BRAIN COMPUTER INTERFACES - NEUROFEEDBACK AS A TREATMENT FOR PARKINSON ‘S DISEASE

ARTS-KLINISCH ONDERZOEKER THESIS YEAR 1

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Parkinson’s disease (PD) is characterized by a total dysfunction of the motor system resulting in tremor, rigidity, bradykinesia, postural instability and cognitive decline. Current treatment options have varying effects per patient, and may pose considerable adverse effects resulting in the need for new, non-invasive treatments. BCI neurofeedback using EEG is a valid treatment option. Using neurofeedback patients can be trained to influence the aberrant brain waves that are associated with the disease. In the case of PD, neurofeedback protocols are aimed at changing oscillatory rhythms and increasing the amplitude of the readiness potential. However, randomized controlled trials have shown varying results of neurofeedback on the symptoms of PD and the clinical efficacy is still unknown. As for ethical concerns, there are no known serious side effects, but as the effect of neurofeedback on the central nervous system are still unidentified, there is a concern of the effect on the “sense of self”. Next to that, the risk-benefit ratio and the cost-effectiveness of neurofeedback treatment for PD still need to be evaluated. Should neurofeedback show to be efficacious and with a good risk-benefit ratio it could be implemented in the care of both early and late-stage PD patients.
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Parkinson’s disease (PD) is the second most common degenerative disease of the nervous system (only surpassed by Alzheimer’s disease), and one of the most well-known examples of pathological tremor (1). It is a severely debilitating disease that is characterized by tremor, rigidity, bradykinesia, postural instability as well as cognitive decline. It is caused by extensive loss of dopaminergic neurons in the substantia nigra pars compacta. As the substantia nigra is important in motor control, PD results in a total dysfunction of the motor movement system (1).

The symptoms of PD progress slowly and are often mistaken as normal aging (3). Patients suffer from rigidity and bradykinesia, resulting in slowing of movement and difficulty in initiating movements. However, the most characteristic and debilitating symptom is the tremor. This tremor is a resting tremor, which means that it lessens when the hands are intentionally moved and hence is completely absent in sleep, and is rhythmic. It occurs in 75% of the PD patients (4). Stress, emotions and tension can increase the tremor (5). PD is progressive and the symptoms will worsen relentlessly (6).

So far, there is no curative treatment. Rather, treatment is focused on improving or maintaining the patient’s self-dependence. Current treatment options range from pharmaceuticals to brain surgery, and their efficacy in suppressing the symptoms of PD vary per patient. Moreover, they have considerable side effects or surgical risks, emphasizing the need for the development of new, non-invasive treatments. A valid, non-invasive, treatment that has little to no side-effects is a form of Brain Computer Interface treatment (BCI treatment) otherwise known as neurofeedback.
2. DESCRIPTION OF THE PROBLEM

2.1 EPIDEMIOLOGY

The prevalence of PD in Western Europe is 160/100,000 (7). In Holland the prevalence of PD it is estimated at 40,000 patients and approximately 4000 new cases have been reported in The Netherlands in 2011 (3, 5). Moreover, 1300 people have died of PD in 2011. The disease usually presents itself at a later age, 4% of the population over 80 years old suffers from PD (7), but 10% of patients are under 40 (5). Some susceptibility genes have been identified, such as the α-synuclein, parkin, UCH-L1, PINK 2, DJ-1 and LRRK2 genes (7), but familial forms of the disease caused by a single gene mutation account for less than 10% of all cases (1). It is thought that environmental factors might predispose to developing PD, but so far it has been difficult to identify them. Some factors thought to be associated are living in a rural area and exposure to pesticides and wood preservatives. In contrast, a strong negative link has been found between cigarette smoking and PD development (7).

2.2 BURDEN TO SOCIETY

As stated above, approximately 1300 people have died of PD in The Netherlands in 2011 (3). The prevalence of PD is highest in the population above age 60 (3). Because the disease affect mainly affects retired individuals there is a smaller burden of the disease on society as compared to autism, schizophrenia and other mental disorders that appear in childhood or early adulthood. Nonetheless, a significant group of patients is younger than 40 (10%) (3) and PD can decrease the quality of life of patients significantly (8). Especially daily actions such as closing the buttons of a shirt or lacing shoes become very difficult as the small muscles of the hand are the first to be affected (5). On top of that, the disease is progressive and patients require more help as the symptoms worsen. In late-stage disease motor symptoms can be severe, and non-motor complications become more troublesome; approximately 40% of patients show symptoms of depression (7). The burden of PD can be visualized using “years lived with disability” (also known as “disability adjusted life years” or DALYs) which quantifies not only how many people suffer from the disease and how long, but also considers the severity of the disease. PD is considered a
very disabling disease, with a weighting factor of 0.68 out of 1 (9). In 2010 7.762 have been lost in The Netherlands. This adds up to a total of 23.900 DALYs in 2010 (9).
3. PATHOGENESIS OF PARKINSON’S DISEASE

3.1 CHANGES IN NEURAL CIRCUITRY

The symptoms of PD are caused by a dysfunction of the basal ganglia. The basal ganglia influence the activity of upper motor neurons in the cortex and consist of multiple nuclei deep within the cerebral hemispheres: the caudate, putamen, globus pallidus, subthalamic nucleus and the substantia nigra (see Figure 1) (1). The neurons in these areas form a loop from cortex to basal ganglia and back (cortico-basal ganglia-cortical loop), and respond in anticipation of and during movements. They are needed to aid in initiating voluntary and decreasing involuntary movement. In Parkinson’s disease there is a progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNPC, turquoise) resulting in a total dysfunction of the motor movement system (1). This loss of dopaminergic neurons is thought to be caused by Lewy body deposition. Lewy bodies are α-synuclein-immunoreactive inclusions consisting of multiple neurofilaments (6, 7). The reason for this deposition is as of yet unknown, but may be caused by a combination of genetic and environmental factors (7).

Without input from the SNPC voluntary movements cannot be initiated, resulting in bradykinesia (slowing of movement) and stiffness of muscles, and involuntary movements cannot
be suppressed, resulting in the characteristic resting tremor (1). Other symptoms that are associated with PD, such as postural instability, cognitive decline and psychological problems cannot be as easily linked to a specific brain region.

These changes in the neural circuitry of the basal ganglia have been visualized using EEG; PD patients show distinct brain wave patterns that can be associated with specific symptoms of the disease. Studies of neuronal firing provide evidence that patients suffering from PD show disturbances in brain oscillatory rhythms in the basal ganglia and over the supplementary motor area (10). The aberrant oscillatory rhythms in the basal ganglia, more particularly the thalamus and subthalamic nucleus, may play a role in the formation of limb tremor (10, 11), while those in the whole basal ganglia may underlie bradykinesia (10). These oscillatory rhythms are recorded in the 15-30 Hz “beta” range and the 3-10 Hz “theta” range. The low frequency theta waves are often in synchrony with the tremor (4, 10). This EEG pattern corresponding to the tremor can be seen in the contralateral hemisphere of the tremulous hand (11). Moreover, EEG studies show an underactivity of the supplementary motor areas which may be associated with the difficulties in preparing to move that PD patients experience (2). This underactivity is particularly visible as a decrease in the amplitude of the “readiness potential” (RP), also called Bereitschaftspotential. The RP is a slowly rising negativity on the EEG graph that occurs 1-2 seconds before the onset on a self-initiated movement. In PD patients the first part of the RP (RP1 or BP 1) is significantly smaller compared...
to healthy controls (see Figure 2), and may be a reflection of the difficulties PD patients have with initiating movement (2).

### 3.2 CURRENT TREATMENT

There is currently no curative treatment for Parkinson’s disease and disease progression cannot be slowed (12, 13). Most pharmaceuticals target the dopamine system (12). However, these have a variable effect on the resting tremor (5) and can have serious side effects (8, 13). When treated with levodopa, a dopamine precursor, 50-80% of patients will suffer from dyskinesia, which is defined as alternating periods of diminished voluntary movements and increased involuntary movements (7, 14). Twenty to thirty percent of DP patients treated with levodopa (a dopamine precursor) develop dyskinesia after less than 2 years of treatment and in young patients this number is even higher. Almost all patients under the age of 40 develop motor complications after 6 years of treatment. (7). Another downside to pharmacological treatment is that after some years of stable use, the effect of a dose becomes progressively shorter, leading to fluctuations in motor performance. This effect is called “wearing-off” and is prominent in levodopa treatment (7). Between 5 and 10 years of use 50% of patients will develop motor fluctuations (7).

Another treatment option is deep-brain-stimulation, where the subthalamic nucleus is continuously stimulated with high-frequency electrical pulses by a surgically implanted device (7, 8). This intervention has a great effect on the tremor; in some cases the tremor disappears completely (7). Although the operation is technically difficult, when performed by an experienced surgeon the risk of adverse events is low, but the infrastructure and support team required to assess, carry out and monitor patients restricts the availability of this treatment (7). Furthermore, this treatment can have serious psychiatric side effects such as depression, which is cause for hesitation in choosing to perform the surgery (7). On top of that, patients most suitable for surgery are under the age of 75 without significant systemic co-morbidity and should respond to levodopa treatment (7). This greatly limits the amount of patients for which this treatment is applicable, and shows the need for a treatment that is suitable for those who are not eligible for DBS treatment.
Novel therapeutic approaches, such as gene therapy, are in development. However, ethical, practical and political considerations have limited their use (1). Therefore, it is of great importance to develop a treatment option with less side effects that is suitable for more patients and that can be easily implemented in the health care system.
4. INNOVATIVE ASPECTS OF NEUROFEEDBACK

4.1 PROPOSED MECHANISM OF ACTION

It has been shown that the tremor and dyskinesia in Parkinson’s disease have a specific pattern that can be discerned using electroencephalography (see chapter 4.1 and Figure 2) (2, 4, 10, 11, 15). Using brain-computer interfaces (BCIs), patients can be made aware of these patterns and can learn to influence them. This is also called “neurofeedback”. In neurofeedback treatment a patient’s brain waves are measured and visualized on a computer screen. The patient is then trained to influence these brain waves using operant conditioning principles; healthy brain waves are rewarded with visual or auditory stimulation, while undesirable brainwaves are ignored or punished (16, 17).

Neurofeedback is currently used as a treatment for several neuropathologies, such as attention-deficit-hyperactivity disorder (ADHD) and depression (17, 18). Studies have shown that as children become successful in regulating their brain electrical activity, improvements in cognition and behavior follow (17, 19). This change in phenotype is triggered by a functional network reorganization; fMRI studies have shown marked changes in brain activation after effective neurofeedback training (17). It is thought that neurofeedback training for PD patients can trigger a similar network reorganization which increases the performance of the malfunctioning cortico-basal ganglia-cortical loop.

The following section will clarify the evidence that neurofeedback protocols can influence the pathological EEG patterns that underlie the symptoms of PD.

4.2 APPLICATION IN THE CLINICAL SETTING

4.2.1 ALPHA WAVE AMPLIFICATION AND THETA & BETA WAVE INHIBITION

The spontaneous oscillatory EEG rhythms are traditionally classified according to frequency; delta (0.5-4Hz), theta (4-7Hz), alpha (8-12Hz) sensorimotor rhythm or SMR (12-15Hz), beta (13-30Hz) and gamma (30-100Hz) (17). As explained in chapter 4.1 PD patients show abnormal EEG wave oscillations in the 15-30 Hz “beta” range and the 3-10 Hz “theta” range.
Treatment protocols in randomized controlled trials therefore focus on inhibiting the theta and beta waves, and increasing the alpha and SMR waves (20).

In a randomized controlled trial by Erickson-Davis and colleagues 9 PD patients underwent a 24 session neurofeedback protocol (20). Five of the Patients underwent the experimental neurofeedback protocol and 4 a sham protocol. In the experimental protocol audio feedback rewards were given when subjects enhanced a 3Hz band within the 8-15 Hz amplitude (alpha and SMR waves). As a control, 4 of the 9 subjects underwent a “sham protocol” in which the audio feedback did not correspond with the subjects EEG pattern. The primary outcome measure was a change in the clinical measures of dyskinesia compared to baseline. Unfortunately no significant difference was found. However, a non-significant decrease in motor fluctuation and dyskinesia was observed, which were accompanied by significant changes in subject’s resting state cortical activity and decreases in high beta activity. These results show that neurofeedback training can influence the EEG patterns of individuals with PD and signify the importance of further exploring the clinical outcomes. The researchers report that possibly the small sample size and the sensitivity of the outcome measures may have attributed to the lack of significant findings (20).

Another randomized controlled trial investigated the effects of alpha wave amplification on physical balance of PD patients (21). 16 PD patients were randomly divided in experimental and control groups. The experimental group underwent an 8 session protocol of neurofeedback in which SMR waves (15-15Hz) were reinforced and theta waves (4-7Hz) were inhibited. The control group underwent a sham-protocol that presented random feedback which was not linked to the EEG of the subject. The results showed statistically significant differences (p≤0.001) in physical balance between the experimental and control group. This provides evidence that increasing SMR waves and decreasing theta waves can contribute, at least temporarily, to the improvement of balance of PD patients (21).
4.2.2 AUGMENTATION OF THE READINESS POTENTIAL

It has been reported that the symptoms of bradykinesia, and more specifically the problems with movement initiation, are caused by a decrease in the readiness potential over the SMA. Therefore it has been hypothesized that increasing the amplitude of the RP may alleviate the symptoms of bradykinesia in PD patients. A study by Fumuro and colleagues investigated whether it is possible for PD patients to increase their RP using a neurofeedback protocol (22). A neurofeedback training was given in between two button-press protocols. The neurofeedback training was aimed at regulating slow-cortical potentials (SCPs) as these are related to RP. Before and after the training the subjects and controls were asked to press a button 100 times, with approximately 10s in between each button press. The results showed that when neurofeedback training was successful (SCP amplitude exceeded a defined target level and remained at least 2 seconds) RP was significantly augmented (22). Fumuro and colleagues do not report in improvement in clinical motor function of PD, which warrants further investigation.

4.3 CLINICAL EFFICACY

As explained in the previous chapter, neurofeedback training for PD relies on the amplification and inhibition of multiple types of brain waves, just as the symptoms are dependent on multiple structural pathways in the brain. Neuromodulation of some of these pathways has been shown to be more effective than others. Augmentation of the SMR waves to improve physical balance has been shown to be effective after a mere 8 sessions (21). Unfortunately, the effect on other symptoms of PD are less substantial. A decreasing trend, but no significance in severity of the symptoms has been reported by Erickson-Davis and colleagues (20). Therefore the clinical efficacy is still debated. Nevertheless, it is expected that successful neurofeedback treatment will activate compensatory mechanisms in the cortico-basal ganglia-cortical loop, thereby sustaining neurological functions despite progressive loss of dopaminergic input. This slows down the progression of the clinical symptoms because of normally redundant neural pathways becoming functionally relevant when the original pathways lose their function (this is also called degeneracy) (23). Further research needs to be done that evaluates the effect on the specific symptoms of tremor and bradykinesia.
5. ETHICAL CONSIDERATIONS

5.1 SAFETY AND SIDE-EFFECTS

It is generally assumed that neurofeedback treatment does not cause serious side effect (21, 24). Nevertheless, it is important to report on studies that have reported any adverse events. Lansbergen and colleagues measured safety using the Pittsburgh side effects rating scale (PSERS) before training, and after 6, 10, 20 and 30 training sessions (25). This scale measures the presence and severity of several side effects; tics, skin picking, sleepiness, headache, stomach ache, irritability, appetite loss, epileptic seizures, nausea and feeling agitated. They also rated sleep problems on the Sleep Disorder Questionnaire (SDQ). Although some adverse events were observed, they found that EEG-neurofeedback training did not evoke significant adverse effects or sleep problems (25). Therefore, neurofeedback as a treatment for PD might work in analogy to physical stimulation techniques such as DBS, but is less invasive and has substantially less adverse effects. Noteworthy is that drop-out rates from neurofeedback studies are very low, probably due to the low incidence of side effects (24).

5.2 RISK BENEFIT RATIO

Although there are no serious side effects, because the efficacy and clinical benefits of neurofeedback treatment still need to be properly characterized, it is impossible to make a risk-benefit ratio. Nevertheless, the risks of the treatment are minimal when protocols are properly followed. To prevent possible adverse events it is recommended that neurofeedback training is conducted at a clinic under supervision of a trained professional (21). Moreover, it is important to assess whether the patients follow the treatment protocol properly. Treatment compliance has always been a difficult issue in PD treatment; compliance to medical treatment is reported to be around 50% (26). Because the effect of neurofeedback treatment will be best when professionals and patients adhere to protocol it is important to assess the factors that can influence compliance. The most important factors for PD patients are apathy and depression. In a meta-analysis of the effects of depression on treatment compliance in several diseases non-compliance was three times as great among depressed patients as compared to controls (26). Depression coexists affects 30-40% of PD patients, and can therefore greatly influence adherence
to the treatment regimen (26, 27). Apathy is a collection of behavioral, emotional and motivational features that include a reduced interest, lack of initiative, lack of concern, indifference, a flattening of affect and problems with completing activities. Apathy has been observed in patients with PD with differing prevalences; 16.5% to 42% depending on the instrument used for assessment (28). Moreover, there is evidence that apathy and depression correlate in PD patients. Apathy poses difficulties for clinical management and care; it greatly affects motivation and reduces interest in treatment outcome.

Compliance can best be increased using health psychology principles of seeking patient’s personal beliefs, involving them in treatment decisions and designing a treatment that suits the patient’s daily schedule. Because neurofeedback treatment asks patients to put an effort in their own treatment, they have to change their brainwaves themselves, it is expected that less problems with treatment compliance will arise. Moreover, patients report on a noticeable improvement in symptoms, which will most likely increase compliance as well (20).

5.3 INFORMED CONSENT AND THERAPEUTIC MISCONCEPTION

An important issue in the decision making surrounding treatment options of PD patients is their ability for informed consent. Informed consent protects the rights of patients and human research subjects and requires the patient or research participant to be informed, voluntary and competent (29). Especially the last part, competency, is of importance in the treatment of PD patients. It refers to the patient’s emotional and cognitive capacity to consent to treatment or research (29, 30). A patient must be able to make a decision regarding accepting or refusing a treatment, or to select an alternative. Patients with PD experience decline in many aspects of their daily life such as in financial abilities and activities of daily living, but they often also experience a cognitive decline (5, 30). On top of that, 40% of PD patients are also affected with some form of dementia (31). Compared to healthy controls PD patients with and without dementia show a marked impairment in medical decision-making capacity (30). This may be related to PD patient’s impairments in short term verbal memory and executive function (30). There are four situations recognized when informed consent is not required; emergency, therapeutic privilege, waiver and incompetency (29). In an emergency situation time is of the
essence and to save the patient’s life the physician can treat without consent. This is not of importance for PD patients as PD does not pose an immediate threat to life when excluding complications such as falls. In the case of therapeutic privilege, the physician withholds information based on the belief that disclosure would have a detrimental effect on the physical or psychological wellbeing of the patient. This may sometimes be the case in the treatment of PD. Waiver indicates that the patient has voluntarily relinquishes his or her rights to informed consent. Finally, there is the exception of incompetence. When a patient is not competent to make decisions regarding treatment options, physicians may start treatment without permission. For this, authorization needs to be received from an authorized legal representative, usually a spouse or the children of a patient (29). This last clause is of importance for PD patients who are demented, or have a significant reduction in cognitive abilities.

Finally, there is also the concern that PD patients with advanced disease may be desperate for a cure and vulnerable for exploitation in high-risk research studies because of therapeutic misconception (32). Their desperation can greatly affect their medical decision making capacity, and is of great importance for studies or treatment options with a poor risk-benefit ratio. Moreover, depression coexists in 30-40% of PD patients. Depressed patients may have significantly less concern for their own lives and might disregard treatment risks. Neurofeedback treatment for PD has limited risks, as there are no severe side effects known (see chapter 6.1). However, as the clinical benefit is still unknown this might pose a problem when PD patients see the treatment as a last resort. Therefore, it is of great importance to assess therapeutic misconception when selecting patients for research studies.

5.4 NEUROMODULATION AND THE SENSE OF SELF

Although there have not been any severe side effects reported for neurofeedback treatment, the mechanisms of action is still rather unknown (17). fMRI Studies have shown changes in brain activation after effective neurofeedback training (17) but to what extend neurofeedback protocols can change neuronal networks in PD patients is still unknown. This means that it is also unknown whether neurofeedback may affect neuronal networks other than the cortico-basal ganglia-cortical loop. Case studies have described PD patients that underwent
radical and extreme changes in identity after deep-brain stimulation (33). Changes as radical as in DBS generate fear in patients as well as health care professionals because of the enormous impact of the treatment. It is unknown whether this may also be the case for neurofeedback treatment. Fortunately, changes in identity are a part of human life and are therefore not necessarily problematic. Because the gravity of neuronal changes after neurofeedback are still unidentified it is important to report on these identity changes and evaluate their significance to every individual patient.
6. IMPLEMENTATION OF THE TECHNIQUE

6.1 ORGANIZATION OF CARE FOR BCI TREATMENT

Understanding the current treatment options and guidelines for PD are paramount to understanding the possible niche for BCI treatment.

6.1.1 ORGANIZATION OF CARE FOR PD

Patient characteristics such as age, general condition, symptoms and reduction in working activities of the patient influence the type and timing of initial treatment. For patients with early disease it is better to start with dopaminergic treatment (L-dopa or dopamine agonists) because they are more efficacious than symptomatic treatments (amantadine, selegiline or anticholinergic drugs) (34). Although L-dopa has a better symptomatic effect it also gives rise to a delayed syndrome involving motor fluctuations and dyskinesias, which may warrant the choice of dopamine agonists. When pharmacological treatment results in a decrease of symptoms of 15-30% it is deemed successful (34). Choice of pharmacological treatment is also dependent on age of onset of symptoms; early onset PD (<50 years) and PD that is diagnosed between 50 and 70 years is usually treated with dopamine agonists. PD that is diagnosed in patients older than 70 are treated with L-dopa (34, 35).

When after a period of satisfactory drug response the effect of L-dopa or dopamine agonist treatment is compromised due to motor complications there are a number of therapeutic options. Motor complications include loss of response, on-off phenomena, freezing, dyskinesias and dystonias (34). First of all, dopamine agonist and L-dopa dual-therapy can lessen the loss of response. Next to that, entacarpone, a COMT inhibitor, or selegeline can be added to the treatment. COMT inhibitors can prolong the half-life of L-dopa and thus allow more stable dopaminergic stimulation. Selegeline has a more moderate effect, but may prolong the benefit of L-dopa (34). Surgery is a last resort in the treatment of PD and should be considered when medical therapy fails to control the symptoms (35). There are multiple surgery options; uni- or bilateral pallidotomy, bilateral subthalamic surgery, lesioning or deep brain stimulation (35).
Deep brain stimulation of the thalamus is the most effective and safe treatment for Parkinson tremor and is therefore the procedure of choice (35).

6.1.2 THE NICHE FOR NEUROFEEDBACK

When pharmacological treatment fails due to side effects or the wearing off effect that is frequently seen in treatment of PD, the only alternative is surgery. Deep brain stimulation of the thalamus is the most effective surgery and has the advantage of being reversible. Unfortunately there are serious adverse effects associated with DBS surgery: infection, cutaneous erosion, lead breaking or disconnection, hematoma or contusion (36). Although most papers find the risk-benefit ratio of DBS to be favorable, a less invasive and less dangerous treatment option would be a beneficial development. If the clinical efficacy of neurofeedback is high the risk-benefit ratio will most definitely surpass that of DBS. Moreover, neurofeedback might be a valid option for dual treatment next to pharmacological treatment thereby abolishing the need to resort to surgical treatment.

Neurofeedback may also have a place in the treatment of early stage PD patients as a sole treatment, or in combination with pharmacological treatment. It is expected that neurofeedback will slow down the progression of symptoms by inducing plasticity in the brain (23). The studies of Subramanian and colleagues (23) and Azarpaiakan and colleagues (21) which both showed a significant improvement in symptoms after neurofeedback treatment used participant with early stage PD (Hoehn and Yahr scale I-III and I-II respectively). Erickson-Davis and colleagues (20), who showed no significant improvement, but did show a decreasing trend in symptom severity, used PD patients with varying progression of the disease. This might suggest that neurofeedback may have a better effect when used in early PD, but this trend needs further investigation. However, Fumuro and colleagues showed that PD patients can increase their RP even when they suffer from late stage PD (22). They did not report on the clinical efficacy, but these results suggest a change in neural pathways and therefore changes in symptoms are to be expected.
6.2 PATIENT SELECTION

Before neurofeedback can be implemented as a treatment option, guidelines concerning patient selection need to be published. As explained in the previous chapter the efficacy of neurofeedback may be greater in early stage PD thereby suggesting that a possible selection using the Hoehn and Yahr scale needs to be made (37). Moreover, various characteristics of the patient, such as age and cognitive ability may interfere with the effect of neurofeedback. Finally, it is important to take into account possible drug interactions. So far, none have been described for neurofeedback protocols.

6.3 HEALTH INSURANCE AND GOVERNMENTAL REGULATIONS

The accessibility of devices capable of recording, analyzing and providing feedback of EEG signals are limited to a handful research labs. However, recent advancements in the technology of these devices will most probably result in more research and treatment centers purchasing an EEG-BCI device (17). There are two institutions in The Netherlands that currently provide neurofeedback treatment: Biometrisch centrum in Geleen and Neurofeedback Instituut Nederland in Eindhoven (38, 39). Neurofeedback already has several evidence based implementations, including ADHD, anxiety disorders, depression and autism spectrum disorder (38). Unfortunately the Dutch health care system does not completely reimburse neurofeedback treatment. Only the part of the treatment that involves counseling is part of the basic insurance policy. For reimbursement, patients need to have a referral letter from a medical specialist. The neurofeedback treatment itself is not reimbursed. However, some insurance companies have included neurofeedback in their supplementary insurance policies (38, 40).
7. ECONOMICAL ASPECTS

7.1 OVERVIEW OF THE COSTS

In 2007 the Dutch government has estimated the costs for the care and treatment of PD at 196 million euros (3). This is 0.3% of the total costs that the Dutch government spends on health care per year. The largest part of these costs (65%) are dedicated to the care for elderly people. Medical treatment only accounts for 11% of these costs (3). A great reduction in the costs could thus be achieved when symptoms of PD are alleviated. This would result in less aid needed for activities of daily living, and less nursing home admissions. The next section will explain the costs of medical treatment of PD and will compare neurofeedback treatment with current treatment options.

7.2 COSTS PER QALY

Next to the clinical efficacy, side effects and the organization of care, assessment of the cost-effectiveness of a treatment is an important step in evaluating the viability of implementing it in patient care. Health care providers and government institutions use the cost of one quality adjusted life year to assess the cost-effectiveness of a treatment. One quality adjusted life year is one life year that is gained in which a patient has lived a 100% healthy life. It does not only measure the gain in life years, but also at the quality of life during that period (41). In the case of PD this is very important as a cure is not available and almost all patients will experience a loss in quality of life due to the symptoms of the disease. This will also be a factor for BCI treatment of PD. As has been explained in chapter 5.3 this treatment cannot cure the disease and quality of life will most likely decrease with disease progression. Usually the cost of a QALY gained by a new treatment is compared to the most widely used current practice alternative (41). Unfortunately, at this time, there are no papers describing the cost-effectiveness of BCI treatment for PD because it has not yet been used in the medical field. Nevertheless, it is possible to give an overview of the costs and compare these with the costs of medical treatment and deep-brain stimulation.
The amount of sessions needed to diminish or completely eliminate the symptoms of Parkinson’s disease using BCI treatment is unknown. In a paper by Erickson-Davis in an experimental setting 24 sessions were used (20), but how many sessions are needed can differ greatly between patients. For instance, BCI treatment for ADHD is usually effective after 30 treatments, but patients suffering from depression can need 20 to 60 treatments before effects can be seen (18). For depression (major depressive disorder, MDD), organizations that offer BCI treatment therefore consider an average of 40 treatments (18). Because ADHD and depression are both partly dependent on a malfunction of dopamine pathways the assumption is made that the amount of sessions needed to treat these pathologies will closely resemble the amount needed to treat PD. The estimated costs for the treatment of ADHD and MDD can be found in Table 1 and 2 respectively.

<table>
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<th>ADHD treatment</th>
<th>Average costs (30 sessions)</th>
</tr>
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<tbody>
<tr>
<td>Intake</td>
<td>€75,-</td>
</tr>
<tr>
<td>1 session</td>
<td>€45,- €1350,-</td>
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<tr>
<td>Progress measurement after 15 sessions</td>
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<td>Progress measurement end</td>
<td>€75,- €75,-</td>
</tr>
<tr>
<td>Total</td>
<td>€1575,-</td>
</tr>
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Table 1 average costs of attention deficit hyperactivity disorder treatment using neurofeedback. (18)

<table>
<thead>
<tr>
<th>MDD treatment</th>
<th>Average costs (40 sessions)</th>
</tr>
</thead>
<tbody>
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<td>Intake</td>
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<td>1 session</td>
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</tbody>
</table>

Table 2 average costs of major depressive disorder treatment using neurofeedback (18)

It can therefore be expected that brain computer interface treatment for PD will cost €1500-2500 per patient per round of sessions. How many rounds of neurofeedback are needed in the lifetime of a patient to maintain the improvement in symptoms is as of yet unknown. But, assuming that patients can learn to transfer the strategies learned during neurofeedback training
sessions into real-life settings, regular sessions might be unnecessary to maintain the clinical benefits (21, 23). In comparison, the costs for DBS surgery are estimated at €24 640 by Dams and colleagues (42). A battery replacement for the stimulation device is, at €3050, more expensive than one round of treatment of BCI, and is needed every 4 years (42). According to Dams and colleagues DBS treatment will result in a lifetime cost of €133 200 (42). Medical treatment is less expensive but results in a lifetime cost of €126 200 (42). These figures indicate that a cost-effectiveness analysis using the clinical efficacy of BCI treatment would be very interesting as it could lower the costs of PD treatment significantly.
8. CONCLUSION

Parkinson’s disease (PD) is the second most common degenerative disease of the nervous system. It is characterized by a total dysfunction of the motor system due to Lewy body deposition in the substantia nigra pars compacta, resulting in tremor, rigidity, bradykinesia, postural instability and cognitive decline. Treatment, pharmacological or surgical, is symptomatic and progression of the disease cannot be slowed. Because these treatments have varying effects per patient, and may pose considerable adverse effects there is the need for new, non-invasive treatments. BCI neurofeedback using EEG is a valid treatment option.

EEG measurements show distinct brain wave patterns that are associated with the symptoms of PD. Aberrant oscillatory rhythms in the theta, SMR and beta ranges are associated with limb tremor, while a decrease in readiness potential causes problems with initiating movements. Using brain-computer interfaces it is possible to make patients aware of these brain waves and teach them to modify them. Indeed, randomized controlled trials have shown that amplification of SMR waves using neurofeedback improves PD patient’s physical balance. Results of a neurofeedback protocol for oscillatory rhythms on the other symptoms of PD are less obvious; a non-significant decrease was seen but no conclusions can be drawn yet. Amplification of the readiness potential in PD patients is possible, but the clinical effect on movement initiation problems still needs to be examined. These results show the validity of neurofeedback as a treatment option, but also display the need for further research into the clinical efficacy.

This absence of proven clinical efficacy poses ethical concerns because a risk-benefit ratio cannot be established. Even though there are no serious side effects associated with neurofeedback treatment it is unknown how it may affect the “sense of self”. Because of this, and because there is no information about the cost-effectiveness of this treatment, neurofeedback as a treatment for PD needs to be researched further before it can be implemented into the current treatment plan. After high-quality research is available into its clinical efficacy, it can be established for whom, and when, neurofeedback is a valid treatment option.
9. REFERENCES


