with cognitive measure deterioration in Parkinson's disease. J Parkinsons Dis.5(1):117-24

- Chaudhuri KR, Healy DG, Schapira AH. 2006 Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 5:235-45.
- Cortoos A1, De Valck E, Arns M, Breteler MH, Cluydts R. 2010. An exploratory study on the effects of tele-neurofeedback and tele-biofeedback on objective and subjective sleep in patients with primary insomnia. Appl Psychophysiol Biofeedback. Jun;35(2):125-34. doi: 10.1007/s10484-009-9116-z.
- Delorme, A. and S. Makeig, 2004; EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods,. 134(1): p. 9-21.
- Domellof M., Elgh E., Forsgren, L. 2011; The relation between cognition and motor dysfunction in drug-naïve newly diagnosed patients with Parkinson's disease. Mov Disord; 26: 2183–2189.
- Emre M. et al. 2003; What causes mental dysfunction in Parkinson's disease? Mov Disord Suppl 6:S63-71
- Enriquez-Geppert S. et al. 2013; Boosting brain functions: Improving executive functions with behavioral training, neurostimulation, and neurofeedback. Int J Psychophysiol.;88(1):1-16. doi: 10.1016/j.ijpsycho.2013.02.001.
- Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A et al. 2004; Levodopa and the progression of Parkinson's disease. N Engl J Med; 351: 2498-508.
- Fumuro T. et al. 2013 Bereitschaftspotential augmentation by neuro-feedback training in Parkinson's disease. Clin Neurophysiol. Jul;124(7):1398-405. doi: 10.1016/j.clinph.01.026.
- Gelb DJ et al. 1999; Diagnostic criteria for Parkinson disease Arch Neurol; 56: 33-9.
- Gevensleben H, Rothenberger A, Moll GH, Heinrich H. 2012; Neurofeedback in children with ADHD: validation and challenges. Expert Rev Neurother. ;12(4):447-60.
- Gibb WRG, Lees AJ. 1988; The relevance of the Lewy body to the pathogenesis of idiopathic Parkison's disease. J Neurol, Neurosurg and Psych; 51: 745-52.
- Gibb WR. 1997; Functional neuropathology in Parkinson's disease. Eur Neurol.; 38. 21-25.

- Holtmann M, Sonuga-Barke E, Cortese S, Brandeis D. 2014; Neurofeedback for ADHD: a review of current evidence. Child Adolesc Psychiatr Clin N Am,; 789-806.
- Hughes A., Daniel S., Kilford, L. and Lees A. 1992; Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry; 155: 181–184.
- Katzenschlager R, Sampaio C, Costa j, Lees A. 2002. Anticholinergics for symptomatic management of Parkinson's disease. Cochrane Database of Systematic Reviews.
- Klassen BT1, Hentz JG, Shill HA, Driver-D unckley E, Evidente VG, Sabbagh MN, Adler CH, Caviness JN. 2011; Quantitative EEG as a predictive biomarker for Parkinson disease dementia. Neurology.;77(2):118-24.
- Kish S., Shannak K. and Hornykiewicz O. 1988; Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. N Engl J Med; 318: 876–880.
- Knopman DS, Boeve BF, Petersen RC. 2003; Essentials of the proper diagnoses of mild cognitive impairment, dementia, and major subtypes of dementia, Mayo Clin Proc.; 78(10):1290-1308.
- Kueider A., Parisi M., Gross A., Rebok G.W. 2012; Computerized Cognitive Training with Older Adults: A Systematic Review; Alexandra M. Published journal DOI: 10.1371
- Lezak MD. 1995; Neuropsychological Assessment. 2nd ed. New York: Oxford University Press.
- Lopes da Silva, F., 2004; Functional localization of brain sources using EEG and/or MEG data: volume conductor and source models. Magn Reson Imaging,. 22(10): p. 1533-8.
- McKinnon, K.I.M., 1999; Convergence of the Nelder-Mead simplex method to a non-stationary point. SIAM J Optimization,. 9: p. 148-158.
- Miyake A, Friedman N. 2012; The nature and organization of individual differences in executive functions: four general conclusions. Curr Dir Psychol Sci; 21: 8–14.
- Mohlman J, Chazin D, Georgescu B. 2011; Feasibility and acceptance of a nonpharmacological cognitive remediation intervention for patients with Parkinson disease. J Geriatr Psychiatry Neurol.24(2):91-7

- Muslimovic D., Post B., Speelman J., Schmand, B. 2005; Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology; 65: 1239–1245.
- Nagai Y. 2014; Biofeedback treatment for epilepsy Nihon Rinsho. ;72(5):887-93.
- Olanow CW, Watts RL, Koller WC. 2001; An algoritm (decision tree) for the management of Parkinson's disease: treatment guidelines. Neurology; 56: S1-S88
- Pagano G, Rengo G, Pasqualetti G, Femminella GD, Monzani F, Ferrara N, Tagliati M. 2014; Cholinesterase inhibitors for Parkinson's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 308764
- París AP Saleta HG, de la Cruz Crespo Maraver M, Silvestre E, Freixa MG, Torrellas CP, Pont SA, Nadal MF, Garcia SA, Bartolomé MV, Fernández VL, Bayés AR. 2011; Blind randomized controlled study of the efficacy of cognitive training in Parkinson's disease. Mov Disord. 26(7):1251-8. doi: 10.1002/mds.23688.
- Parkinson's Study Group 1997; Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Ann Neurol; 42: 747-55.
- Pillon B., Dubois B., Cusimano G. et al. 1989; Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? J Neurol Neurosurg Psychiatry 52(2):201-206
- Poletti M., Bonuccelli, U. 2012; Orbital and ventromedial prefrontal cortex functioning in Parkinson's disease: Neuropsychological evidence. Brain Cogn; 79: 23–33.
- Poletti M, Bonuccelli U. 2013; Acute and chronic cognitive effects of levodopa and dopamine agonists on patients with Parkinson's disease: a review. Ther Adv Psychopharmacol.;3(2):101-13
- Rajput AH, Rozdilsky B, Rajput A. 1993; Alzheimer's disease and idiophatic Parkinson's disease coexistence. J Geriatr Psychiatry Neurol.; 6:170-176
- Rascol O et al. 2011; A double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study): prespecified and post-hoc analyses of the need for additional therapies changes in UPDRS scores, and non-motor outcomes. Lancet Neurol; 10: 415-23.

- Rebolledo-Mendez, Dunwell, Martínez-Mirón, Vargas-Cerdán, de Freitas, Liarokapis, García-Gaona R. 2009; Assessing NeuroSky's Usability to Detect Attention Levels in an Assessment Exercise. Human-Computer Interaction, Part I, 149–158
- Rippon GA, Marder KS. 2005; Dementia in Parkinson's disease. Adv Neurol; 96: 95-113.
- Sawamoto N., Piccini P., Hotton G., Pavese N., Thielemans K., Brooks, D. 2008; Cognitive deficits and striato-frontal dopamine release in Parkinson's disease. Brain; 131: 1294–1302.
- Schutz LE, Trainor K. 2007; Evaluation of cognitive rehabilitation as a treatment paradigm. Brain Inj. Jun; 21(6):545-57.
- Stacy M, Hauser R. 2007; Development of a Patient Questionnaire to facilitate recognition of motor and non-motor wearing-off in Parkinson's disease. J Neural Transm; 114: 211-217.
- Stoffers D1, Bosboom JL, Deijen JB, Wolters EC, Berendse HW, Stam CJ. 2007; Slowing of oscillatory brain activity is a s table characteristic of Parkinson's disease without dementia. Brain ; 130(Pt 7): 1847-60.
- Stowe R et al. 2008; Dopamine agonist therapy in early Parkinson's disease. Cochrane Database of Systematic Reviews; 2: CD006564.
- Suppa A. 2013; Boosting neural activity in cortical motor areas through neurofeedback in Parkinson's Disease. Clin Neurophysiol. 2013 Jul;124(7):1262-3
- Talati R, Reihart K, Baker W, White CM, Coleman CI. 2009; Pharmacologic treatment of advance Parkinson's disease: a metanalysis of COMT inhibitors and MAO-B inhibitors. Parkinsonism Relat Disord.
- Turnbull K et al. 2012; Monoamine oxidase B inhibitors for early Parkinson's disease. Cochrane Database of Systematic Reviews; 3: CD004898.
- Yogev-Seligmann G, Hausdorff JM, Giladi N. 2008; The role of executive function and attention in gait. Movement Disorders. ;23(3):329–342.