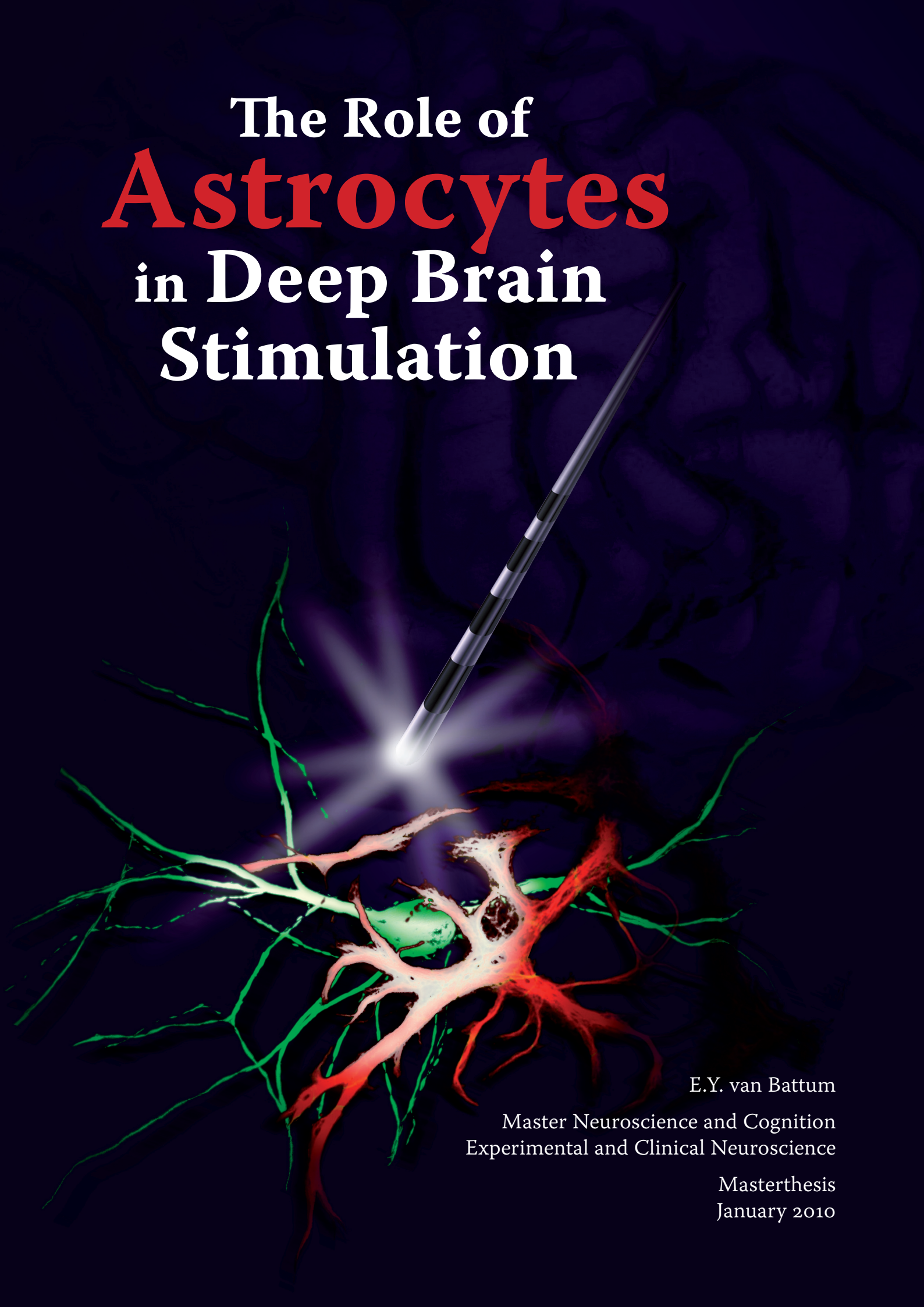
The Role of Astrocytes in Deep Brain Stimulation



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Master Neuroscience and Cognition
Experimental and Clinical Neuroscience

Masterthesis
January 2010

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Under the supervision of Dr. E.M. Hol

Outline

On the cover

Artist impression of deep brain stimulation electrode that stimulates a neuron (green) and an astrocyte (red). Made by E.D. van Battum.

Abstract

Deep brain stimulation (DBS) has been used in the treatment of many neurological disorders already some decades and its clinical benefit has frequently been marked. The mechanism by which DBS affects neuronal signalling is still elusive and extensively studied. Although most studies are only concerned with the effect that DBS has on neurons, it is unlikely that DBS solely affects these cells in the brain. It is hypothesised that DBS also affects glial cells and that these cells underlie, at least partly, the beneficial effects of DBS on brain function. Since DBS is thought to interfere with neural network activity and astrocytes are deeply involved in the regulation of neural network signalling, astrocytes seem the perfect candidates. In this review, the role of astrocytes in the working mechanism of DBS is investigated. It is shown that astrocytes can be triggered to release signalling proteins and to proliferate upon high-frequency stimulation, such as DBS. Interestingly, it has been shown that astrocytes after proliferation might differentiate in neural stem cells as a result of the electrical stimulation. The line of evidence for the contribution of astrocytes in the mechanism of DBS is still very thin, but compelling and therefore, much more work has to be done in this field. Future studies need to point out to what extent astrocytes play a role in the effect of DBS on brain function and the therapeutic effect of this. If astrocytes are truly involved in the mechanism of DBS, this has important implications for the future application of the method.

Abbreviations

DAAO	D-amino acid oxidase
DBS	Deep brain stimulation
GP	Globus pallidus
NO	Nitric oxide
OCD	Obsessive-compulsive disorder
PD	Parkinson's disease
SN	Substantia nigra
SR	Serine racemase
STN	Subthalamic nucleus
Str	Striatum
VIM	Ventral intermediate nucleus of the thalamus

Introduction

Deep brain stimulation (DBS) has already been used successfully for some decades to treat various neurological diseases. Predominantly, movement disorders in which the basal ganglia are affected, such as Parkinson's disease (PD), are treated with this therapeutic method. Historically, these illnesses were treated by lesioning certain thalamic or striatal regions in patients. In the early 1960s it became clear that high frequency electrical stimulation in these areas, used to determine the area of lesion, had beneficial effects on the disease symptoms (Ohye et al. 1964). At that point in time, almost nothing was known about how the technique worked and why it had these beneficial effects. However, based on its positive effects it became a more general tool in treating these disorders. Nowadays, there is a lot of research done to decipher the mechanism of action of DBS. Still, it is not entirely clear how DBS affects neuronal network communication. In spite of this, DBS has now also been tried in many other neurological diseases such as obsessive-compulsive disorder and Tourette's syndrome (Visser-Vandewalle et al. 2003, Sturm et al. 2003).

The generally accepted mechanism of action of DBS is currently that pathological neuronal network signalling patterns are modulated in a way that their disturbance of the normal functioning of the network is decreased (Gubellini et al. 2009, McIntyre, Hahn 2009). The elements that are indicated to be the main target of DBS are large myelinated axons (Ranck 1975). Due to antidromic axonal propagation of the depolarisation induced by DBS, the effect spreads over multiple brain areas (Grill, Cantrell & Robertson 2008). In the target brain nucleus, it seems that the net effect is suppression (Gubellini et al. 2009, McIntyre et al. 2004), however functional brain imaging studies almost all show an increased activity around the electrode (Ballanger et al. 2009).

Although the majority of studies only concerns the effect of DBS on neuronal signalling and the modulation of that, it is not likely that DBS exclusively interferes with neurons. It is hypothesised that there are also other, non-neuronal cells in the brain that are influenced by DBS and possibly contribute to its (therapeutic) effect. In principle, astrocytes are non-neuronal elements that do have electrophysiological properties, they are excitable and they can respond to electrical stimuli (Bevan, Raff 1985). Furthermore, astrocytes play an important role in the preservation of neuronal activity. This makes them a primary candidate to study in relation to high-frequency electrical stimulation.

Astrocytes are very much involved in the regulation of neuronal network activity (Fellin, Pascual & Haydon 2006). By the release of various gliotransmitters, they can interfere with synaptic activity and plasticity (Perea, Navarrete & Araque 2009, Henneberger et al. 2010). It has even been indicated that astrocytes form neuronal stem cells in the adult brain (Doetsch et al. 1999). Primarily, astrocytes are thought to divide and develop into neuronal stem cells in response to neuronal damage (Buffo, Rolando & Ceruti 2009). It is suggested that the effect of DBS might rely, at least partly, on both the way astrocytes influence neuronal networks and astrocytic stem cell properties (Jun et al. 2007, Bekar et al. 2008).

In this review, it is attempted to provide an overview of the current status of DBS and the role astrocytes may play in the mechanism of action of DBS. At the end of this review current knowledge is put in perspective and future lines of research are considered. These future studies need to provide clearer insight in the relation between astrocytes and the effect of DBS. To what extend astrocytes are involved in the process is still elusive. However, it can be concluded that astrocytes are presumably involved in the working mechanism of DBS.

Deep brain stimulation

In the early 1960s it was discovered that electrical high-frequency stimulation (100Hz) of the ventrolateral thalamic area had very positive effects in patients suffering from Parkinson's disease (Ohye et al. 1964). The electrical stimulation was used in this case to determine the precise location to lesion the thalamus, which was a common procedure in treating Parkinson's disease. Though these effects were very promising, it was not until the 1970s that this method was first used therapeutically to treat movement disorders from the cerebellum (Cooper 1973, Cooper et al. 1976). Treating movement disorders using cerebellar stimulation eventually fell out of favour since other studies failed to show consistent benefit (Penn 1982), but there appeared other promising reports of chronic brain stimulation as a treatment for movement disorders in the 1980s (Brice, McLellan 1980). In the 1990s the technology of chronic implanted pacemakers was combined with chronic implanted deep brain electrodes (Benabid et al. 1991) and since then, deep brain stimulation (DBS) has become an increasingly popular treatment for a variety of disorders. However, the exact mechanism of its therapeutic effect is still far from understood.

In DBS, microelectrodes are implanted uni- or bilaterally in the brain in specific nuclei and these electrodes are powered by a pulse generator. The pulse generator is typically implanted under the clavicle of the patient. A schematic representation of the placing of DBS electrodes and pulse generators in a patient is given if figure 1B. The electrodes themselves can be of various types. Electrodes consisting of a smooth 1.27mm by 28cm to 40cm urethane outer jacket which have four annular platinum/iridium electrode contacts near the lead tip (see figure 1A), are mostly used in human patients (Gubellini et al. 2009). This is because platinum is relatively non-toxic to the brain compared to other metals. Differences in size, shape and area of the microelectrode affect the spatial distribution of the current density and the shape and volume of the electrical field generated within the brain tissue. Naturally, the size of the electrode contacts

on the tip of the lead must respect the boundaries of the targeted brain structure. Therefore, in experimental DBS in rodents, electrodes differ much in size and shape from those used in humans.

Not only size and shape of the electrode affect the effect of electrical stimulation, also other parameters such as pulse form and the polarity of stimulation are important issues. Biphasic stimulation is preferred over monophasic pulses since biphasic stimulation minimises the accumulation of unrecoverable current and in that way, reduces cell damage (Gubellini et al. 2009). In addition, different pulse waveforms have different efficiency levels (Yousif, Bayford & Liu 2008). Furthermore, monopolar electrodes are favoured in human patients since lower current is needed for efficient DBS compared to bipolar electrodes, which has positive consequences for the battery life of the pulse generator. Thereafter, a brain nucleus has an anisotropic nature, different cell types are located in a nucleus and these elements have different electrophysiological properties. Furthermore, the orientation of the fibers in a nucleus influences the effect of stimulation (Ranck 1975).

It has been shown that minimal variation in the location of electrode placement can make a big difference in stimulation efficacy (Papavassiliou et al. 2008). This is still a shortcoming of the method. If the electrode is misplaced, treatment will not work properly and the patient has to cope with more negative side effects. Fortunately, techniques for more precise electrode placement are currently under investigation. For instance, electrode targeting can be improved with electrophysiological recordings that type the target neurons very precisely (Chan et al. 2010).

In summary, DBS is a relatively new therapeutic method, which therapeutic value and mechanism are currently studied excessively. The effect of DBS is influenced by many factors of both electrophysiological and neuro-anatomical kind. Below, some principals of DBS are described and important studies into the mechanism of action of DBS are reviewed.

Principles of deep brain stimulation

In many articles about DBS sentences like: 'electrical stimulation of the subthalamic nucleus' are used, which is actually short for: 'an electrode was placed in the subthalamic nucleus and an unknown number and unknown kinds of cells at unknown locations in the vicinity of the electrode were affected by stimulation' (Ranck 1975). To develop a better understanding about how deep brain stimulation may actually work, first it is needed to see how brain tissue is affected by electrical stimulation. Not all cells in the brain have the same electrical properties. This makes studying the effect of electrical deep brain stimulation as a whole very complex and difficult to comprehend. In this part, some points of interest considering the effect of electrical pulses on different brain cell types are explained.

One of the most important principles of electrical stimulation as a whole is the relation between stimulus amplitude and duration. To produce a constant effect in stimulation, when current amplitude decreases, then pulse duration has to increase and the other way around. For most neural tissue elements is the amplitude-duration curve an exponential decay. The minimal electric current of infinite duration resulting in an action potential is the amplitude asymptote in this formula and is called the rheobase. The amplitude-duration curve is described by the following equation:

$$I_{th} = I_{rh}(1 + t_{ch}/t)$$

in which I_{th} represents the threshold current, I_{rh} is the rheobase, t_{ch} represents the chronaxie and t is the pulse width (duration) (Gubellini et al. 2009). The chronaxie distinguishes different types of neural elements and represents the minimum time over which an electric

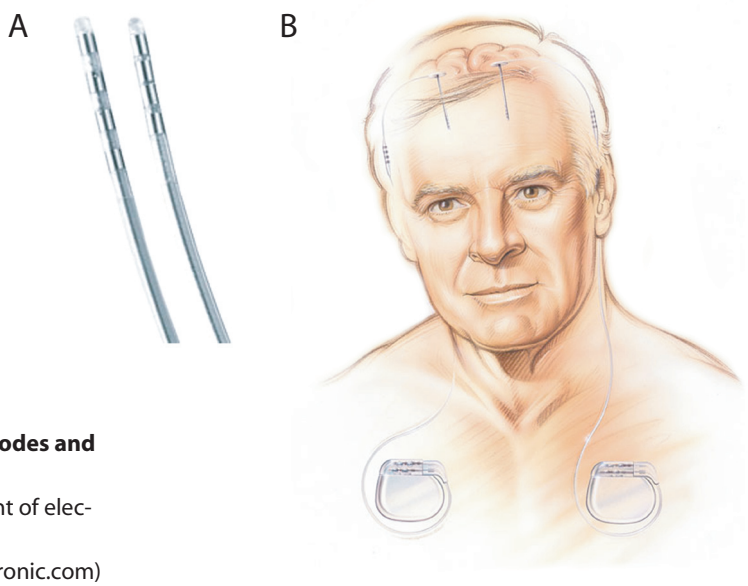

Figure 1. Schematic representation of DBS electrodes and placement in a patient.
A. Different types of electrodes. B. Bilateral placement of electrodes and pulse generators in a patient.
Adapted from Medtronic United States (www.medtronic.com)

current double the strength of the rheobase, needs to be applied in order to stimulate a nerve cell. Therefore, different tissue types have different chronaxies. Large myelinated fibers have chronaxies ranging around 30-200μs, whereas cell bodies and dendrites have chronaxies ranging in a 1-10ms scale (Ranck 1975). Thus, under normal stimulation conditions, postsynaptic responses from electrical stimulation result from the activation of large myelinated axons rather than cell bodies or dendrites (Holsheimer et al. 2000).

The responsiveness of the elements is determined by several factors. First, the orientation of the cell body and axons in relation to the current flow induced by the microelectrode determines the responsiveness. More specifically, the responsiveness of axons relies completely on the voltage gradient parallel to the axons (Ranck 1975). For example, if the axon is totally transverse of the voltage gradient of the electric field, the axon is not stimulated. Second, gray and white matter have different resistivities, which also holds true for myelinated and unmyelinated axons. Lastly, the distance of the element to the microelectrode is important for the responsiveness of the element (Holsheimer et al. 2000). For instance, axons very close to the tip of the electrode will not be stimulated although axons farther away from the electrode, but still in the induced electric field, will.

Since monopolar extracellular stimulation is mostly the case, both outward and inward current is of importance. Any outward current that locally depolarises an axon, has elsewhere an inward current that will hyperpolarise the axon. It is thought that the inward current spreads over a larger area so the magnitude of hyperpolarisation will be less than the magnitude of depolarisation (Ranck 1975). Therefore, a depolarisation of an axon can travel through a lightly hyperpolarised field.

As stated above, axons are the predominant neural elements activated by electrical stimulation. Not all axons are located in the same direction in a nucleus. Electrical stimulation can therefore propagate in two different ways in the axon, that is: orthodromic and antidromic. Orthodromic propagation is that the action potential induced by electrical stimulation travels away from the cell body to the synaptic terminal. Antidromic action potential propagation goes the other way around, so towards the cell body. It has been indicated with functional imaging studies that the area that is activated by the electrode is larger than theoretically calculated (Asanuma et al. 2006). Furthermore, it has been shown that after subthalamic nucleus (STN) stimulation a correlated activity decrease resulted in the motorcortex (Haslinger et al. 2005). Antidromic propagation was studied recently by the usage of computational models. The authors indicate that antidromic axonal stimulation is responsible for these kinds of effects (Grill, Cantrell & Robertson 2008). In addition, it was suggested that the antidromic axonal action potential travelling also interferes with the pathological patterns of activity within the basal ganglia-thalamus-cortical loops, against which DBS is most frequently used (see below).

In summary, electrical stimulation of brain tissue has many facets, which make studying the effects of deep brain stimulation rather complex. Although there is much known of the possible types of mechanism, it is still very difficult to oversee all the effects DBS actually has in the brain.

Effects on brain tissue and function

Much work is conducted in various modalities of neuroscience, trying to answer the question what neuronal mechanism underlies the therapeutic effect of DBS. In this field, there are many contradictory theories and even study results are very inconsistent. In the following paragraphs, a brief overview is given of the current thoughts about how DBS is working.

In the first place, it is shown by the use of functional brain imaging techniques that DBS increased neural activity in the area near the electrode (Ballanger et al. 2009, Haslinger et al. 2005, Perlmutter et al. 2002). In addition, many electrophysiological studies point out that the DBS target nucleus is excited upon stimulation (McIntyre et al. 2004). On the contrary, the effect of DBS closely resembles the effect of lesioning the target area (Gross, Lozano 2000). There are also electrophysiological studies that find an inhibitory effect of DBS, corresponding to the lesion effect (Lozano et al. 2002). It is thought that this inhibitory effect could be the result of indirect synaptic inhibition or because of transmitter depletion and synaptic fatigue due to extensive high frequency synaptic firing (McIntyre et al. 2004, Wang, Kaczmarek 1998). However, there exist much contradictory evidence for these hypotheses.

The direct net result of stimulation correlates with the type of fibers that is activated (McIntyre, Hahn 2009). For instance in the subthalamic nucleus (STN) glutamatergic neurons are located, so DBS has a downstream excitatory effect. On the other hand, when GABAergic neurons are stimulated such as those in the globus pallidus pars interna (GPi), an overall inhibitory effect is seen. When polysynaptic pathways are involved, a combination of excitation and inhibition is observed. In this framework, also orthodromic and antidromic propagation, as described above, is of importance. In addition and to further complicate matters, de-coupling of cell body and axon activity also affects the eventual stimulation effect (Gubellini et al. 2009, McIntyre et al. 2004). This concept relies on the depolarisation of nearby axons and hyperpolarisation of axons and cell bodies farther away from the electrode. This then results in silenced neuronal firing or the target structure but increased synaptic output.

After all this is illustrated, the question is, what then is a main effect of DBS, which accounts for the therapeutic benefit. The answer might lie in the following. There is seen more regularity in the firing pattern of neurons after DBS (Dorval et al. 2008, Hahn et al. 2008). This regularity is associated with the existing therapeutic benefit of DBS (McIntyre, Hahn 2009, Birdno et al. 2008). It is thought that during stimulation, the neural network is not

restored to pre-pathological stages, but rather to some third state that allows for function to improve relative to the disease state (McIntyre, Hahn 2009). Taken together, this suggests that DBS has no local effect, but affects a whole neural network at once. It is thought that this best represents the way DBS is working (McIntyre et al. 2004).

In addition to stimulation effects, DBS affects the brain another way. The insertion of microelectrodes in brain tissue has major consequences for the tissue integrity. The space directly around the electrode is called peri-electrode space (PES). This space is initially filled with spinal fluid. After a period of time, the PES becomes filled with giant cells, which eventually form scar-like tissue around the electrode (Moss et al. 2004). The thickness and conductivity of this encapsulation layer around the electrode affects the electrode impedance during DBS (Butson, Maks & McIntyre 2006). This tissue reaction distorts the stimulation waveform and in that way the stimulation efficacy is decreased (Yousif, Bayford & Liu 2008). It is thought that the degree of gliosis is influenced by the shape of the electrode (Griffith, Humphrey 2006). The more surface irregularities, the higher degree of gliosis. It would be interesting to see whether this around-electrode gliosis can be reduced by pharmacological intervention. This would be beneficial to the lifetime of the electrodes and their stimulation efficacy.

On the other hand, gliosis around the electrode has implications for the health of the neural systems. It is thought that the sheath around the platinum electrode, made of polyurethane, initiates the glial reaction (Moss et al. 2004). An inflammatory reaction in the brain can be life-threatening and this is a major risk for the patient. In addition, inflammatory cells and the proteins that are released affect neuronal communication. Interesting to note is that in some cases, only electrode insertion without stimulation is enough to overcome the symptoms of the disorder (Derrey et al. 2009). This might be due to the induction of a microlesion by bringing in the electrode, but it can also be the case that a certain inflammatory response disrupts a pathological neural pathway.

Taken together, despite an effect on neuronal signalling, DBS and its putting in place procedure induce gliosis in the target nucleus and this affects the stimulation efficacy. In many cases gliosis stays in mild forms and only surrounds the electrode, but in some cases the gliosis escalates. This is an important risk for patients and a disadvantage of the therapeutic method.

Current therapeutic usage of DBS

Nowadays, DBS is used for a variety of brain disorders. Although for every individual patient the most optimal parameters have to be determined, current standards for DBS in human patients are monopolar cathodic electrode with 1–5 V stimulus amplitude, 60–200 ms stimulus pulse duration and 120–180 Hz stimulus frequency (McIntyre et al. 2004). Generally, DBS is used in movement disorders of the basal ganglia, such as Parkinson's disease (PD) or dystonia. To understand the way DBS can help in patients suffering from PD or other movement disorders, the circuits of the nuclei that are stimulated by DBS have to be understood.

The basal ganglia are a neural network involved in motion initiation and control. The basal ganglia consist of multiple brain areas: the striatum (Str, which resembles the caudate nucleus and the putamen), the globus pallidus (GPe pars externa and GPi pars interna), the substantia nigra (SNc pars compacta and SNr pars reticulate) and the subthalamic nucleus (STN) (Parent, Hazrati 1995a, Parent, Hazrati 1995b). They receive input from various cortical areas and send output via the thalamus to the motorcortex. In simple terms, there are two pathways that cooperate in regulating movement. In the direct pathway inhibitory projections from the Str project to the tonically active inhibitory neurons in the GPi, which in turn project to the thalamus. The Str receives excitatory input from the SNc. This pathway functions in the release of tonic inhibition of movement. The other pathway, the indirect pathway, begins with an inhibitory projection from the Str to the tonically active inhibitory neurons of the GPe. The GPe neurons project to the STN, which also receive a strong excitatory input from the cortex. The STN sends its excitatory neurons to the SNr and to the GPi, which tonically inhibits the thalamus. This pathway can be seen as a brake on the normal function of the direct pathway. Furthermore, STN projects to the GPe, VP, pedunculopontine nucleus, Str and nucleus accumbens. In figure 2, the circuits of the basal ganglia are schematised. Black lines represent the direct pathway and grey arrows form the indirect pathway.

In PD, the normal signalling route is disturbed since dopaminergic neurons of the substantia nigra pars compacta are degenerated. Basically, this means that the direct pathway of the basal ganglia is inhibited and the indirect pathway is excited. Therefore, the initiation and termination of movements is impaired and a hypokinetic state occurs. Loss of SNc dopamine neurons results in a decreased activity of the thalamus, which is partly due to an increased bursting activity of the STN (DeLong 1990). This means that in PD, the regular firing pattern of the STN is affected. In figure 2, the implications of the loss of the SNc on the circuits of the basal ganglia are shown.

PD patients are often implanted with microelectrodes in the subthalamic nucleus (STN), ventral intermediate nucleus of the thalamus (VIM) or globus pallidus interna (GPi) and receive high-frequency stimulation. Currently, the most common form of clinically used DBS is stimulation of the STN in PD. Therefore, this type of DBS will be described in more detail.

High-frequency stimulation of the subthalamic nucleus

Both the knowledge about basal ganglia circuits and the historical STN lesioning for PD, lead to the rationale for targeting the STN in DBS treatment of PD, which functionality was first shown in monkeys in 1993 (Benazzouz et al. 1993). It has been shown that both uni-

and bilateral STN stimulation can help in PD patients (Kumar et al. 1999), but bilateral stimulation is mostly preferred. Beneficial to STN DBS in PD patients is that dopaminergic treatment can be reduced (Kumar et al. 1998), which is helpful since dopaminergic treatment itself is a source of movement dysregulation (see for review Voon et al. 2009). Approximately half of the STN neurons is spontaneously tonically active at resting membrane potential, the other half switches from tonic activity to burst firing voltage-dependently (Overton, Greenfield 1995). This results in glutamatergic output to other basal ganglia nuclei as described above. Hyperpolarisation of STN neurons results in silencing of action potential firing. In PD, a high rate of abnormal synchrony in firing patter of STN neurons is observed (Bergman et al. 1994). It has been shown that DBS disrupts this abnormal synchrony (Meissner et al. 2005) but instead of bringing it back to normal levels, it lifts the firing pattern to a certain third state.

There have been many studies into the effect on neuronal firing of DBS in the STN. It has been reported that in rat brain slice preparations after bipolar high-frequency stimulation similar to that in PD patients, the tonically active STN neurons switch to burst activity and after a short period of time completely cease firing (see figure 3A) (Magarinos-Ascone et al. 2002). Bursting cells responded by a brief burst period followed by prolonged inactivation. Overall, the study showed that STN high-frequency stimulation induced first a sustained depolarisation followed by bursts and eventually a total inhibition of firing throughout the stimulation period. Furthermore, it was suggested that this is a postsynaptic effect. This indicates that the beneficial effect of DBS in PD comes from suppression of STN firing. Prolonged inactivation was also suggested by another study that used bipolar high-frequency stimulation to rat STN slice preparations (Beurrier et al. 2001). The latter study indicates a change in membrane properties rather than a synaptic effect of stimulation.

When in slice preparations stimulation parameters were used that more closely resembled clinical DBS in PD patients, it was found that spontaneous firing of STN neurons was blocked and a stimulus-driven firing was induced instead (Garcia et al. 2003). Stimulus driven firing looked like bursts of spikes that were time-locked to the stimulus pulses (see figure 3B). Important to note is that these experiments were conducted in dopamine depleted rat brain slice preparations. These results represent more closely the idea of a third state of network activity and show that much of the effect depends on stimulus parameters.

In vivo effects of STN high-frequency stimulation have also been investigated. Important to note is that in vivo electrophysiological studies are mostly conducted in anaesthetised animals and that anaesthesia seriously affects neuronal signalling (Mahon, Deniau & Charpier

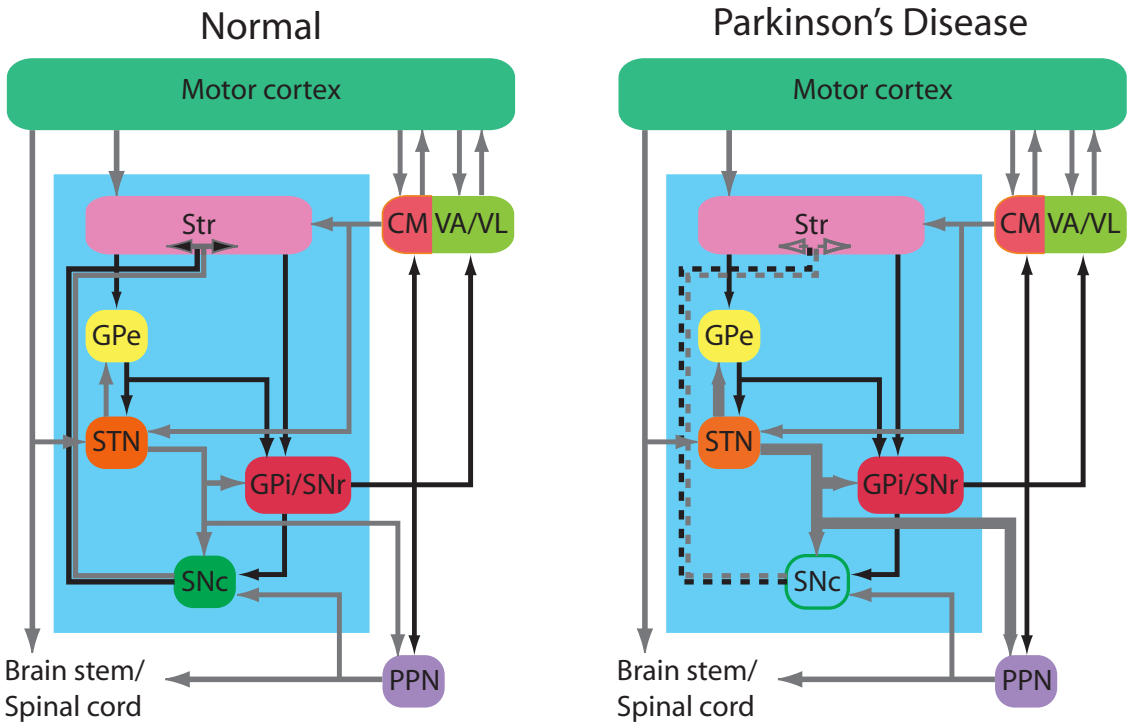

Figure 2. Schematic representation of basal ganglia circuit in normal situation and in Parkinson's disease. Direct (black arrows) and indirect pathway (grey arrows) are indicated in the projections of the basal ganglia. In PD patients (right figure), neurons of the SNc are lost and therefore, projections from the SNc are diminished. This results in an overactive STN, which has major consequences for the rest of the circuit. (CM centromedian nucleus, GPe globus pallidus pars externa, GPi globus pallidus pars interna, PPN pedunculopontine nucleus, SNc substantia nigra pars compacta, SNr substantia nigra pars reticulata, STN subthalamic nucleus, Str striatum, VA/VL ventral anterior/ventrolateral thalamus.)

2001). It was found that in anaesthetised rats, STN neurons were depressed of firing post-stimulation (Benazzouz et al. 2000). Furthermore, also in the SNr there was found a suppressed activity, other than in the ventrolateral thalamus where an increased activity was recorded. It is suggested that high-frequency stimulation of the STN blocks transmission of information through the STN (Perlmutter, Mink 2006). Also downstream effects can be investigated in intact animals. In Parkinsonian monkeys, the effects of STN stimulation on GPe and GPi were investigated (Hashimoto et al. 2003). It was indicated that the firing pattern of the GPe and GPi was changed during clinically relevant DBS in these monkeys. STN stimulated created short-latency excitatory responses that thonically increased firing in both pallidal parts. It was suggested that antidromic GPe axonal activaton was involved in this process. Once more it was suggested that this form of interference with the pathological basal ganglia network activity, is although not normal, disrupting the pathological pattern to a less disturbing one.

Another in vivo study shows that dopamine neurons in the SNc are preserved from degeneration in high frequency stimulated animals (Harnack et al. 2008). This study was based on the theory that dopamine neuronal degeneration in PD is the result from an overactive STN (Rodriguez, Obeso & Olanow 1998). Suppression of the STN activity had a positive effect on the preservation of dopamine neurons in rats that were treated with 6-OHDA, a frequently used animal model for PD. This indicates that network activity change induced by DBS has actual physical effects.

Taken together, from these studies can be concluded that DBS in fact disturbs the pathological activity in the basal ganglia and changes the network activity pattern in one that is less distressing the normal function of the system. It is mainly believed that this is the foremost mechanism of action of DBS, also when DBS is used in other nuclei for other purposes.

Other therapeutic targets of DBS

DBS is also used in patients suffering from obsessive-compulsive disorder (OCD), Tourette's syndrome and treatment resistant depression (Visser-Vandewalle et al. 2003, Sturm et al. 2003, Mayberg et al. 2005). DBS was tried in these disorders since, in the past, these disorders were generally treated by lesioning the brain. Stimulation occurs in the regions that were commonly lesioned before. OCD patients are mostly stimulated in the internal capsule and the nucleus accumbens (Larson 2008). Results are promising, but not yet very consistent. When at least 35% reduction in symptoms is achieved by this method, it is considered as useful. However, different nuclei are currently being tested as DBS target for optimal results.

Tourette's patients receive DBS mostly bilaterally in the medial thalamus, which was selected based on historical lesioning studies (Visser-Vandewalle et al. 2003). DBS brings a 60-90% reduction of ticks in these patients. The GPi has also been used as target for DBS in Tourette's syndrome, since it is thought that GPi stimulation alleviates hyperkinetic symptoms in Parkinson's disease and Tourette's ticks can be thought of as hyperkinetic states. Even as medial thalamic DBS, GPi DBS in Tourette's patients seems to bring positive results (Larson 2008).

DBS is also tried in patients suffering from treatment-resistant depression. The DBS target, Brodmann area 25 inside the frontal lobe, was found using neuro-imaging techniques and symptoms were reduced with at least 50% (Mayberg et al. 2005). Furthermore, the nucleus accumbens has also been described as a DBS target in treatment-resistant depression (Schlaepfer et al. 2008). It showed the same striking results as stimulation in the frontal lobe, but seemed to have less negative side effects.

In summary, despite the lack of knowledge about the precise working mechanism of DBS, it is already

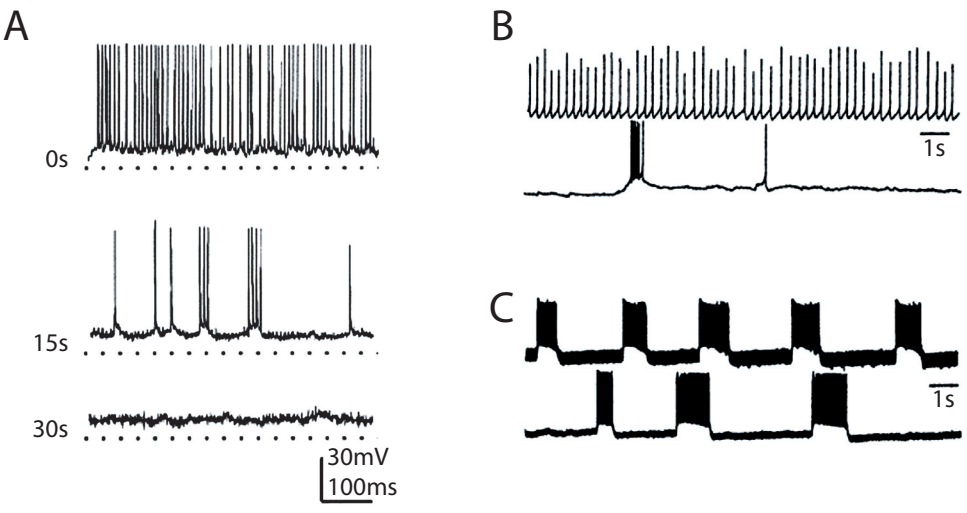

Figure 3. Change in firing pattern of STN neurons after high-frequency stimulation.
A. Reaction of tonically active neurons after 120Hz stimulation. Initial activity (0s) switched to a bursting mode (15s) and then to silence (20s). Adapted from Magarinos-Ascone et al. 2002. B. Reaction of tonically active neurons in dopamine depleted slice preparations before (above) and during (below) 135Hz stimulation. Adapted from Garcia et al. 2003.

frequently used for a variety of movement and psychiatric disorders. In addition, DBS functionality is being researched very extensive and new applications for DBS are studied. For instance, in the future for DBS might be used as a treatment for schizophrenia (Mikell et al. 2009) or for addiction (Vassoler et al. 2008).

Positive and adverse effects of DBS

Currently, DBS is even preferred over other surgical procedures in psychiatric brain disorders (Larson 2008). This is mainly since DBS is adjustable, by monitoring its many stimulation parameters. Furthermore, DBS is non-destructive and reversible. It is thought that the presence of the electrode itself does not disturb network activity in the brain. In addition, when stimulation is set off, there is no effect anymore.

Although DBS is a very promising therapy, it has also some serious adverse effects. One of the most reported side effect of DBS is that STN stimulated patients develop depression (Berney et al. 2002). Furthermore, patients receiving DBS in STN complain about apathy (Krack et al. 2003), anxiety (Houeto et al. 2002), mania (Kulisevsky et al. 2002), sexual disinhibition but also hypersexuality (Romito et al. 2002), euphoria (Kumar et al. 1999), hallucinations (Burn, Troster 2004) and mood changes (Okun et al. 2003). The latter of these adverse effects is also associated with GPi stimulation. Except for these behavioural effects there are also some other serious adverse effects of DBS. These include cerebral hemorrhage, infections and other problems related to the surgical procedure, but also skin erosion, foreign body reaction, granulama, seroma and pain over the pulse generator. Furthermore, sometimes hardware problems occur, such as electrode fracture, wire failure and lead migration (Weaver et al. 2009). Frequent battery changes are also a drawback for patients.

It has also been studied whether cognition is affected by DBS. Most important are negative effects on cognition. For instance, it is shown very recently that face recognition, in the recognition of fearful or sad faces, can be impaired after chronic STN DBS in patients (Peron et al. 2010). Noteworthy is also a study, which claims that cognition can be improved after DBS (Hu, Eskandar & Williams 2009). In this study it is stated that stimulation of the striatum enhanced memory formation and recall. Note, this effect was seen in monkeys and claimed to be dopamine dependent, so it is unlikely that this also occurs in PD patients.

Taken together, while DBS is already a frequently used therapeutic method, it is becoming more and more clear that also negative effects are concerned with it. Sometimes, the chronic behavioural adverse effects are for the patient a reason to drop the therapy. Other acute adverse effects can be overcome by just changing stimulation parameters. If possible, problems with the electrodes and their wiring have to be repaired before DBS can function properly.

As is described above, the mechanism of action of DBS is extensively studied and at the same time it is already used in the clinic. It is thought that mostly axons are activated by electrical stimulation and that the stimulation progresses either orthodromically or antidromically. Antidromic stimulation results in the recruitment of brain areas other than the stimulated nucleus. The most likely and most widely accepted mechanism of DBS is that it shifts the pathological neuronal network activity not to pre-pathological levels, but rather to a third state of less-disturbing network activity. Although it is hard to investigate neuronal networks, it is necessary to further explore this proposed effect of DBS. It would be interesting to see which elements are further included in the effect and it would be of significance to know whether the effect is due to direct change of membrane properties or if there is another party involved.

Since DBS is thought to be interfering with neuronal network activity, it is interesting to look at a party which is deeply involved in the working of neuronal activity: the astrocytes. It could be that the effect DBS partly relies on the function of these elements in the brain. In the following piece of this thesis, astrocytic function in neuronal communication is reviewed. Hereafter, the possible involvement of this third party in neuronal communication in the working of DBS is hypothesised.

Astrocytes

In the nervous system there are three major classes of neural glial cells. The oligodendrocytes produce myelin sheaths around axons, microglia represent the immune cells of the nervous system and the third group: the astrocytes. Astrocytes form the predominant glial cell type and basically, their function is to maintain, in a variety of ways, an appropriate chemical environment for neuronal signalling (Kandel, Schwartz & Jessell 2000). This includes the regulation of neurotransmitter signalling and recycling, synaptic transmission, synaptogenesis, the control of blood flow (astrocytes predominantly form the blood-brain barrier) and K^+ homeostasis.

Astrocytes possess small somata (<10μm) and numerous highly branched processes that can reach distances up to 100μm (Bushong et al. 2002). The fine branches of an individual astrocyte stand in contact with each other and with those of other astrocytes via gap juctions. It was found that astrocytes are connected to hundreds of others when a single astrocyte was filled with a gap junction-permeable dye by the use of patch clamp techniques (Konietzko, Muller 1994). In addition, these branches make contact with neuronal processes at the synapse pre- and post-synaptically (Ventura, Harris 1999). The magnitude of these neural contacts made by a single human astrocyte is estimated around 1 million, which suggest a very important role of astrocytes in synaptic regulation. After the discovery of the intimate

relation between astrocytes and synapses, the term 'tripartite synapse' has been introduced (Araque et al. 1999). In the following part, the role of astrocytes in neuronal communication is reviewed.

Astrocytes and neural communication

It is nowadays generally accepted that astrocytes actively participate in neuronal and synaptic function. Communication between neurons and astrocytes is thought to run in both ways. Astrocytes can sense neural communication since they express many neurotransmitter receptors on their membrane. In situ, astrocytes are found to be responsive to purinergic, adrenergic, muscarinic, glutamatergic, GABAergic, histaminergic, endothelin, endocannabinoid, bradykinin, thrombin, opiate and substance P receptors (Agulhon et al. 2008). It is thought that in vivo, astrocytes at least can respond to four different transmitters. On the other hand, astrocytes themselves can release a number of compounds when signalling to neurons. For instance, glutamate, D-serine and ATP released by astrocytes can bind to receptors on neurons pre- and post-synaptically. These astrocytic signalling compounds are called gliotransmitters. Thus, astrocytes can not only sense neural activity, but also modulate neural activity by releasing gliotransmitters.

Primarily, the communication between astrocytes and neurons proceeds through the action of G_q-coupled G protein-coupled receptors (G_q GPCRs) (Agulhon et al. 2008). These receptors function via a phospholipase C/inositol 1,4,5-triphosphate (PLC/IP_3) mediated pathway to release Ca^{2+} from intracellular calcium stores, such as the endoplasmatic reticulum. Calcium is thought to fulfil the main part of neuron-astrocyte, intra-astrocyte and inter astrocyte communication. A schematic representation of calcium signalling in the communication between an astrocyte and a synapse is given in figure 4. The protein kinase C/diacylglycerol (PKC/DAG) pathway is involved in the termination of the Ca^{2+} signal in astrocytes.

The elevations in Ca^{2+} levels of astrocytes are oscillatory and called Ca^{2+} waves. At first, they were thought to be induced by simple neurotransmitter spill over from the synaptic cleft. However, this is not true since astrocytes can discriminate between pathways and respond selectively to synapses with different neurotransmitters (Perea, Araque 2005, Schipke, Haas & Kettenmann 2008). Ca^{2+} waves initiate on a specific site in the astrocytic processes, called a microdomain, and then spread into other regions of the astrocyte. It is thought that this form of signalling could be a mechanism, which astrocytes use to pass on information over a large distance. In addition to induced Ca^{2+} waves by neuronal activity, there is also spontaneous occurrence of Ca^{2+} waves in astrocytes in certain brain areas such as the thalamus, as a result of constitutive G_q GPCR activity (Parri, Gould & Crunelli 2001). It has been suggested that neuronal activation synchronises these spontaneous Ca^{2+} waves (Aguado et al. 2002), which results in stronger signalling efficacy. On top of this and of crucial importance, it has been found that Ca^{2+} signalling can be induced by physiological sensory stimuli. For instance, whisker stimulation in mice increased astrocyte Ca^{2+} response in mouse cortex (Wang et al. 2006). In addition, peripheral stimulation or

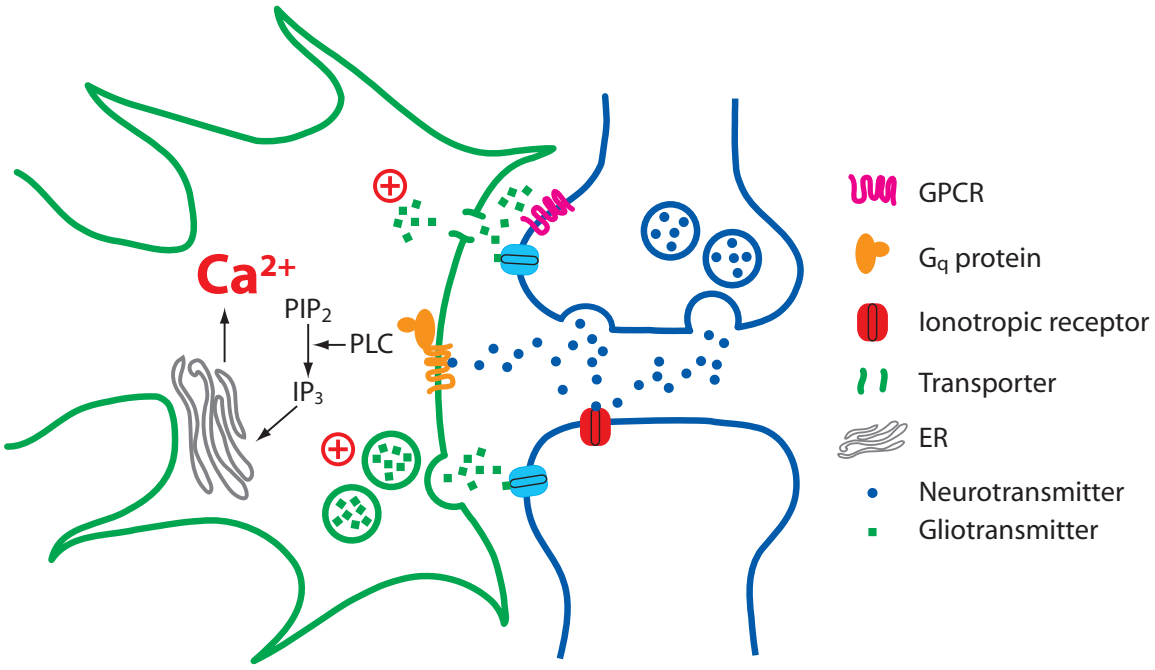

Figure 4. Astrocyte-neuron communication through Ca^{2+} and gliotransmitter signalling in tripartite synapse. Astrocyte process (green) together with pre- and post-synaptic neuron (blue). Neurotransmitters are sensed by the astrocytic G_q-GPCR and this results via a PLC dependent pathway in the release of Ca^{2+}. Ca^{2+} stimulates gliotransmitter release. Gliotransmitters influence both pre- and post-synaptic signalling. (ER endoplasmatic reticulum, GPCR G protein-coupled receptor.)

even direct electrical stimulation of the locus coeruleus elevates astrocytic Ca^{2+} in the cortex of mice in vivo (Bekar, He & Nedergaard 2008).

A single Ca^{2+} wave can travel up to 200µm from its initiation site. This spread of inter astrocyte Ca^{2+} waves is thought to be regulated by ATP. ATP can be released from astrocytes in three different ways: via gap junctions, via P2X7 channels and via Ca^{2+} triggered vesicular exocytosis (Zhang et al. 2003). Vesicular exocytosis of ATP seems to be the predominant cause of Ca^{2+} wave spreading between astrocytes (Bowser, Khakh 2007). Glutamate was found to have no influence on the spread of the Ca^{2+} waves in astrocytes.

Ca^{2+} waves in astrocytes are shown to lead to increased glutamate release from presynaptic terminals in the hippocampus (Fiacco, McCarthy 2006). It was suggested that the release of Ca^{2+} in astrocytes leads to a global intracellular Ca^{2+} elevation and this results in the release of gliotransmitter glutamate, which binds to presynaptic metabotropic glutamate receptors (mGluRs) resulting in enhanced presynaptic glutamate release. In addition, postsynaptic activation of ionotropic glutamate receptors (iGluRs) by astrocyte-derived glutamate has been shown (Pasti et al. 1997). On top of this, there are indications that glutamate released upon astrocytic Ca^{2+} signalling, can cause extrasynaptic NR2B subtype NMDAR-mediated slow inward currents (Fiacco, McCarthy 2004, Shigetomi et al. 2008). By this mechanism, synchrony between neuron populations can be achieved. These form important examples of how astrocytic signalling can influence neurotransmission. Nevertheless, there are many contradictory study results, considering the way astrocyte-derived glutamate modulates neural communication, reviewed by Agulhon in 2008 (Agulhon et al. 2008).

It is interesting to note that not all synapses are thought to be tripartite. Estimated is that only 40% of all synapses is regulated by astrocytes in this intimate way (Perea, Araque 2007). These findings result in questions considering the dynamics of the formation and stability of tripartite synapses. If these tripartite synapses indeed are dynamically regulated, this has consequences for the function of the neuron-astrocyte network.

Astrocytes regulate neuronal network activity

Upon activation, astrocytes release gliotransmitters. There are many compounds known to be used as gliotransmitter, of which glutamate, D-serine and ATP are the most important examples. These gliotransmitters can activate receptors located on neuronal membranes and by that manner, activate signalling cascades. Glutamate, one of the first identified gliotransmitters, is released from astrocytes upon Ca^{2+} signalling and can bind to neuronal metabotropic glutamate receptors, presynaptic kainate receptors and even to postsynaptic NMDA receptors. It has also been found that glutamate can be released from astrocytes after purine receptor activation (Fellin et al. 2006). Astrocytic glutamate has been reported to have many effects on neuronal excitability. Already mentioned is the induction of slow inward currents by NMDA receptor activation through astrocytic glutamate (Fiacco, McCarthy 2004, Shigetomi et al. 2008). Astrocytic glutamate also binds tot presynaptic metabotropic glutamate receptors or presynaptic NMDA receptors and by doing so, it regulates spontaneous and evoked neurotransmitter release (Perea, Araque 2007).

A different compound released by astrocytes through gliotransmission is D-serine. D-serine is transformed from L-serine by serine racemase (SR), an enzyme mostly distributed among astrocytes in the brain (Schell et al. 1997), but is also found in neurons. It is released from astrocytes upon activation of astrocytic metabotropic or ionotropic glutamate receptors (Mothet et al. 2005). D-serine is found to bind as an alternative to glycine to the strychnine-insensitive glycine-binding site of NMDARs and forms a strong endogenous co-agonist for these receptors. It has been found that D-serine modulates NMDAR mediated neurotransmission and plasticity in many different brain regions (Oliet, Mothet 2009). For instance, it has been indicated that D-serine signalling is involved in enhancement of long-term potentiation in the hippocampus (Panatier et al. 2006). Recently, it was pointed out that NMDAR mediated synaptic plasticity in the hippocampus is depending on calcium-induced astrocytic D-serine signalling (Henneberger et al. 2010). In astrocytes, D-serine is broken down by D-amino acid oxidase (DAAO), an enzyme specifically for degradation of D-amino acids (Mothet et al. 2000). Nitric oxide (NO) regulates SR and DAAO in opposite ways. It enhances DAAO function and in the same time, decreases the function of SR. Interestingly, through activation of NMDARs in neurons D-serine stimulates NO production. Therefore, NO is thought to be a negative feedback system to D-serine function.

Another very important gliotransmitter is ATP, which involvement in the regulation of neuronal activity is described by a growing amount of studies. For instance, it has been shown already in 2004 that ATP is deeply involved in the regulation of neuronal communications (Bowser, Khakh 2004), but its role is complex and the precise mechanism still largely unknown. ATP is released from astrocytes by lysosomal exocytosis in a SNARE dependent manner (Pascual et al. 2005, Zhang et al. 2007). ATP release is triggered by a Ca^{2+} elevation, which occurs in astrocytes after synaptic activation or neuromodulatory input. It activates $P2X_{1\text{-}7}$ receptors, which are ligand-operated channels that allow cations such as Ca^{2+} and Na^{+} to enter. These receptors are mostly located on astrocytes, but are also present on astrocytes (Kanjhan et al. 1999). On the other hand, ATP binds to members of the P2Y receptor family. These receptors are G protein-coupled and the different subtypes couple to different G proteins (for an overview, see Brunschweiger, Muller 2006). Since astrocytes express all P2Y subtypes, as well as almost all the P2X receptors (Fumagalli et al. 2003), this seems an important mechanism in inter astrocyte and astrocyte-neuronal communication.

ATP has direct effects on neuronal signalling. This is shown in various studies such as the electrophysiological study of Mendoza-Fernández. ATP, through binding to their P2Y receptor (subtypes that are PTX- and 8-cyclopentyltheophylline-sensitive), inhibits presynaptic glutamate release in hippocampal slices (Mendoza-Fernandez, Andrew & Barajas-Lopez 2000). This occurs even in a tonic way (Zhang et al. 2003). In contrast, in neostriatal slices it was found that ATP or other receptor agonists could not induce measurable effects in neurons, whereas P2X and P2Y receptor presence was indicated to be present (Scheibler et al. 2004). Recently, an interesting mechanism of ATP enhancing neural plasticity in hippocampal slices has been put forward (Gordon et al. 2009). The plasticity occurred within minutes after stimulation of afferent fibers or direct astrocyte stimulation and was long-term. It was suggested that stimulation results in synaptic glutamate release, which activates astrocytic metabotropic glutamate receptors. After this, ATP is released by the astrocytes, which acts on postsynaptic purine receptors to proportionally increase the strength of the glutamatergic synapses. This works as a feed-forward mechanism to increase synaptic efficacy at specific synapses.

ATP is also hydrolysed into adenosine in the extracellular space by ecto-nucleotidases (Pascual et al. 2005). The process of adenosine production induced by astrocytes can be seen in figure 5. This process has a delay of approximately 200ns. Adenosine can bind to adenosine A_1 receptors (A_1Rs) on neurons, which results in neuro-inhibition. The A_1R is a $G_{i/o}$ protein-coupled receptor and activates the adenylyl cyclase-signalling pathway, which

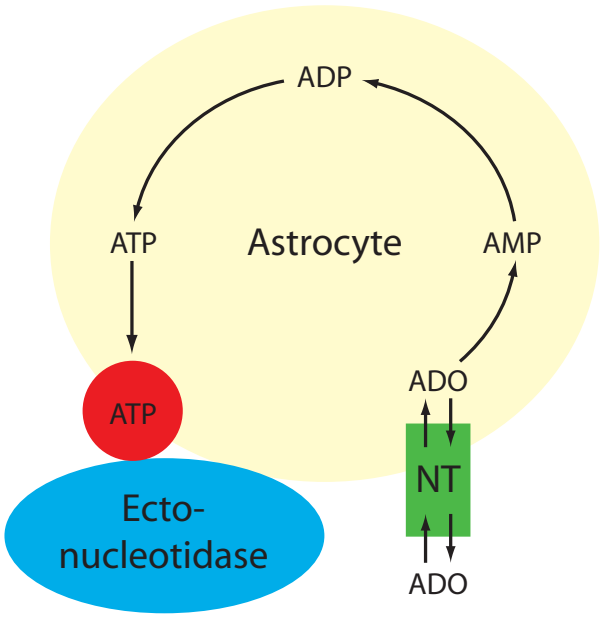

Figure 5. Adenosine cycle.
ATP is released from astrocytes after Ca2+ signalling. It is transformed into adenosine (ADO) in the extracellular space by ecto-nucleotidase. On the other hand, adenosine can be taken up by the astrocyte through a nucleotide transporter. It can be changed via AMP and ADP into ATP again.

eventually leads to inhibition of Ca^{2+} and the activation of phospholipase C (Dunwiddie, Masino 2001). The net result of this is inhibition of neurotransmitter release. On the other hand, adenosine can bind to adenosine A_{2A} receptors (A_{2A}Rs), which are located predominantly in striatal neurons. A_{2A}Rs are G_s protein-coupled, and their activation results in an increase in cAMP, which has a stimulatory effect (Dunwiddie, Masino 2001). On top of this, it has been indicated that heteromers of A_1R and A_{2A}Rs exist (Ciruela et al. 2006). This heteromer acts as an inhibitory A_1R at lower basal concentrations of adenosine but as a stimulatory A_{2A}R when adenosine levels increase. Furthermore, both A_1R and A_{2A}R can dimerise to other G protein-coupled receptors, such as the dopamine D2 receptor. An overview of these receptor interactions is given by Agnati (Agnati et al. 2003). Thus, adenosine is capable of activating receptors with opposing functions and in doing so, adenosine may be important in the fine-tuning and integration of neuronal network communication.

ATP and adenosine are both associated with a very complex but important process involved in neural network machinery, called heterosynaptic suppression (Zhang et al. 2003). This process was first seen in cultured hippocampal neurons when glutamatergic neurons upon stimulation released glutamate. The glutamate activated AMPA receptors on the nearby astrocytes, leading to ATP release from these cells. The ATP in turn activated presynaptic P2Y receptors in nearby neurons and caused suppression of synaptic activity in the same synapse, but also in neighbouring synapses. In vivo, it was indicated that not ATP but adenosine acting on A_1Rs was responsible for the effect. Two years later, this network coordination by ATP and adenosine was further studied (Pascual et al. 2005). Now, it became clear that ATP and adenosine both are very important in the process. The model that was proposed by Pascual comprises also spatiotemporal regulation by ATP and adenosine and it was stated that astrocytes control the available range for synaptic plasticity in neural networks. This is because the kinetics of ATP hydrolysis into adenosine and the accumulation of adenosine are relatively slow compared to the fast-acting synaptic transmission of glutamate. ATP can prolong the time and distance of glutamate action because ATP in very low concentrations does not interfere with the glutamatergic transmission and the adenosine formation takes time. ATP can diffuse to distant sites due to the delay in adenosine formation and therefore, distant synapses are eventually suppressed by adenosine. This induces long-term depression (LTD) in neighbouring unstimulated pathways. On top of this, ATP itself can excite interneurons by acting on the $P2Y_1$ receptor, which also leads to suppression of neighbouring networks. On the other hand, whereas ATP and adenosine suppress neighbouring pathways, the stimulated pathway is enhanced. Because glutamatergic transmission of the stimulated pathway is not disturbed by low concentrations of ATP, synaptic strength can grow in this time. Furthermore, long-term potentiation (LTP) is enhanced in the stimulated pathway through astrocytic

glutamate release as is described above. In 2006, there was published another clear overview of heterosynaptic suppression (Fellin, Pascual & Haydon 2006).

In summary, by the release of gliotransmitters, of which ATP is one of the most important, astrocytes serve to regulate many aspects of synaptic transmission. Not only are astrocytes able to sense neuronal activation, they can also modulate this activity. In the late nineties, the term 'tripartite synapse' was introduced against the dogma of synaptic communication to be exclusively by neurons, since researchers became aware of the essential role of astrocytes in this process. Over the years, it has become more and more clear that astrocytes provide widespread coordination of synaptic networks. On the other hand, there are still large holes in the knowledge about astrocyte-neuron interactions. For instance about gliotransmittion, it is not known whether different gliotransmitters can be co-released or whether different astrocytes, astrocytic processes or domains release different gliotransmitters. Furthermore, it is important to elucidate upon which specific (neuronal) input and physiological condition the different astrocytic gliotransmitters are released. This all is important to come closer to a full understanding of astrocytic function in neuronal communication.

Astrocytes and the working mechanism of DBS

Although there has been put much effort in deciphering the effect DBS has on neurons, much less is known about whether other elements in the brain collaborate to its neuronal effect. Astrocytes are the first candidates to discuss, since they are so deeply involved in neuronal communication, as is described above. In this part, a possible connection between the neuronal effect of DBS and astrocytic function is described. It is hypothesised that astrocytes partly underlie the effects that are induced in neuronal signalling by DBS. One route is to follow that of the involvement of astrocytic adenosine, but there are also other possibilities.

DBS and astrocytic adenosine

Adenosine itself functions, as is described above (see Astrocytes, Astrocytes regulate neuronal network activity), as an important modulator of neuronal activity. Dysregulation of adenosine signalling often leads to

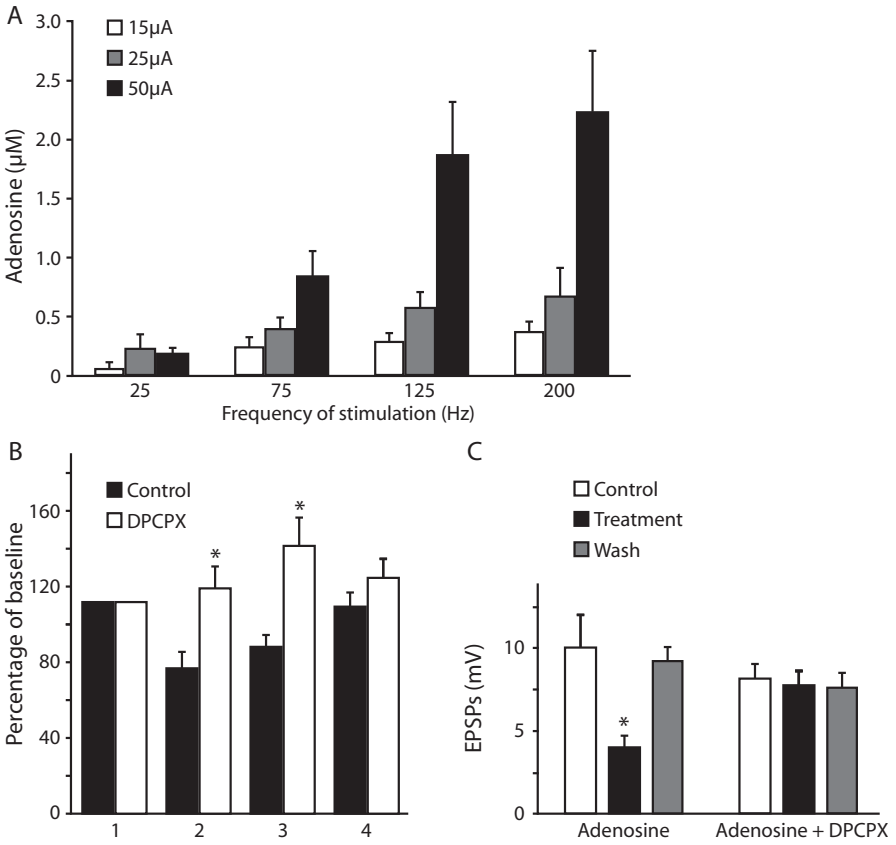

Figure 6. Adenosine is crucial for DBS induced suppression of STN neuronal firing.

A. Extracellular adenosine concentration increased as a function of amplitude and frequency of high-frequency stimulation (HFS) of thalamic slice preparations. (10s HFS, n=4, p<0,01). B. Histogram comparing HFS induced depression of eEPSPs before (bars 1), during (bars 2), and 4s (bars 3) and 40s (bars 4) after HFS of heterosynaptic pathways (n=5, p<0,01). C. Adenosine depression of eEPSPs is reversible since after washout eEPSP amplitude is restored. DPCPX blocks adenosine-induced suppression (n=6, p<0,05). Adapted from Bekar et al. 2008.

pathological affairs, such as epilepsy. Apart from that, adenosine receptors are associated with many neurological diseases, which are also treated with DBS such as chronic pain (Ferre et al. 2007), Parkinson's disease (Fuxe et al. 2007, Schiffmann et al. 2007), Huntington's disease (Popoli et al. 2007) and schizophrenia (Lara et al. 2006). More and more and in many cases, they begin to serve as alternative therapeutic target. For instance, adenosine $A_{2A}R$-based drug therapy is the prime non-dopamine target in treating PD (Schwarzschild et al. 2006).

The rationale for astrocytic adenosine to be involved in the beneficial effect of DBS in PD patients comes from an elegant study of Bekar and her group (Bekar et al. 2008). In this study, high-frequency stimulation was provided simultaneously with whole-cell recordings in thalamic slice preparations obtained from mice. Furthermore, using bioluminiscence techniques, ATP, Calcium and adenosine could be visualised. The first experiment already pointed out that around the stimulation electrode, ATP was accumulating fastly in the extracellular space. This increase in ATP levels only occurred when cathodic stimulation was delivered. Furthermore, the ATP release occurred even when Ca^{2+} was buffered, which suggests a nonsynaptic release of ATP. In addition, astrocytic Ca^{2+} waves were found to occur after stimulation and these waves propagated away from the electrode site. When the adenosine A_1R antagonist DPCPX was used, the high-frequency stimulation-induced suppression of thalamic neuronal activity was abolished. This occurred in both homo- and heterosynaptic pathways, which is also shown in figure 6. Inhibition of high-frequency stimulation-induced depression was also the case when ecto-nucleotidase inhibitor ARL-67156 was used. Amplitude of evoked excitatory postsynaptic potentials (eEPSPs) was decreased when adenosine was superfused through the thalamic slices. This also implies that adenosine is able to suppress neural activity.

Apart from these in vitro and ex vivo experiments, the authors conducted also experiments in intact animals. Most importantly, experiments using several mouse models for tremor, pointed out that adenosine signalling was essential to the anti-tremor effect of high-frequency stimulation. First was shown that adenosine itself could attenuate the tremor in these models and that the level to which adenosine does this closely resembles the anti-tremor effect of DBS. Then it was shown that DBS in combination with A_1R antagonist DPCPX infusion in harmaline treated mice lead to involuntary movements at much lower intensities than without DPCPX infusion. In other words, involuntary movements, which are negative effects of DBS often seen when stimulation intensity is very high, are seen at much lower intensities when adenosine is antagonised. On the other hand, glutamatergic antagonists as CNQX and APV lifted the threshold for these negative DBS effects to much higher levels. This suggests that adenosine reduces the distance over which DBS is spread in the brain and thereby prevents negative effects of DBS. This study indicates that adenosine is involved in the therapeutic effect of DBS, at least in PD. If this anti-spread effect of adenosine is consistent, it is likely that adenosine plays this key role also in many other DBS types. However, this is the only study done so far, considering the involvement of astrocytic signalling with the effect of DBS in this way.

Recently and in response to the study of Bekar, astrocytic involvement in the therapeutic benefit of DBS was tested in a very different but also elegant way. In this study the effect of astrocyte recruitment of DBS was tested in 6-OHDA induced Parkinsonian mice (Gradinaru et al. 2009). By the lentiviral expression of light sensitive ion-channels (channelrhodopsins, ChR2) in STN in combination with fiber optic- and laser diode-based in vivo light delivery, a potent method was born to dissect specific circuit elements in freely behaving

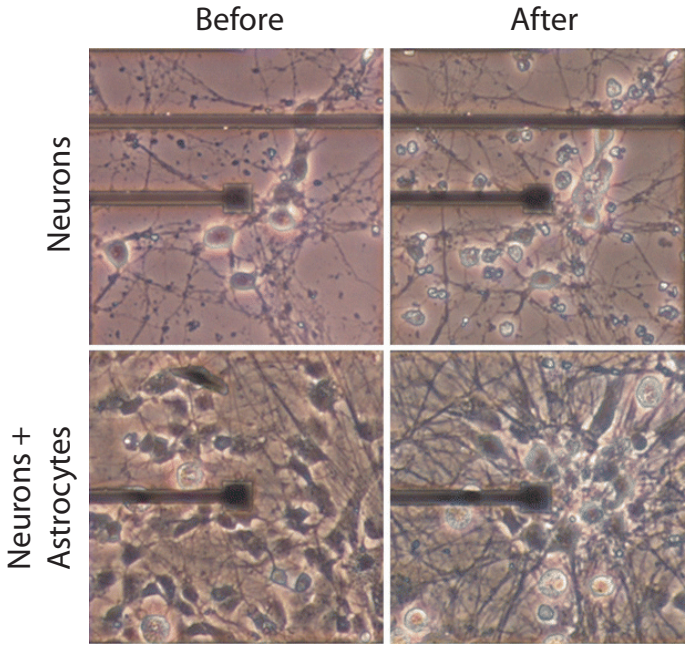

Figure 7. Astrocytes accumulate around DBS electrode.
Cell clusters form 72h after electrical stimulation (20 Hz) only in cultures with both neurons and astrocytes. Adapted from Jeong et al. 2009.

animals. In one particular experiment, astrocytic Ca^{2+} waves were mimicked by opening Ca^{2+} channels by the use of optical activation of ChR2. By this mechanism, it was found that light-mediated astrocyte recruitment and activation was able to diminish STN neuronal firing. However, Parkinsonian motorsymptoms of 6-OHDA mice were not altered. These results do not rule out the involvement of glial inhibition of the STN however, it could be that in addition to astrocyte-related neuronal inhibition, other mechanisms are involved in therapeutic effect of DBS in PD.

The involvement of astrocyte-derived adenosine in the effect of DBS has been investigated by two other studies (Shon et al. 2009, Chang et al. 2009a). However, these studies suggest another field of interference of adenosine and DBS. It has been shown that the procedure of inserting the DBS electrode in the brain releases a high amount of adenosine (Chang et al. 2009b). This corresponds with the fact that mechanical stimulation is a generally used method to induce activation of calcium signalling and ATP release in cultured astrocytes (Newman, Zahs 1998, Kozlov et al. 2006). The astrocytic activation by the DBS electrode is thought to contribute to the microthalamotomy effect of electrode insertion. This is the induction of a micro lesion, which in some cases is enough to overcome the pathological symptoms of patients.

Other possible ways astrocytes are involved in the effects of DBS

Despite their contribution to neuronal signalling, astrocytes serve important neuroprotective and neurosupportive functions in the brain. There are lines of evidence, which state that DBS can induce such neurosupportive function of astrocytes around the electrode that might contribute to the beneficial effect of DBS therapy. Below, a new and very exciting line of research is described. However, a lot of effort has to be put into it before it can be considered as a model for DBS functioning.

The group of Jeong provided an interesting paper last year (Jeong et al. 2009). It was already known that electrical stimulation lead to neuronal migration (Jun et al. 2007). Furthermore, it was suggested that electrical stimulation by this manner also induces higher levels of neurons, as well as higher levels of synaptic contacts. The authors of the present paper hypothesised that astrocytes, since they are deeply involved in neuronal signalling, could underlie this process. They show, as is seen in figure 7, that when there are astrocytes co-cultured with neurons on a microelectrode array, after chronic electrical stimulation over three days, high levels of neuron cell bodies have gathered around the electrode. On the other hand, it was told that astrocytes themselves showed none of this effect. It was thought that the effect showed was the result of calcium signalling, since a sodium channel blocker (TTX) abolished the effect.

The question remains how this effect occurs and where the neurons come from. The authors hypothesise that the neurons can be partly derived from neuroprogenitor cells (Jeong et al. 2009). This might be a very interesting line of future research. A distinct type of astrocytes is thought to have the neuroprogenitor properties in the adult brain and is associated with repair after neuronal damage (Buffo et al. 2008). If the proliferation of these astrocytes could be promoted by electrical stimulation, then this would bring major exciting possibilities for therapeutic methods to treat a broad spectrum of neurological diseases.

In summary, although the amount of research into the involvement of astrocytes in the mechanism is still very limited, this is a very interesting research direction. Astrocytes can be triggered by electrical stimulation to induce the production of adenosine, an important neuromodulator. Adenosine has been shown to be involved in the regulation of neuronal synaptic networks. Therefore, it is possible that the DBS-induced suppression of network activity is partially due to adenosine signalling. On the other hand, astrocytes are suggested to proliferate into neurons when they are electrically stimulated. This particular theory is very interesting, but requires a lot of research before it can be accepted.

Discussion

In the present review, it was attempted to provide a clear overview of the current knowledge about DBS and its working mechanism and to see which elements in the brain play a role in its effect. The majority of studies into the mechanism of DBS only considers neurons as target cells of the electrical stimulation method. However, it is not likely that other cells with electrophysiological properties in the brain, such as astrocytes, are excluded from the effect of DBS. It was hypothesised that also elements of the brain other than neurons would be recruited by DBS. As is described in this review, this is indeed the case. However, there is not much knowledge about the exact contribution of astrocytes to the effect of DBS. There has been put only very little effort in the participation of astrocytes in the therapeutic effect of DBS, although this has very interesting implications.

In the past decades, DBS has become a very popular tool to treat various brain disorders. In the beginning, mostly movement disorders of the basal ganglia were treated with DBS (Benabid et al. 1991) but nowadays it is used also in many psychiatric disorders (Larson 2008) and new purposes are currently under development (Mikell et al. 2009, Vassoler et al. 2008). Despite its general usage, little was known about how DBS works and why it was beneficial to patients. Nowadays, a massive amount of research suggests that neuronal networks that are involved in the pathology of the disorders are modulated by DBS (McIntyre, Hahn 2009).

In principle, DBS is thought to activate large myelinated axons rather than cell bodies (Ranck 1975).

On cellular level, DBS is thought to induce inhibition of the neurons in the target nucleus. For instance, it was shown that STN glutamatergic neurons, which are normally spontaneously active, are ceased from firing after DBS (Magarinos-Ascone et al. 2002). Another reaction seen in the STN is a stimulus based firing pattern (Garcia et al. 2003). The electrical field, which is induced by the stimulation electrode, consists of a depolarising part just around the electrode and a hyperpolarisation field surrounding that. Therefore, depolarisation and hyperpolarisation occur next to each other in the same element. It is thought that this results in an uncoupling between axon and cell body (Gubellini et al. 2009). As a result of that, neuronal cell bodies are suppressed and synapses can be activated at the same time. On top of this, afferent axons can be activated and via antidromic axonal propagation of the action potentials, regions projecting to the DBS target nucleus can be recruited in the effect (Grill, Cantrell & Robertson 2008). This recruitment of other parts of the brain can be nicely visualised using functional brain imaging techniques.

Fact is that in neuronal network signalling neurons are closely regulated by astrocytes. This type of glial cells responds to neural activity and is even excitable itself (Bevan, Raff 1985). Astrocytes regulate synaptic transmission (Perea, Araque 2007), synaptic plasticity but are also involved in the spread of activation and they are in charge of the possible amount of plasticity in a network (Pascual et al. 2005, Gordon et al. 2009). A primary signalling method of astrocytes is through Ca^{2+} waves (Agulhon et al. 2008). These elevations in Ca^{2+} levels are driven by ATP (Bowser, Khakh 2007) and make it possible for astrocytes to communicate with their own processes and other astrocytes. Astrocyes also communicate with neurons using gliotransmitters such as ATP, D-serine and glutamate. Foremost, astrocytic ATP and its derivate adenosine are important in the regulation of neuronal network activity (Bowser, Khakh 2004).

On the other hand, astrocytes serve a neuro-supportive function in harmful circumstances. They respond to damage with gliosis. Astrocytes then become hypertrophic (Wilhelmsson et al. 2006) and express progenitor cell markers such as nestin (Sofroniew 2005). Most importantly, damage can induce astrocyte differentiation into neuronal stem cells (Buffo et al. 2008). This fact in particular, is relevant to this discussion.

Since they are so closely involved in neuronal function, it is likely that at least some of the network effects of DBS are mediated by astrocytes. At this moment, there are two lines of evidence for the involvement of astrocytes in DBS. The first line of evidence considers the contribution of astrocytic adenosine to the DBS effect (Bekar et al. 2008). The other line of evidence suggests that astrocytes might differentiate upon DBS-induced activation and form neuronal stem cells (Jeong et al. 2009). Below these two lines are discussed and future perspectives are given.

A first indication astrocytes are in fact recruited by DBS is that DBS induces Ca^{2+} waves in the astrocytes surrounding the stimulation electrode that moved away from the electrode (Bekar et al. 2008). This shows that astrocytes are sensitive to electrical stimulation and respond to it. When these DBS induced Ca^{2+} waves were imitated in an elegant study by using light-sensitive ion channels in combination with fiber optic- and laser diode-based in vivo light delivery techniques, it was shown that these in fact resulted in suppression of neuronal firing (Gradinaru et al. 2009). Together this indicates that astrocytes might be important in the inhibition of the target nucleus that is induced by DBS. If Ca^{2+} waves themselves are also important in the effect of DBS is not known. It would be interesting to see if high frequency electrical stimulation in a calcium-depleted model is as effective as control. This could be done in striatal slice preparations. If high-frequency stimulation still results in suppression of the neuronal activity in the slice after calcium is washed away, then astrocytic function is not necessary for the effect of DBS.

Apart from the recruitment of astrocytes by DBS, it is suggested that astrocytes are crucial to the therapeutic effect of DBS in Parkinson's patients (Bekar et al. 2008). Astrocyte-derived adenosine contributes to the anti-tremor effect of DBS. This was shown when specific adenosine antagonists diminished the effect of DBS in animal models. It was suggested that the induced adenosine is important in restricting the spread of the electrical stimulation by inhibiting surrounding neural networks. To date, this is the only study performed in this field and therefore, to be sure it has to be repeated and also investigated in other animal models. However, the suggested adenosine effect in DBS is underlined by the fact that adenosine-based therapy is first in line after dopamine replacement therapy in PD pharmacological treatment (Schwarzschild et al. 2006). It has been shown that adenosine treatment is very effective against motor symptoms (Pinna et al. 2007). Noteworthy, pharmacological treatment is based on antagonising adenosine A_{2A}Rs and at the same time it is shown that the adenosine effect in the DBS study primarily activated A_1Rs. This seems a big contradiction, but stimulation of A_1R and inhibition of A_{2A}R basically results in the same molecular signal since these receptors are coupled to G proteins with opposing functions (Dunwiddie, Masino 2001).

Further research to decipher the exact way adenosine is involved in the mechanism of DBS is needed. Primarily, since there is only one study done at this moment and it would be of interest to see whether the results can be duplicated. If this is the case, this would mean a revolution in the current theory about the mechanism of DBS. This has also implication for the future use of DBS in a variety of disorders. For instance in PD, it would be interesting to find out if the benefit of adenosine A_{2A}R-based pharmacological treatment and the A_1R effect of DBS adds-up.

It is also possible that the astrocytic adenosine response is a reaction on the synaptic activation that is induced by DBS. Therefore, it is important to see the timescale of the events. If there is more than 200us delay of adenosine accumulation after the initiation of DBS

stimuli, the question is whether astrocytes are directly triggered by DBS. Furthermore, it would be interesting to test if high frequency electrical stimulation results in calcium and adenosine signalling in cultured astrocytes only. If it turns out that DBS cannot excite astrocytes by itself, than the astrocytic effect observed is indirect.

Based on the other line of evidence, it is possible that during chronic high-frequency stimulation such as DBS astrocytes can be recruited to proliferate into neuronal stem cells. This was suggested after it was seen that neurons gather around the electrode only in combined neuron-astrocyte cultures (Jeong et al. 2009). It was also noted that this seemed unlikely since the neuronal cell numbers were not significantly increased after chronic stimulation compared to before. However, a previous study of this research group pointed out that around the stimulation electrode astrocyte clustering appeared and that these astrocytes had increased glial fibrillary acid protein (GFAP) expression (Jun et al. 2007). Furthermore, this study also indicated that astrocytes only clustered around stimulated electrodes, not around unstimulated control ones. Both of these findings suggest that electrical stimulation might result in astrocyte proliferation and possibly differentiation. Increased GFAP expression is one of the markers for proliferating astrocytes (Imura, Kornblum & Sofroniew 2003). Furthermore, the fact that around DBS electrodes always develops a mild form of gliosis (Moss et al. 2004, Griffith, Humphrey 2006), also contributes to this theory. In addition, it was shown that among other glial cells, only astrocytes react this way and form multipotent neurospheres upon neuronal injury (Buffo et al. 2008). It is possible, though very precarious to claim, that astrocytes can do this trick also upon electrical stimulation. If that is the case, this has major implications for the therapeutic use and purposes of DBS.

Since this might have important consequences for the future use of DBS, it is essential to further investigate this effect. In the first place it is needed to see whether in intact animals these reactive astrocytes gather around DBS electrodes. For that, fate-mapping technique as used in (Buffo et al. 2008) can be performed to follow astrocytes surrounding stimulation electrodes after chronic high-frequency stimulation compared to unstimulated controls. By this way it is possible to see if the close-by astrocytes are activated by electrical stimulation and answer with differentiation. Furthermore, it is needed to see whether stimulation parameters influence the efficacy of astrocyte proliferation. In addition, other proliferation and differentiation markers, such as nestin and vimentin (Sofroniew 2005), have to be tested in the astrocytes around DBS electrodes. On the other hand, it might be interesting to see if in post-mortem brain tissue of DBS receivers also increased neuronal numbers are located around the electrode. It would be of help if the age of these neurons could be determinened and to see if there are newly differentiated cells present. The tissue around the DBS electrode has been studied post-mortem many times (Moss et al. 2004, Henderson et al. 2002, Nielsen et al. 2007, Sun et al. 2008), although researches have never looked into the types of neurons surrounding the electrode since the foremost goal was to see if DBS induced inflammatory responses. Therefore, it could be that they always have overlooked this effect.

In summary, both astrocytic activation and astrocyte proliferation have been observed around DBS electrodes. This suggests that astrocytes are recruited by DBS, either in a direct or an indirect way. Already some evidence for astrocytic contribution to the therapeutic effect of DBS is presented. However, since to date most researchers have only put their efforts in neuronal effects of DBS, much is there to be discovered. Future research directions point towards astrocytic activation by high frequency electrical stimulation and towards astrocytic proliferation upon high frequency electrical stimulation. If it is found that astrocytes are in fact stimulated by DBS, then this has major implication for the future usability of the method.

Conclusion

DBS is a very potent tool in the treatment of many neurological disorders ranging from movement disorders to psychiatric disorders. The mechanism in which DBS affects neuronal signalling is extensively studied. However, an important thing has always been left out. Namely, that it is unlikely that DBS affects solely neurons. In this review, the role of astrocytes in the working mechanism of DBS is investigated. Since astrocytic signalling closely regulates neuronal networks and DBS is thought to interfere with a pathological activity pattern in a neural network, astrocytes are the primary candidate to investigate. The most important reasons to presume astrocytes are involved in the effect of DBS are based on two recent studies. First, electrical stimulation induces activation Ca^{2+} waves, one of the most important astrocytic communication processes, and it results in asterocytic adenosine release (Bekar et al. 2008). Second, electrical stimulation induces astrocytic expression of GFAP, which is a marker for astrocytic activation and proliferation, and astrocytic and neuronal clustering is observed around stimulation electrodes (Jun et al. 2007, Jeong et al. 2009). Even though the line of evidence is still very thin, it can be concluded that astrocytes are indeed affected by DBS, either in a direct or indirect way.

Although it is very hard to investigate the precise effect of DBS since whole networks of neuronal and presumably astrocytic cells are involved, there is much more to discover about the way DBS is affecting brain function then is already known by now. Future studies may contribute to determine the exact way and to what extend astrocytes are involved in the working mechanism of DBS. If the future study results are in agreement with the hypothesis that astrocytes are involved in the therapeutic effect of DBS, then this might cause a revolution in the way DBS is used as a therapeutic instrument.

Acknowledgements

I wish to thank Dr. E.M. Hol (Netherlands Institute for Neuroscience) and Dr. P.N.E. de Graan (Division Neuroscience of the University Medical Center Utrecht, Rudolf Magnus Institute of Neuroscience) for their kind supervision. Furthermore, I would like to thank E.D. van Battum for his graphical assistance.

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